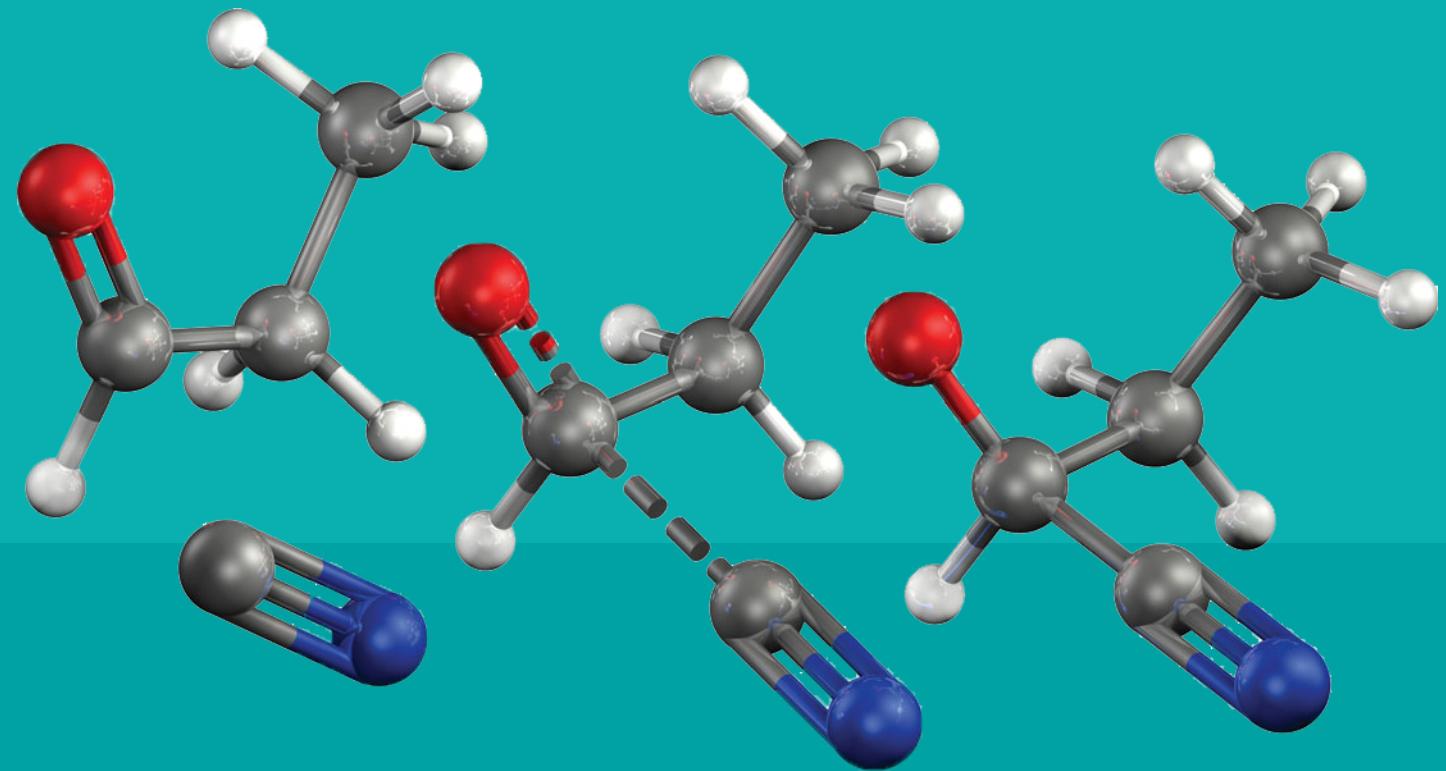


# 有机化学

ORGANIC CHEMISTRY

原书  
第二版



[英] Jonathan Clayden Nick Greeves Stuart Warren 著

OXFORD  
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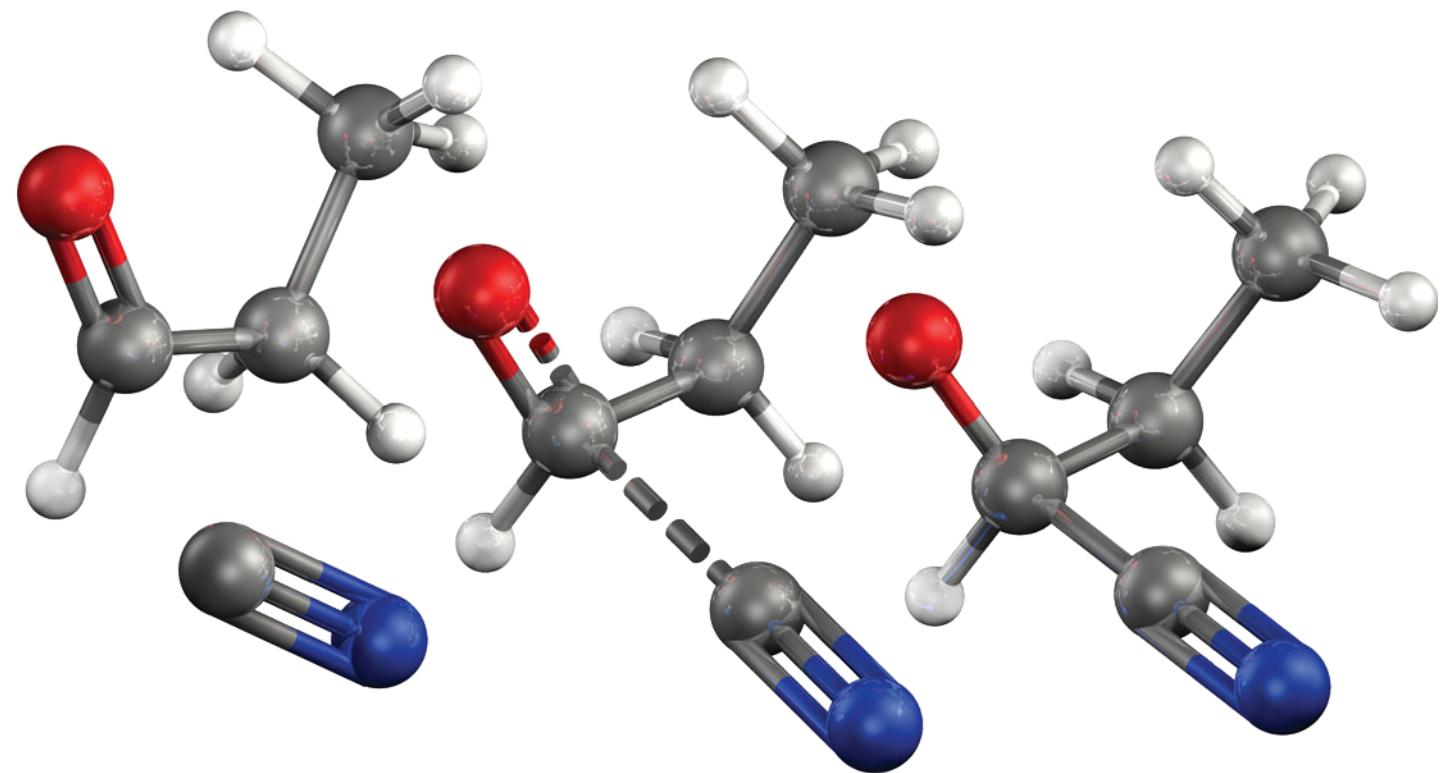
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## Organic Chemistry

## 有机化学



### Organic Chemistry (有机化学)—在线支持

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# 缩写对照

Ac	乙酰基	DMS	二甲硫醚
Acac	乙酰丙酮盐	DMSO	二甲亚砜
AD	不对称双羟基化	DNA	脱氧核糖核酸
ADP	52-二磷酸腺苷	E1	单分子消除反应
AE	不对称环氧化	E2	双分子消除反应
AIBN	偶氮二异丁腈	E <sub>a</sub>	活化能
AO	原子轨道	EDTA	乙二胺四乙酸
Ar	芳基	EPR	电子顺磁共振
ATP	三磷酸腺苷	ESR	电子自旋共振
9-BBN	9-硼杂双环[3.3.1]壬烷	Et	乙基
BHT	丁基羟基甲苯 (2,6-二叔丁基-4-甲基苯酚)	FGI	官能团相互转化
BINAP	双(二苯膦基)-1,1'-联萘	Fmoc	芴甲氧羰基
Bn	苄基	GAC	普通酸催化
Boc, BOC	叔丁氧羰基	GBC	普通碱催化
Bu	丁基	HMPA	六甲基磷酰胺
s-Bu	仲丁基	HMPT	六甲基磷酰三胺
t-Bu	叔丁基	HOBt	1-羟基苯并三唑
Bz	苯甲酰基	HOMO	最高占据分子轨道
Cbz	苄氧羰基	HPLC	高效液相色谱
CDI	碳酰二咪唑	HIV	人类免疫缺陷病毒
CI	化学电离	IR	红外光谱
CoA	辅酶 A	KHMDS	六甲基二硅基氨基钾
COT	环辛四烯	LCAO	原子轨道的线性组合
Cp	环戊二烯	LDA	二异丙基氨基锂
DABCO	1,4-二氮杂二环[2.2.2]辛烷	LHMDS	六甲基二硅基氨基锂
DBE	双键等价物	LICA	异丙基环己基氨基锂
DBN	1,5-二氮杂双环[4.3.0]壬-5-烯	LTMP, LiTMP	2,2,6,6-四甲基哌啶锂
DBU	1,8-二氮杂双环[5.4.0]十一-7-烯	LUMO	最低未占据分子轨道
DCC	N,N-二环己基碳二亚胺	m-CPBA	间氯代过氧苯甲酸
DDQ	2,3-二氯-5,6-二氰基-1,4-苯醌	Me	甲基
DEAD	偶氮二甲酸二乙酯	MO	分子轨道
DIBAL	二异丁基氢化铝	MOM	甲氧基甲基
DMAP	4-二甲氨基吡啶	Ms	甲磺酰基
DME	1,2-二甲氧基乙烷	NAD	烟酰胺腺嘌呤二核苷酸
DMF	N,N-二甲基甲酰胺	NADH	还原型 NAD
DMPU	1,3-二甲基-3,4,5,6-四氢-2(1H)-嘧啶酮	NBS	N-溴代琥珀酰亚胺
		NIS	N-碘代琥珀酰亚胺
		NMO	N-甲基吗啉-N-氧化物

<b>NMR</b>	核磁共振	<b>SOMO</b>	单占分子轨道
<b>NOE</b>	核 Overhauser 效应	<b>STM</b>	扫描隧道显微镜
<b>PCC</b>	氯铬酸吡啶鎓	<b>TBDMS</b>	叔丁基二甲基硅基
<b>PDC</b>	重铬酸吡啶鎓	<b>TBDPS</b>	叔丁基二苯基硅基
<b>Ph</b>	苯基	<b>Tf</b>	三氟甲磺酰基
<b>PPA</b>	多聚磷酸	<b>THF</b>	四氢呋喃
<b>Pr</b>	丙基	<b>THP</b>	四氢吡喃
<i>i</i> - <b>Pr</b>	异丙基	<b>TIPS</b>	三异丙基轨迹
<b>PTC</b>	相转移催化剂	<b>TMEDA</b>	<i>N,N,N',N'</i> -四甲基-1,2-乙二胺
<b>PTSA</b>	对甲苯磺酰胺	<b>TMP</b>	2,2,6,6-四甲基哌啶
<b>Py</b>	吡啶	<b>TMS</b>	三甲基硅基，也指四甲基硅烷
<b>Red Al</b>	二(2-甲氧基乙氧基) 氢化铝钠	<b>TMSOTf</b>	三氟甲磺酰基三甲基硅烷
<b>RNA</b>	核糖核酸	<b>TPAP</b>	过钌酸四-N-丙基铵
<b>SAC</b>	特别酸催化	<b>Tr</b>	三苯甲基
<b>SAM</b>	S-腺苷蛋氨酸	<b>TS</b>	过渡态
<b>SBC</b>	特别碱催化	<b>Ts</b>	对甲苯磺酰基
<b>S<sub>N</sub>1</b>	单分子亲核取代反应	<b>UV</b>	紫外光
<b>S<sub>N</sub>2</b>	双分子亲核取代反应	<b>VSEPR</b>	价层电子对互斥

# 第二版序言

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Students of chemistry are not hard-pressed to find a text to support their learning in organic chemistry through their years at university. The shelves of a university bookshop will usually offer a choice of at least half a dozen—all entitled ‘Organic Chemistry’, all with substantially more than 1000 pages. Closer inspection of these titles quickly disappoints expectations of variety. Almost without exception, general organic chemistry texts have been written to accompany traditional American sophomore courses, with their rather precisely defined requirements. This has left the authors of these books little scope for reinvigorating their presentation of chemistry with new ideas.

We wanted to write a book whose structure grows from the development of ideas rather than being dictated by the sequential presentation of facts. We believe that students benefit most of all from a book which leads from familiar concepts to unfamiliar ones, not just encouraging them to *know* but to *understand* and to understand *why*. We were spurred on by the nature of the best modern university chemistry courses, which themselves follow this pattern: this is after all how science itself develops. We also knew that if we did this we could, from the start, relate the chemistry we were talking about to the two most important sorts of chemistry that exist—the chemistry that is known as life, and the chemistry as practised by chemists solving real problems in laboratories.

We aimed at an approach which would make sense to and appeal to today’s students. But all of this meant taking the axe to the roots of some long-standing textbook traditions. The best way to find out how something works is to take it apart and put it back together again, so we started with the tools for expressing chemical ideas: structural diagrams and curly arrows. Organic chemistry is too huge a field to learn even a small part by rote, but with these tools, students can soon make sense of chemistry which may be unfamiliar in detail by relating it to what they know and understand. By calling on curly arrows and ordering chemistry according to mechanism we allow ourselves to discuss mechanistically (and orbitally) simple reactions (addition to C=O, for example) before more complex and involved ones (such as S<sub>N</sub>1 and S<sub>N</sub>2).

Complexity follows in its own time, but we have deliberately omitted detailed discussion of obscure reactions of little value, or of variants of reactions which lie a simple step of mechanistic logic from our main story: some of these are explored in the problems associated with each chapter, which are available online.<sup>1</sup> We have similarly aimed to avoid exhuming principles and rules (from those of Le Châtelier through Markovnikov, Saytseff, least motion, and the like) to explain things which are better understood in terms of unifying fundamental thermodynamic or mechanistic concepts.

All science must be underpinned by evidence, and support for organic chemistry’s claims is provided by spectroscopy. For this reason we first reveal to students the facts which spectroscopy tells us (Chapter 3) before trying to explain them (Chapter 4) and then use them to deduce mechanisms (Chapter 5). NMR in particular forms a significant part of four chapters in the book, and evidence drawn from NMR underpins many of the discussions right through the book. Likewise, the mechanistic principles we outline in Chapter 5, firmly based in the orbital theories of Chapter 4, underpin all of the discussion of new reactions through the rest of the book.

We have presented chemistry as something whose essence is truth, of provable veracity, but which is embellished with opinions and suggestions to which not all chemists subscribe. We aim to avoid dogma and promote the healthy weighing up of evidence, and on occasion we are content to leave readers to draw their own conclusions. Science is important not just to scientists, but to society. Our aim has been to write a book which itself takes a scientific

<sup>1</sup> See [www.oxfordtextbooks.co.uk/orc/clayden2e/](http://www.oxfordtextbooks.co.uk/orc/clayden2e/).

standpoint—‘one foot inside the boundary of the known, the other just outside’<sup>2</sup>—and encourages the reader to do the same.

The authors are indebted to the many supportive and critical readers of the first edition of this book who have supplied us over the last ten years with a stream of comments and corrections, hearty encouragements and stern rebukes. All were carefully noted and none was overlooked while we were writing this edition. In many cases these contributions helped us to correct errors or make other improvements to the text. We would also like to acknowledge the support and guidance of the editorial team at OUP, and again to recognize the seminal contribution of the man who first nurtured the vision that organic chemistry could be taught with a book like this, Michael Rodgers. The time spent on the preparation of this edition was made available only with the forbearance of our families, friends and research groups, and we thank all of them for their patience and understanding.

## Changes for this edition

In the decade since the publication of the first edition of this book it has become clear that some aspects of our original approach were in need of revision, some chapters in need of updating with material which has gained in significance over those years, and others in need of shortening. We have taken into account a consistent criticism from readers that the early chapters of the first edition were too detailed for new students, and have made substantial changes to the material in Chapters 4, 8, and 12, shifting the emphasis towards explanation and away from detail more suitably found in specialised texts. Every chapter has been rewritten to improve clarity and new explanations and examples have been used widely. The style, location, and content of the spectroscopy chapters (3, 13, 18, and 31) have been revised to strengthen the links with material appearing nearby in the book. Concepts such as conjugate addition and regioselectivity, which previously lacked coherent presentation, now have their own chapters (22 and 24). In some sections of the first edition, groups of chapters were used to present related material: these chapter groups have now been condensed—so, for example, Chapters 25 and 26 on enolate chemistry replace four previous chapters, Chapters 31 and 32 on cyclic molecules replace three chapters, Chapter 36 on rearrangements and fragmentations replaces two chapters, and Chapter 42 on the organic chemistry of life replaces three chapters (the former versions of which are available online). Three chapters placed late in the first edition have been moved forward and revised to emphasize links between their material and the enolate chemistry of Chapters 25 and 26, thus Chapter 27 deals with double-bond stereocontrol in the context of organo-main group chemistry, and Chapters 29 and 30, addressing aromatic heterocycles, now reinforce the link between many of the mechanisms characteristic of these compounds and those of the carbonyl addition and condensation reactions discussed in the previous chapters. Earlier discussion of heterocycles also allows a theme of cyclic molecules and transition states to develop throughout Chapters 29–36, and matches more closely the typical order of material in undergraduate courses.

Some fields have inevitably advanced considerably in the last 10 years: the chapters on organometallic chemistry (40) and asymmetric synthesis (41) have received the most extensive revision, and are now placed consecutively to allow the essential role of organometallic catalysis in asymmetric synthesis to come to the fore. Throughout the book, new examples, especially from the recent literature of drug synthesis, have been used to illustrate the reactions being discussed.

<sup>2</sup> McEvedy, C. *The Penguin Atlas of Ancient History*, Penguin Books, 1967.

# 序言：有机化学与本书

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您可以从书名中看出，本书是讲解有关有机化学的。但事实上本书将教给您更多：它会告诉您了解和诠释有机化学的方法。它会告诉您有机化学的事实，也会告诉您我们如何发现这些事实；他会告诉您各种各样的有机反应，也会告诉您如何预测反应的发生；它告诉您分子的结构，也会告诉您如何合成它们。

我们最后一段中使用了“它告诉”，也许我们应该换成“我们告诉”，因为本书中包含的更多的是我们的话语，我们希望您能从中受到启发并产生自己的思想。您应当看出，本书有三位作者，它们有不同的思想，解释问题的角落亦不同。有机化学的内容十分丰富，无法用简单的教条规则所制约。不同的思考方式都是允许的，我们通常无法具体的说明谁对谁错。在许多情况下，这也许并不是个问题。

我们虽然不时会提到有机化学史，但我们更多的是讨论当下有机化学的进展。虽然缓慢，但有机化学的思想是始终在发展的，就像从最初的小分子到大分子和复杂结构一样。我们只能保证您一件事。我们不会因为想避免尴尬而对您撒谎。我们的目标是诚实，因此我们会在分享喜悦的同时，整理我们对于这些问题的理解与困惑。

## 章节设定

那么我们如何开始呢？本书将开始于简单分子的结构。您不但会学习分子结构，还会学习解释分子结构的理论。这些理论被用于解释实验，并且用于预测未发生的现象。然后您会学习一些反应，同时学习机理——一种讨论反应过程的动态语言。

本书将开始于介绍部分，即前四章：

1. 什么是有机化学？
2. 有机结构
3. 有机结构的确定
4. 分子结构

Chapter 1 的主题是一个“粗略的指南”——它会介绍有机化学主要的应用领域，也会向您展示有机化学发展的诸多里程碑。在 Chapter 2 中，您会看到我们如何在纸面上表示分子。有机化学本来是三维的，因此您在纸面上不同的表示方式直观地反映了您的思考方式。我们会教您目前最好的分子结构的画法，比那些古老而不准确的画法要好得多。

然后在 Chapter 3 中，在开始了解那些解释分子结构的理论之前，我们会向您介绍一些实验性的技术方法，它们直接地告诉我们分子客观的真实结构。这意味着我们将学习光谱法上辐射与分子之间的相互作用——X-rays 通过分子形成形成的电磁光谱。只有在 Chapter 4 中，我们才会开始学习那些在幕后的，解释原子和它们结合方式的理论。Chapter 3 中光谱分析得到的结论在一百年后仍然是事实，但 Chapter 4 中的解释理论也许会过时。

这三章的内容大致可以总结为三个问题：

- 2.** 有机分子有什么样的结构？
- 3.** 有机分子的结构怎样为人所知？
- 4.** 有机分子为什么会有那样的结构？

在您学习有机反应之前，您必须先掌握这三个问题的答案。这正是接下来要开始的任务。我们将在 Chapter 5 中开始介绍反应机理。任何化学研究的反应都是分子与分子之间的转换。这一动态过程发生的原理被称为反应机理，它可以说是有机化学的语法——一个分子变成另一个分子的方式。然后，我们在 Chapter 6 中准备了一类重要的反应，用于练习反应机理，因此这两章分别为：

- 5.** 有机反应
- 6.** 羰基上的亲核加成

Chapter 6 也同时为您揭示了我们如何对有机化学的内容进行划分：我会使用机理分类而不是使用结构分类；这意味着，本书中的每一节都介绍一类反应而不是一类化合物。剩下的章节中，有绝大部分章节都是从机理角度对某一类反应的介绍。下面节选了部分章的标题：

- 9.** 使用有机金属试剂构建 C–C 键
- 10.** 羰基上的亲核取代
- 11.** 伴随羰基氧失去的羰基亲核取代
- 15.** 平衡、速率和机理
- 17.** 消除反应
- 19.** 烯烃的亲电加成
- 20.** 烯醇和烯醇盐的形成和反应
- 21.** 芳香亲电取代
- 22.** 共轭加成和芳香亲核取代

这些章节穿插着其他关于分子结构、反应性、立体化学、结构确定等等物理方面的内容，这些内容告诉您为什么我们讲述的反应是正确的，并且教您如何聪明地解释反应。

- 7.** 离域与共振
- 8.** 酸性、碱性和  $pK_a$
- 12.** 平衡、速率和机理
- 13.**  $^1\text{H}$  NMR: 核磁共振氢谱
- 14.** 立体化学
- 16.** 构象分析
- 18.** 光谱分析综述

在 Chapter 22 结束时，您就已经遇到大部分有机化学的重要反应了，然后我们会花费两章来从选择性（selectivity）的角度回顾前面章节学到的一些反应：如何实现您想要的反应，并且避免您不想要的反应的发生。

- 23.** 化学选择性和保护基
- 24.** 区域选择性

现在准备材料已经备齐了，我们会向您展示如何利用学过的反应机理。我们将花费四章用碳化物，以及 Si, S, 和 P 的化学知识找到并解释构建 C–C 和 C=C 键的方法。然后我们会在下一章将它们整合起来，为您提供一个用于合成自己想要的特定分子的工具。

- 25. 烯醇盐的烷基化
- 26. 烯醇盐和羰基化合物的反应：羟醛反应和 Claisen 反应
- 27. 有机化学中的硫、硅和磷
- 28. 逆合成分析

大多数有机化合物都包含环，许多环状结构都涉及这两个特殊层面中的一个：方向性或清晰的构象。这几章将引导您通过含环化合物，获得一种用于解释为什么非环状化合物，通过反应，也可以生成含有特定空间构型的物种的工具。

- 29. 芳杂环 1: 反应
- 30. 芳杂环 2: 合成
- 31. 饱和杂环和立体电子效应
- 32. 环状分子中的立体选择性
- 33. 非对映选择性

我们曾说过截至 Chapter 22，大多数有机分子反应的重要途径都已经被介绍过了——但还不是全部。接下来的一部分，我们将考察一些不太常见，但极为重要的另类机理。这部分内容将以有关如何查明有机分子遵循什么样的机理的内容收尾。

- 34. 周环反应 1: 环加成
- 35. 周环反应 2:  $\sigma$  迁移和电环化反应
- 36. 参与、重排和碎片化
- 37. 自由基反应
- 38. 卡宾的合成与反应
- 39. 确定反应机理

本章的最后几张将带您进入一些有机化学中最富挑战性的内容，我们呼吁您了解有机化学的一些前沿内容。这几章将告诉您迄今最复杂的有机分子是如何合成的，并且会阐明有机化学构成生命体的方式。

- 40. 金属有机化学
- 41. 不对称合成
- 42. 有机化学与生命
- 43. 如今的有机化学

## “联系” 板块

全部的 43 章以线性排列，但化学绝不是一个线性排列的学科！每次介绍一个新话题，然后简单地从头到尾讲述一遍是不可能涵盖整个有机化学的，因为化学是相互交联的思想组成的网络。不幸的是，一本书，自然而然就是一种从头到尾的东西。我们已经尽可能地按照难易程度将这些章节做了排序，但我们还是需要在每章开头拜访一个“联系”板块来帮助您找到学习的整体脉络。这个板块会告诉您三件事：

- (a) “基础”栏：您在学习本章前应该熟悉的内容——换句话说，与本章密切相关，因此您应当先学习的内容。
- (b) “目标”栏：您在本章将要学习内容的大纲。
- (c) “展望”栏：后续章节中对本章内容有补充和拓展作用的介绍。

当您开始阅读一个章节时，请确保您已经度过 (a) 中的全部章节了。当您对本书更加熟悉时，(a) 与 (c) 中标出的内容会让您感受到化学是如何与它自己相联系的。

► 这种类型的页边注作为章节的交叉索引，帮助您进一步在其他章找到当前内容的有关信息。您会在 p. 10 看到一个例子。

■ 有时正文中的一些内容需要澄清和补充，这种页边注可以对您理解难点提供一点帮助。它有时也会通过带您回顾其他内容，来阐明此处的内容。您最好在第一次阅读每一章时，同时读这些内容；当您已经熟悉这些知识点时可以跳过它。

 这个图标表示当前内容包含可用的在线资源。具体的检索方法在每章开头的紫色底框中可以找到。

## 文字框和页边注

另一件您应该注意到的事物是文字框和页边注，共四种：

- 这是最重要的一种文字框。任何出现在这种文字框的内容都是要点或总结。您最好在阅读时把它们牢记在脑子里，或者将它们记在笔记上。

像这样的文字框会包含一些附加的例子、有意思的背景信息，和有趣的、但可能不重要的类似材料。您在第一次阅读每一章时，也许想将它们跳过，然后您可以在之后阅读这些内容并且丰富该章的主题。

## 在线支持

有机结构和有机反应都是在三维世界中的，而本书的呈现是二维的。因此我们开发了一个全面的在线资源作为本书的补充，您可以从三维视角欣赏这些材料。ChemTube3D 包含了对于有机化学中的重要主题的交互式的 3D 动画与结构，并附有说明信息，它们可以帮助您掌握本书提到的概念。在线资源会通过页边注的方式标注在页面上。每个网页都包含对这个反应的介绍信息，和控制显示的方法。3D 的弯曲箭头会揭示反应机理，同时断键、成键、电荷和孤对电子的移动等过程都会通过动画展示。整个过程都可以由操作者控制，并且在任意角度观察。

ChemTube3D 基于 Jmol 展示动画，用户不仅可以仅通过浏览器浏览，还可以仅通过控制台中的按钮进行交互。这使得理想化的自主学习和开放式研究成为可能。我们建议您在读完本书中的章节后，通过这些互动资源，来巩固您对于化学的理解，同时增进您对于空间排布的理解。

本书的第二版做了很多实质性更改，例如第一版最后四章的内容有删除或压缩。在本书的官网中保存了第一版中的原始材料以便需要 [www.oxfordtextbooks.co.uk/orc/clayden2e/](http://www.oxfordtextbooks.co.uk/orc/clayden2e/):

- |   |  |
|---|--|
| <ul style="list-style-type: none"> <li>• The chemistry of life</li> <li>• Mechanisms in biological chemistry</li> <li>• Natural products</li> <li>• Polymerization</li> </ul> | <ul style="list-style-type: none"> <li>( • 生活中的化学</li> <li>• 生物化学的机理</li> <li>• 天然产物</li> <li>• 聚合物 )</li> </ul> |
|---|--|

## 延伸阅读

读完每一张后，您也许想要获得更多有关这些内容的材料。我们在每张末尾准备了一些延伸阅读的建议——包括其他书籍、综述性文献，甚至一些独创的研究论文。本书中几千个例子，但绝大多数时候我们不会引导您去浏览那些原始研究报告——您可以通过一个简单的电子数据库检索到它们。相反，我们更多提供给您的是与章节主题密切相关的，且有意思的一些内容。如果您想找一本化学的百科全书，这本书并不适合您。您可以去购买 *March's Advanced Organic Chemistry* (M. B. Smith and J. March, 6th edn, Wiley, 2007)，那里有成千上万的补充资料。

## 习题

您不可能学到有机化学的全部——那太多了。您虽然可以从本书中举的例子中学到琐碎的知识点，例如某些化合物的命名，但您也许仍然不理解这个学科背后的原则。因此为了理解这些原则，您必须通过实践。这就是为什么我们提供了很多习题，您可以从本书的官网获取。它们会帮您了解自己是不是真正懂得了每章的内容。

如果某一章是谈论一种有机反应的，例如消除反应 (Chapter 19)，那么文章本身会对反应发生的各种方式（“机理”）做出描述，而习题部分则会对每种机理给详尽的例子。Chapter 19 中包含三种机理和 60 个例子。您也许认为这有点多了，但实际上这三种机理的例子都数以百万计，而习题中只是触及了它的表面。这些习题会确保您理解的是正确的，并且它会使您经得起解释现实中的化学内容的严格考验。

通常来说，章末的 10–15 个习题会由浅入深、由易及难。它们可以分为三个部分。第一个部分通常是简短而容易的，其中一些是对文中原有例子的重温；它们会帮助您温习本章的内容，并且检查您是否能在与书中相似的情境下运用那些知识。第二个部分可能包含从本章的不同部分抽取知识点，并组成的具体问题，例如问您为什么两种相似的化合物反应性却完全不同。最后一个部分包括一些有挑战性的内容，可能会拓展到您不熟悉的分子，在本书的后半部分还会涉及多章知识点的综合性考察。

章末习题带领您找到自己的路线，但并不意味着本章内容理解之旅的终点。本书也许作为您的大学课本，那么您应该继续探索和练习考试中的题。您的导师会在您成长的不同阶段给予您合适的建议。



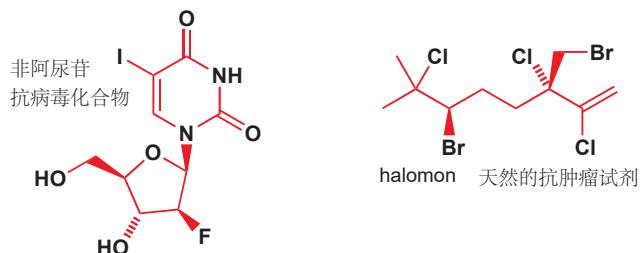
想要获取习题，您只需要访问 [www.oxfordtextbooks.co.uk/orc/clayden2e](http://www.oxfordtextbooks.co.uk/orc/clayden2e)。它们都是免费的，您唯一需要的是在本书最前面提供的用户名和密码。

## 习题解析

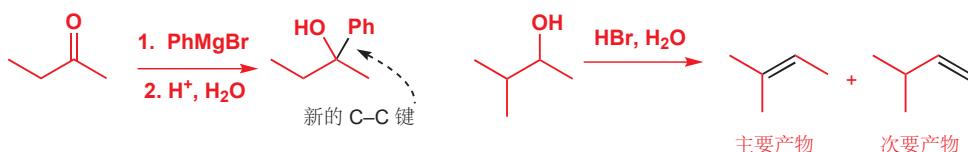
如果做完后不能及时订正，那么习题对于您的意义就很微小了。为了最大程度受益，您应该首先在完成一章的学习后独立完成部分或全部的习题。然后您可以在《习题解析 (Solutions manual)》(需要单独购买) 中找到我们对问题的讨论。对待一个题目，我们首先会对其进行说明和解释。然后，如果问题很简单，就会直接给出答案；如果问题相对复杂，那么我们会给出多个可能的答案，并且给出对于每个答案价值的评判。最后，我们可能会给出习题出处，您可以将其作为参考。

## 颜色

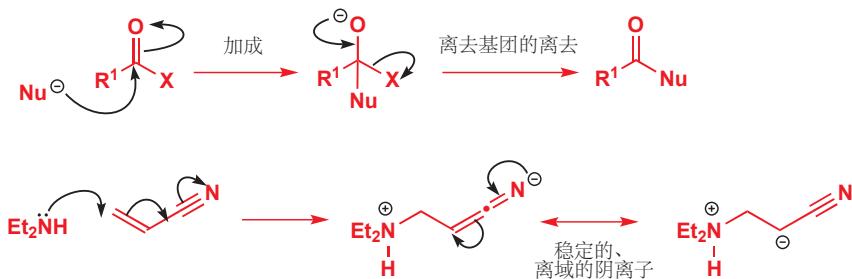
如果您粗略翻看过这本书，您会注意到一些不寻常的现象：几乎所有的化学结构都用红色画出。这是有意而为之的：红色强调了结构在有机化学中，比文字更重要。当我们讨论有机化学中的一些杂原子（除C、H外的原子）时，在结构中使用了其他颜色，下面是 p. 12 的一个例子。



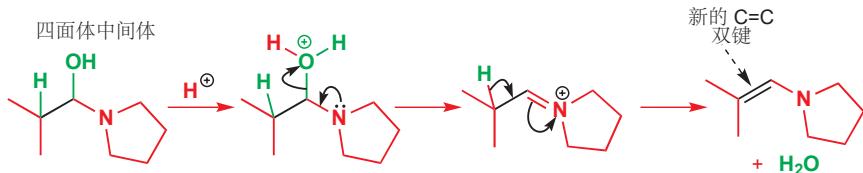
为什么我们要用黑色画这些原子？因为我们想让它们在分子中的其他部分中突出。一般来说，您会看到黑色被用于标记分子中重要的细节——也许是参与反应的集团，或者在反应结束后发生改变的片段。下面是 Chapters 9 和 17 中的例子。



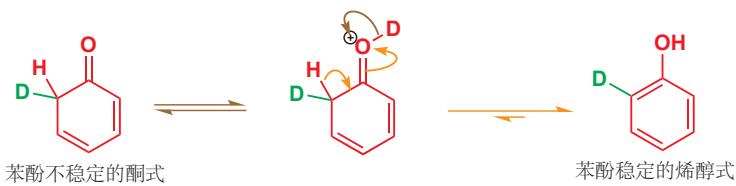
我们也经常使用黑色去强调“弯曲箭头”，弯曲箭头是一种展示电子流向的方法，您会在 Chapter 5 中具体地学到。下面是 Chapters 11 和 22 中的例子：注意到黑色也被用作凸显“+”和“-”电荷。



偶尔，我们也会使用绿色、橘色、棕色等其他颜色去突出次要的重点。下面的例子来自 Chapter 19 中的一个反应：我们想展示水分子 ( $H_2O$ ) 的形成。绿色代表了组成水分子的原子原始的位置。注意黑色的弯曲箭头，和用黑色凸显的新化学键的形成。



当事情变得复杂时，其他颜色也会出现——在下面这个来自 Chapter 21 的例子中，我们想展示这个反应两种可能的结果：棕色和黄色箭头表示了两种可能的电子流向，绿色标注出了两种情况都会保留的氮原子。



在 Chapter 14 中，颜色帮助我们看到携带四个不同基团的碳原子和携带三个不同基团的碳原子的区别。我们要告诉您的是：如果您看到有区别于红色的不同颜色出现，请特别注意——这种颜色出现是有它的原因的。



# 译者的话

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问题及修改意见请联系邮箱<sup>1</sup>。

最新版本可于互联网下载<sup>2</sup>。

<sup>1</sup> lawaxilawaxi@gmail.com

<sup>2</sup> update.lawaxi.net

# 1

## 什么是有机化学?

### 有机化学与您

您已经是一个炉火纯青的有机化学家了。当您读这些文字时，您的眼睛正在使用有机化合物(视觉色素)将可见光转化为神经冲动。当您拿起这本书时，糖发生的化学反应提供肌肉所需的能量。如您所理解，您脑细胞之间的缝隙正在被简单的有机分子(神经递质胺)所弥合，这样神经冲动就可以在您的大脑中传递。而您在做这些事情的时候，并不需要有意识地思考。在您还没有理解这些过程如何发生时，您就可以让它们在您大脑和身体中运作。您并不孤单。无论多么聪明的有机化学家，都无法完全了解它们的运作情况。

即便如此，我们也希望能在本书中向您展示自十九世纪早期，科学产生以来，我们在理解有机化学方面取得的巨大进步。有机化学起源于为了理解生命而产生的许许多多次尝试。如今它正在为许多现代工业提供理论保障，为数以百万计的人提供食物、衣服和医疗，其中很多人甚至没有意识到化学在他们生活中扮演的角色。化学家与物理学家、数学家合作，以了解分子的行为；与生物学家合作，以了解分子在生命过程中如何相互作用。这些想法可以作为我们在二十一世纪，对分子世界进行革命性研究的启示，它们远远没有完成，而是任重而道远。我们注重的不是给您一个骨架一样的死科学，而是让您了解一个在冲突中具有活力的科学。

和所有科学一样，化学在我们理解宇宙的方法中占有独特的地位。它是分子的科学。有机化学则更加丰富，它会自己成长，并且创造更多的知识。当然，我们需要研究自然分子，因为它们本身很有趣，而且它们在我们的生活中发挥着重要的功能。另外，有机化学也通过制造新的分子来研究生命，这些分子提供生物中原本存在的分子们中无法获得的信息。

人工合成的分子为我们提供了新的材料，比如塑料用来制造东西，合成染料用来为我们的衣服着色，我们还可以喷新的香水，用新的药物来治疗疾病。有些人认为生产是不自然的，他们的产品是危险或不健康的。但是这些新分子是人类用天然的大脑，由地球上天然的分子合成的。鸟筑巢，人盖房子，哪个是不自然的？区分自然与否，对于有机化学家们来说是没有意义的。有毒的化合物和有营养的化合物，有稳定的化合物和活泼的化合物——但是只有一种化学：它在我们的大脑和身体内部，也在我们的烧瓶和仪器里，产生于我们头脑中的思想和我们手中的技术。我们不会以任何方式把自己定义为道德法官。我们认为，尽可能努力地了解我们的世界，并创造性地利用它们才是正确的。这是我们想与大家分享的。

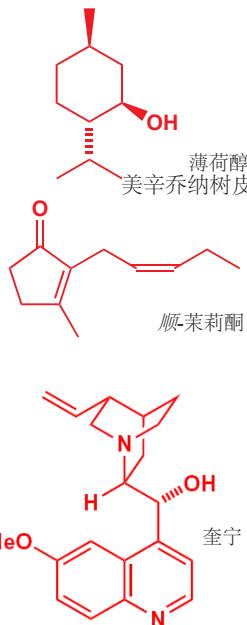


11-*顺*-视黄醛  
视觉色素

血清素  
人类神经递质

■ 在本章的阐述中，我们会配上相应有机化合物的结构图。如果您不理解它们，请阅读文字，我们会给予解释。

■ 在本书的结尾 (Chapter 42) 您会读到那些用于维持生命的，令人惊奇的有机化学知识——来自化学家与生物学家的合作。



Perkin 当时正在和德国的大化学家 Hofmann 在伦敦学习。Perkin 尝试用这种方法制备奎宁是相当困难的，因为当时人们并不清楚奎宁的结构。

## 有机化合物

有机化学最早指的是研究生命的化学，当时被认为是不同于实验室的化学的。然后来它演变成了研究碳化合物的化学，尤其是在煤中找到的那些碳化合物。但现在其实两者都是。有机化学研究碳和其他元素形成的化合物，那些可以在生命体中，有关生命的产品中，和一切能找到碳的地方找到的化合物。

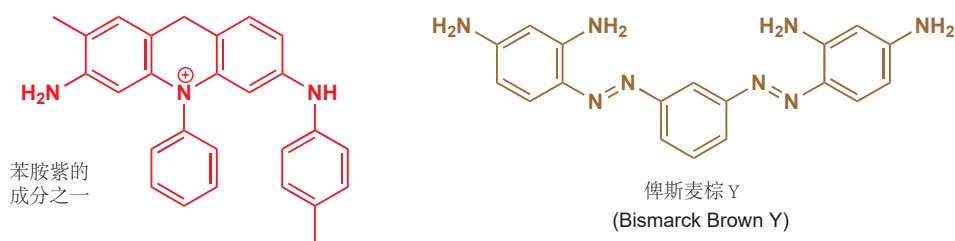
最丰富的有机物存在于生命中，包括那些存在于活着的生物中的，和数百万年前死亡的生物经变化得到的。早些时候，人们从自然界中获取有机物，例如通过蒸馏植物获得精油，通过酸提取获得生物碱。从绿薄荷 (spearmint) 中可以提取薄荷醇 (menthol)，一种用于调味的化合物；蒸馏茉莉花 (jasmine flowers) 可以得到顺-茉莉酮 (*cis*-jasmone)，一种香水的成分。

天然产品被用于治疗疾病也有很长的历史了，在十六世纪，著名的药物奎宁 (quinine)，就是从南美辛乔纳树皮中提取的，可以用于治疗发烧，特别是疟疾。发现它的那位耶稣会士 Jesuits (这种方案也被称为“耶稣会士的树皮 Jesuit's bark”) 显然并不知道奎宁的结构，但是我们现在知道了。更重要的是，奎宁的结构启发了现代药物分子的设计，我们有了比奎宁更有效的治疗疟疾的分子。

十九世纪化学家的主要化学品储备来源是煤。煤蒸馏出的气体用于照明和加热（主要是氢气和一氧化碳），棕色的煤焦油中也包含丰富的芳香化合物，例如苯，丙胺，苯酚，苯胺，噻吩。



十九世纪，苯酚被 Lister 用作外科消毒剂，苯胺被作为染料工业 (dyestuffs industry) 的基础这是人们在生活中利用自己合成的有机物替代天然产物的开始。在 1856 年，一位 18 岁的英国化学家 William Perkin 正想通过苯胺合成奎宁时，意外地生产出了一种紫红色残留物，即苯胺紫 (mauveine)，这种紫红色残留物彻底革新了衣物的颜色，并且催生了染料工业。与之相关的另一种染料，俾斯麦棕 (Bismarck Brown)，至今仍在使用：很多早期的染料工作都发生在德国。

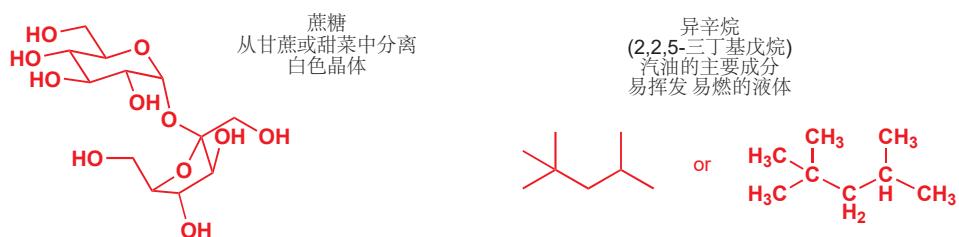


在二十世纪，石油取代煤成为人们大量获得有机化合物的又一新来源，因此简单的烃类例如甲烷 (CH<sub>4</sub>，“天然气” )，丙烷和丁烷 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>3</sub> 和 CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>，“calor 气” 或 LPG) 成为了新的燃料。与此同时，化学家开始从其他的资源中寻找有机分子，例如真菌、珊瑚、细菌。另外，两种化学工业开始并行发展——大宗化学和精细化学。油漆和塑料等作为大宗化学品通常是多吨量

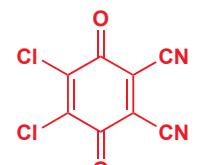
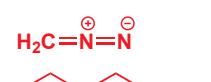
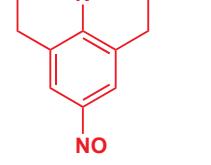
生产的简单分子，而药物、香水和调味料等精细化学品则制造量较小，但种类丰富。

我写这本书时大约已经有 1600 万种已知的有机化合物了。这个数字还会增加到多少？通过计算那些 30 个碳原子以内的中等大小的分子（像上文苯胺紫那样大的），就大约有  $1,000$  ( $10^{63}$ ) 种可能的稳定化合物。宇宙中全部的碳原子都不能足够把它们造出来。

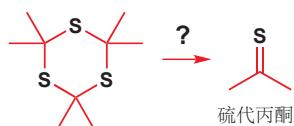
在已经制得的 1600 万种化合物之间，就有各种各样的分子展现出令人惊奇的各种各样的性质。它们长什么样子？也许是晶状，油，蜡，塑料，橡皮，流动的或者挥发性的液体，或者是气体。我们熟悉的分子包括糖，一种廉价的从植物中分离得到的白色固体；石油，一种无色、易挥发、易燃的碳氢化合物。



有机化合物并不缺乏颜色。事实上我们可以轻松地用有机化合物填满整张光谱，更不用说棕色和黑色了。在下表中，我尽量避免了染料，并举出了结构尽可能多样的化合物。

颜色	描述	化合物	结构
红色	暗红色六角片状	3-甲氧基苯并环庚三烯-2-酮	
橙色	琥珀色针状	二氯二氰基苯醌 (DDQ)	
黄色	有毒的黄色爆炸性气体	重氮甲烷	
绿色	绿色三角柱状 有刚蓝色光泽	9-亚硝基久洛尼定 (julolidine)	
蓝色	深蓝色固体 有胡椒味	薁 (azulene)	
紫色	深蓝色气体 紫色固体	三氟亚硝基甲烷	

臭鼬雾中包含：



颜色不是我们识别化合物的唯一依据。很多时候，化合物的气味让我们知道它们在附近。有些有机化合物有极难闻的恶臭气味，例如臭名昭著的臭鼬雾就是两种硫醇的混合物，硫醇是含有 SH 基团(巯基)的一类化合物。

有史以来最糟糕的气味当属 1889 年导致德国弗莱堡市疏散的气味。三硫丙酮 (trithioacetone) 分解产生了硫代丙酮 (thioacetone)，“令人反感的气味”迅速在小镇的一大片地区蔓延，居民开始有昏厥、呕吐感，在恐慌中疏散过后，实验室工作也停止了。

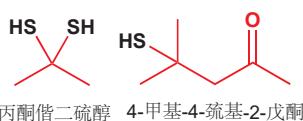
1967 年，牛津南部一个埃索研究站的几名研究人员重复了三硫丙酮分解的愚蠢实验。他们这样讲述了这个故事：“最近我们发现自己身上的气味问题超出了我们最坏的预期。在早期的实验中，一个瓶塞从装有残留物的瓶子上蹦了出来，尽管立即更换了瓶塞，但却登时引起了至少二百码外的楼内工作的同事的恶心和不适。我们的两位化学家只是研究了微量三硫丙酮的分解反应，他们却发现自己已经成了一家餐馆的敌对目标，并遭受了被女服务员喷洒除臭剂的羞辱。那种气味几乎无视稀释带来的影响，然而实验室里的实验员却说自己并没有感觉到无法忍受，因为实验一直在封闭环境中完成，他们不认为自己应当负责任。为了说服他们，我们一同在实验室观察了这样的实验，相隔四分之一英里，在一端滴下一滴丙酮偕二硫醇 (acetone gem-dithiol) 或者结晶完三硫丙酮的母液后，实验结果表明另一端通风橱的下风方向在几秒内就检测到了气味。”

两位正在争夺这种可怕气味的候选人是一—丙二硫醇 propane dithiol (上文称作丙酮偕二硫醇) 与 4-甲基-4-巯基-2-戊酮。别的物质不大可能有足够的勇气去争夺这一称号。

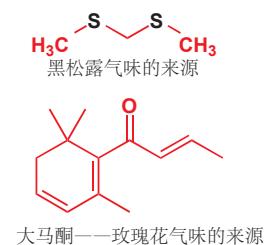
难闻的气味也有它们的用途。管道输送到家中的天然气中含有很少的人为添加的含硫化合物，如叔丁基硫醇 ( $\text{CH}_3)_3\text{CSH}$ 。这里的很少是非常非常少——人类可以辨别出天然气中 50,000,000,000 分之一的含硫化合物。

化合物中一些也有令人愉快的味道。为了挽回含硫化合物的尊严，我们必须提到黑松露中气味的来源，让猪可以透过一米厚的土壤闻到的香味，十分令人愉快，闻到这种松露的成本价要高过相同重量的黄金。大马酮是玫瑰花气味的来源。如果您闻到一滴纯品的大马酮 (damascenone)，您也许会失望，因为它的味道像是松节油或者樟脑；但第二天醒来后，您会发现所有您的衣服都出现了玫瑰的清香。很多气味需要稀释后才能得到。

人类不是唯一有嗅觉的生物。我们可以用许多的感官寻找对象，而在一个拥挤的世界里，昆虫只能通过气味辨别自己的异性同类。大多数昆虫会生产具有挥发性的香味化合物，可以被它们潜在的配偶在极微量的情况下拾取。从 65,000 只雌性烟草甲虫中，我们只能分离出 1.5 mg 的 serricornin，烟草甲虫的性诱引素，平均到每只甲虫身上的则更少。尽管如此，这仍然不妨碍它们靠着这一点点的气味聚集在一起，尝试交配。雌性日本金龟子的性诱引素已经被化学家成功合成，仅仅 5  $\mu\text{g}$  (是微克，看清楚！) 都要比四个处女吸引男性更加有效果。



世界最臭气味的两位候选人  
(没有人想去知道到底谁会赢)

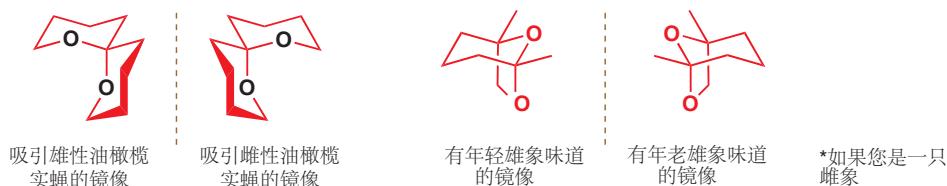


舞毒蛾的性诱引素，disparlure，可以从这些飞蛾中分离并识别出几  $\mu\text{g}$ ：雄性舞毒蛾在田野诱因雌性时只需要使用  $2 \times 10^{-12}$ 。上文介绍的三种信息素都可以被用作捕捉这些害虫的诱饵。



油橄榄实蝇

不要以为雌性总是做所有的工作；对于油橄榄实蝇，雌性与雄性都会产生性诱引素并吸引异性。值得注意的是，这种构造的一种镜像吸引雄性，而另一种镜像吸引雌性！对于雄象，它们能产生名为 **frontalin** 的一对镜像（一对对映体），而雌象则可以从每个异构体的数量上判断雄象的年龄，和它们作为潜在伴侣的吸引力。



对于味道呢？拿一个西柚。西柚主要的味道来自于另一种含硫化合物，人类可以从每十亿份中分辨出  $2 \times 10^{-5}$  份。这是一个几乎无法相信的微量，相当于每吨中的  $10^{-4}$  mg 或者滴在一面相当大的湖中的一滴。究竟为什么进化让我们对西柚的味道如此敏感，这个问题留给您来想象。

有关刻意制造讨厌味道的例子，我们应该提一下“苦味剂 (bittering agents)”，它们被加进厕所清洁剂这样家庭常用的危险物质中，阻止孩子们误食。请注意，这种复合物实际上是一种盐——季铵阳离子与羧酸阴离子——这使得它溶于水。



西柚香味的来源



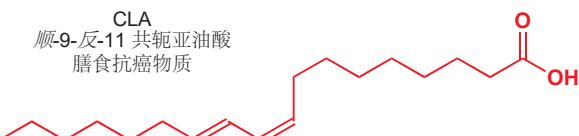
“苯甲地那铵 (denatonium benzoate)”，苦精 (Bitrex)  
苯甲酸 苯基二乙基[(2,6-二甲苯基氨基甲酰基)甲基]铵



其他有机化合物对人体也有各不相同的影响。多种多样的“毒品”例如酒精、可卡因 (cocaine) 会给人类以短暂的愉悦。它们的危险各不相同。过量的酒精会让您感受到很大的痛苦，而任何剂量的可卡因都会让您沦为它一辈子的奴隶。



我们不要忘了其他生物。猫似乎可以在任何时间，任何地点轻易地睡着。从猫的脑脊液中可以分离出下面这个令人惊讶的简单化合物，它似乎是猫睡眠控制机制的一部分。它可以让猫立即入睡，同样可以让老鼠和人类立即入睡。





这个化合物(图在上一页)和 **disparlure**(上文)都是脂肪酸衍生物。脂肪酸在饮食上受到广泛关注,新闻上经常提起好的、坏的,饱和的、不饱和的,单不饱和的、多不饱和的脂肪酸:众多膳食分子中的一员, **CLA (conjugated linoleic acid 共轭亚油酸)**, 估计有可以证实的抗癌功效;它在乳制品中有所存在,您也许知道,它在袋鼠肉中也很丰富地存在。

白藜芦醇是另一种具有良好功效的膳食化合物。它可能是红酒预防心脏病功效的主要帮手。它是有机物中很特别的一类,有两个苯环相连。

第三个可食用的分子,说说维生素 C 怎么样?它是您饮食中一个非常重要的基本要素——这就是为什么它被算作维生素——它也存在于其他灵长类生物,例如豚鼠,果蝠的饮食中(其他一些哺乳动物拥自己制造它的生化机制).在过去几个世纪的长途航海时,很多水手遭遇了软组织的退化,这种疾病是由于缺乏维生素 C 造成的。它也是一个通用的抗氧化剂,可以用于清理那些可能破化 DNA 的自由基。有些人还认为,额外的摄入还可以用于防止普通感冒。

## 有机化学与化工

维生素 C 由瑞士罗氏集团大规模生产。在全世界各地,都有专门的化工企业,每年生产从几千克到数千吨不等的有机分子产品。这对学习有机化学的学生是一个好消息:了解分子的行为和合成方法是社会广泛需求的能力,它有很好的国际就业市场。

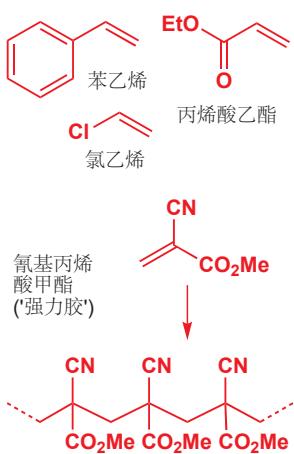


石油化工行业消耗大量的原油:世界上最大的炼油厂,位于印度的贾姆纳加尔,每年加工 2 亿升原油。其中令人惊讶的一大部分仍然被用作燃料,但也有一些经过精炼或者转化为有机产品,进而被用作其他化工产业。

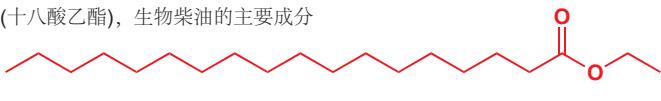
一些简单的化合物既可以通过石油,又可以通植物获取。乙醇通常被用作制备其他化合物的起始原料,或者被用作燃料;主要通过石油中获得的乙烯催化加水得到,在巴西,人们也常常用甘蔗发酵的方法获得乙醇。植物是十分强大的有机化工厂(甘蔗发酵是其中最有效的)。植物在光合作用时可以直接获取大气中的二氧化碳,并通过太阳能转化成含有低价碳的有机分子,燃烧后可以提供能量。例如从植物油中提取的脂肪酸被称为生物柴油。



生产聚合物的单体



硬脂酸乙酯(十八酸乙酯),生物柴油的主要成分



石油化工产品在生产塑料和其他高分子上发挥着重要的用途,石油化工产出聚合所需要的单体,例如苯乙烯,丙烯酸酯,氯乙烯。一切塑料产品,包括塑料家具等,还有纺织使用的化纤(每年超过 2500 吨产量),汽车轮胎,填充包装的泡沫等等,都是庞大的高分子化工的产品。全球每年生产 1 亿吨聚合物,只算 PVC 的制造每年就超过 2000 万吨,需要雇佣 50,000 人。

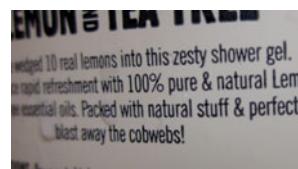
聚合形成高分子,也是生产粘合剂的一种好方案。使用强力胶,你几乎可以将任何两样东西黏在一起,它就是氰基丙烯酸甲酯的聚合物。

洗碗时用到的洗洁精化学工业的另一个分支——像联合利华和宝洁公司,他们生产洗洁精,清洁剂,漂白剂和擦光剂,还生产肥皂,凝胶,化妆品,剃须泡沫等。这些产品闻起来像柠檬,或者薰衣草、檀香,但实际上他们大多来自于石油工业。

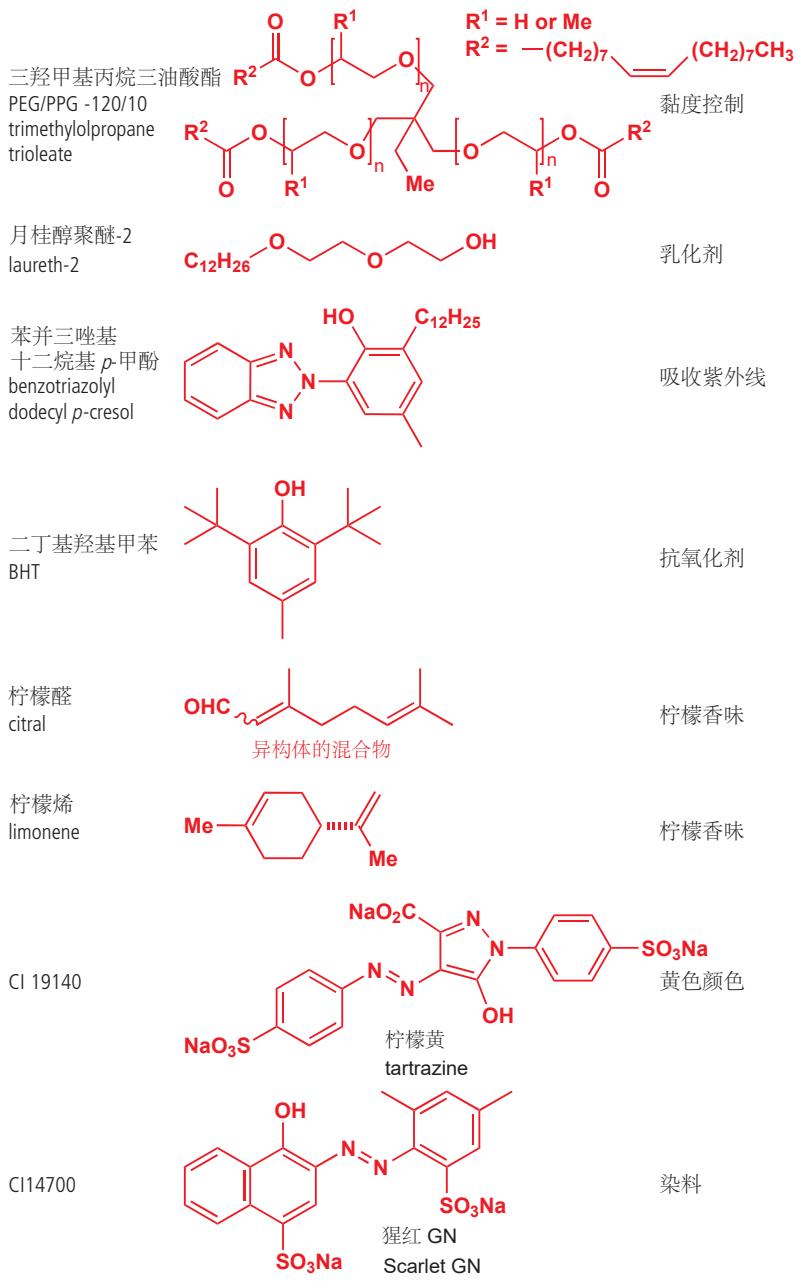
这类产品往往会对来源于石油这件事保持低调,并且宣传它们的清新,自然。除了时尚,他们还

包含什么呢。看看这个离子——一份知名品牌沐浴露的成分清单，它的介绍上写着“含天然物质”（包括十个“真正的”柠檬）并且包含“100% 纯天然柠檬与茶树精油”。

在我看来，这样的介绍并不合情合理。我们希望这本书也会帮您真正了解这些事物的意义（和他们的无稽之谈）。



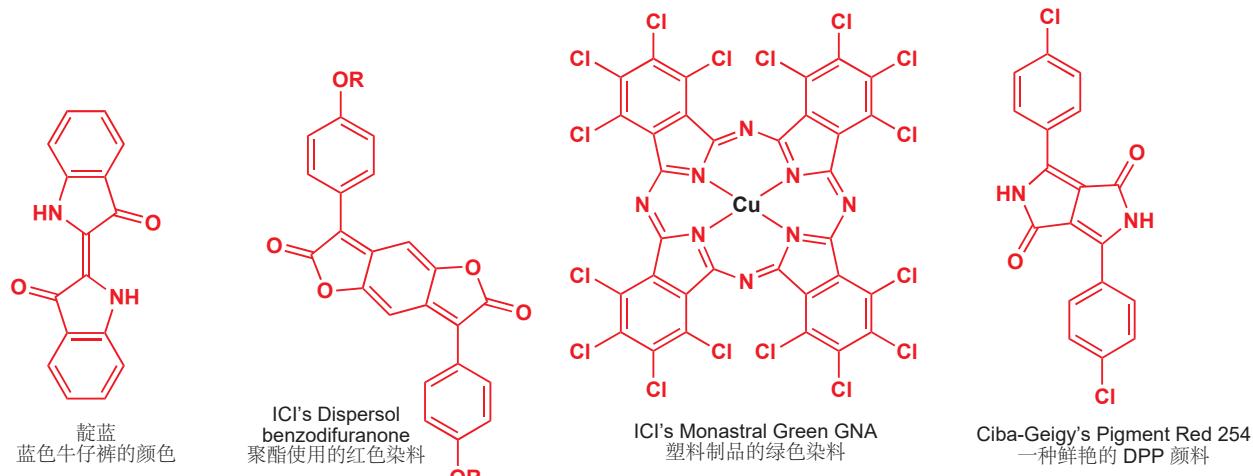
成分	化学组成	作用
aqua		溶剂
月桂醇聚醚 硫酸酯钠 sodium laureth sulfate		洗涤剂
椰子酰二乙醇胺 cocamide DEA		发泡剂
香橼果皮油 <i>Citrus medica limonum</i> peel oil	主要为 	吸引顾客的香味
茶树精油 <i>Melaleuca alternifolia</i> leaf oil	主要为 	吸引顾客的香味; 可能还可以防腐
甘油 glycerin		潜溶剂; 保湿; 确保光滑和弹性
椰油酰胺丙基甜菜碱 cocamidopropyl betaine		洗涤剂 有抗静电作用
氯化钠 sodium chloride	<b>NaCl</b>	控制含 Na <sup>+</sup> 洗涤剂的溶解
乳酸 lactic acid		酸化
苯乙烯/丙烯酸(酯) 共聚物 styrene acrylates copolymer		成膜剂
谷氨酸二乙酸四钠 tetrasodium glutamate diacetate		螯合剂, 防止一些离子 在硬水中沉淀
苯甲酸钠 sodium benzoate		防腐剂



选择特定的洗涤剂、表面活性剂、酸、粘度控制剂等并混合在一起，以产生光滑的凝胶。产物应当摸起来、闻起来、看起来都具有吸引力，并可以成为一个有效的洗发水（一些化合物由于其保湿和抗静电作用也被添加）。黄色和柠檬香味让它看上去新鲜、干净。也有几种通过天然化合物添加的成分，它们不是异构体或聚合物的混合物；最不纯净的是被称作“纯天然”精油的混合烃类。它们真的来自自然吗？确实如此，一切来自自然资源，主要是数百万年前植被碳化形成的产物。

产品着色是一类庞大的业务，染色布料、染色塑料、纸张、墙漆等等都需要鲜艳的色彩。在这一领域有成就的 Akzo Nobel 等公司，在 2010 年销售额达到 146 亿欧元。最常用的染料之一，靛蓝 (indigo)，在古代使用从植物中提取的方法，现在则使用石化原料合成。它是蓝色牛仔裤的颜色。

更现代染料可以以下几个作为代表：使用 ICI 合成的 benzodifuranones，被用作合成布料如聚酯的着色剂（红色），肽菁-金属络合物（通常是蓝色或绿色），“高性能的”红色颜料 DPP（1,4-diketopyrrolo[3,4-c]pyrroles）系列是由 Ciba-Geigy 开发的。

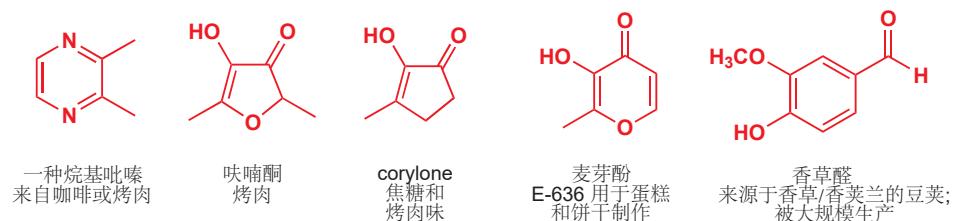


上面所示的沐浴露由植物提取物和纯化合物（事实上是其两种异构体的混合物）柠檬烯混合而成。大型香水和调味剂公司（例如芬美意公司，美国国际香料香精公司，和奇华顿公司）都同时使用天然产物和合成产物——天然产物指的是从植物，如树叶、种子、花朵中提取得到的混合物。合成产物是纯净物，有时是最初来源于植物的，有时是新设计的分子。这二者混合在一起得到了最终的气味。香水通常由 5–10% 的香料分子与乙醇/水（大约 90:10）混合形成。相比于香水溶质，香水工业更需要的是乙醇。事实上，重要的香料，例如茉莉花香香料的年产量为  $a > 10,000$  吨。对于纯溶质，例如顺-茉莉酮（p. 2），茉莉花的主要成分，每克可能价值数百英镑、美元或欧元。

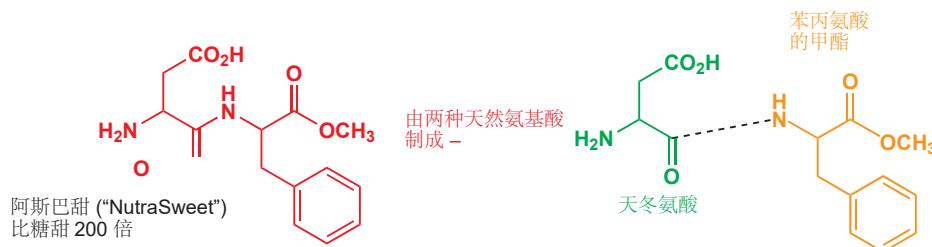
### 香水的世界

香水化学家用令人惊奇的语言描述他所取得的成就：“帕高出色男香 (Paco Rabanne pour homme) 的发明是为了还原在夏天的普罗旺斯山丘，露天散步的效果：草药、迷迭香和百里香的味道，凉爽的海风与温暖的阿尔卑斯山的空气混合形成的生机感和清新感。为了得到这种效果，调香师将草本植物油、木本物质与合成香料二甲基庚醇混合，它敏锐而无法描述的清新与露天的空气和新洗的亚麻布类似。

化学家生产的合成香料还包括“熏培根”甚至“巧克力”。肉类香味来自杂环化合物，例如烷基吡嗪（存在于咖啡和烤肉中）和呋喃酮，最初来源于菠萝。corylone 和麦芽酚等化合物提供焦糖和肉类香味。这些化合物和其他一些合成化合物的混合可以调出烤制食物的味道，从新鲜面包到咖啡，再到烧烤的味道。一点香精化合物可以既作为香水，有作为合成其他化合物的前体。香草醛是香草味道的主要来源，但它也因为其他用途被大规模生产。

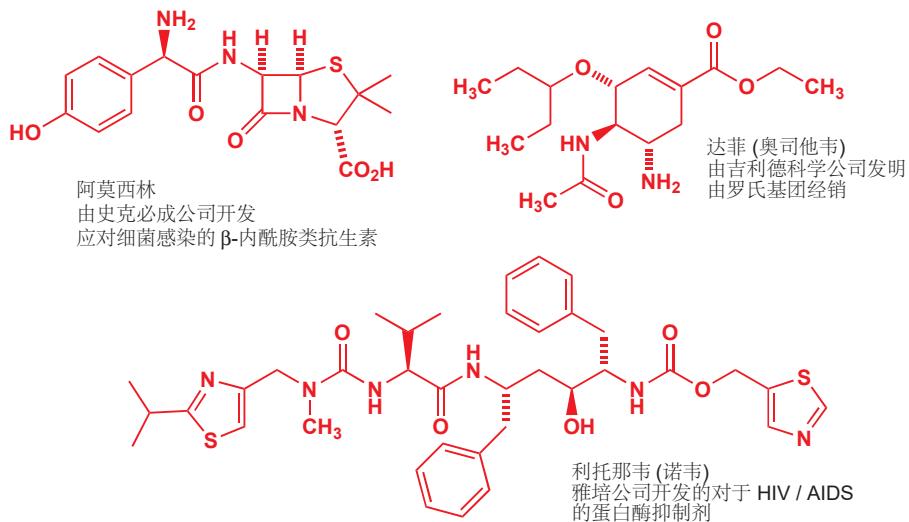


食物化学除去香水外，仍有许多其他内容。糖等甜味剂从植物中的直接分离占据其生产的很大部分。您在 p. 3 看到了蔗糖，但糖精（于 1879 年发现！）和阿斯巴甜（1965）也同样占据了相当大的部分。阿斯巴甜是存在于一切生命体中的两种天然氨基酸的组合，NutraSweet 公司每年生产超过 10,000 吨。

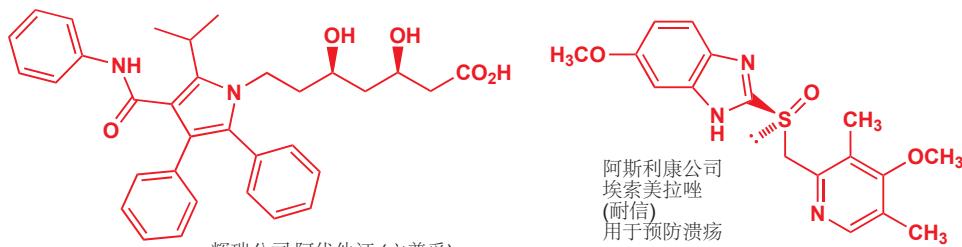


► 有关达菲的故事，以及在确保它们源源不断的供应上，化学家聪明才智的体现，在本书的末尾 Chapter 43 有所介绍。

现代生活最伟大的革命之一是期望能够通过专门设计的治疗手段，使人类在疾病中存活。在发达国家世界中，人可以活到老年，因为那些会导致他死亡的感染都可以被治疗，或者干脆根本无法近身。抗生素作为我们对细菌的防御，作用在于防止细菌增殖。其中最成功的是阿莫西林，由史克必成公司开发的。这个分子的核心是四元环，既  $\beta$ -内酰胺环，它瞄准了致病细菌。药物化学家也同时在病毒的威胁中保护着我们，病毒是依赖人体自身的生物化学环节实现复制的。达菲是抵御流感时重要的防线，而利托那韦是组织抑制 HIV 复制和减缓或预防 AIDS 的最先进手段。

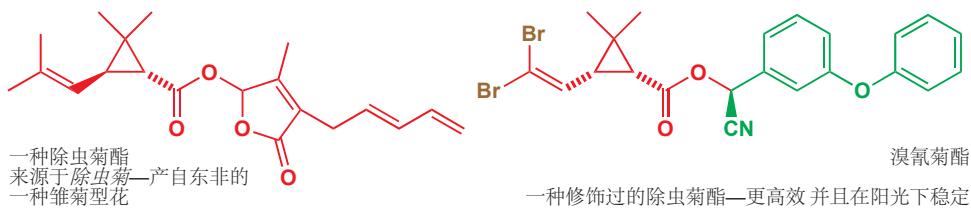


目前最畅销的药物很多是为了治疗人体自身的缺陷而设计的。立普妥和耐信两种药的销售额都在 2009 年达到了最大值的五十亿美元，这一数据说明了开发安全而有效的新疗法，拥有巨大的财富规模。立普妥是他汀类药物的一种，他汀类药物被广泛用于控制老年人的胆固醇水平。耐信是一种质子泵抑制剂，它能减轻消化道溃疡和十二指肠溃疡。格列卫（诺华公司开发并于 2001 年推出）的销售额远小于以上两种，但它是那些患有致命癌症，例如白血病的患者的救命稻草。

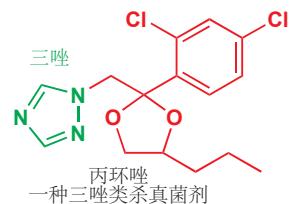


如果我们不能在来自杂草的竞争，和来自昆虫、真菌的攻击中维持我们的食物供应，那么我们就不能保持目前发达国家的高人口密度，也不能解决目前发展中国家的营养不良问题。拜耳作物科学、先正达公司等跨国公司在农用化学品上的全球市场每年超过一百亿英镑，其中可以分为除草剂、杀真菌剂和杀虫剂。

许多早期的农用化学品，由于会对环境造成持久的伤害已经被淘汰，因此现代的农用化学品都必须通过严格的环境安全测试。最著名的现代杀虫剂是以来源于植物的除虫菊酯为模型的，通过化学修饰(溴氰菊酯上的棕色和绿色部分)可以使它在阳光的降解作用下稳定，还可以使其效果只针对某种特定植物上的某种特定昆虫。溴氰菊酯的安全性体现在，它对芥末甲虫的效果超过对哺乳动物>10,000倍，每公顷只需施用10克(大约每足球场一平匙)，而且不会留下任何显著的环境残留。



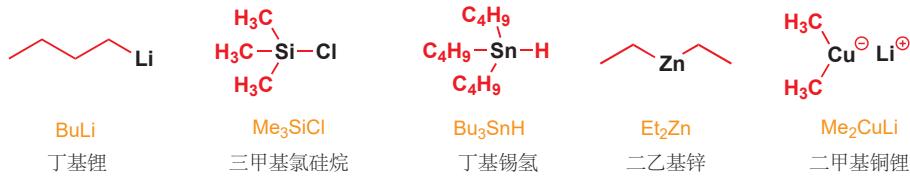
当您学完更多的化学知识后，您会欣赏大自然在这些化合物中创造三元环，并且让化学家可以将它们为主体的化合物泼洒在田间的作物上，是有多么非凡的创造力啊。更引人注目的杀真菌剂是基于含有三个氮的五元环的——即三唑环衍生的。这些化合物抑制真菌中酶的作用，而不会影响植物和动物中的酶。真菌病害对于植物是一个很大的威胁：就像十九世纪爱尔兰发生的马铃薯大灾荒一样，各种真菌引起的枯萎病、斑点病、腐烂病、锈病、黑穗病和霉菌可以在短时间内压倒任何作物。



## 有机化学与元素周期表

我们展示的所有化合物都是建立在碳氢骨架上的。大部分含有氧、氮原子；其中一些还含有硫、磷、卤素。以上便是有机化学中的常见元素。

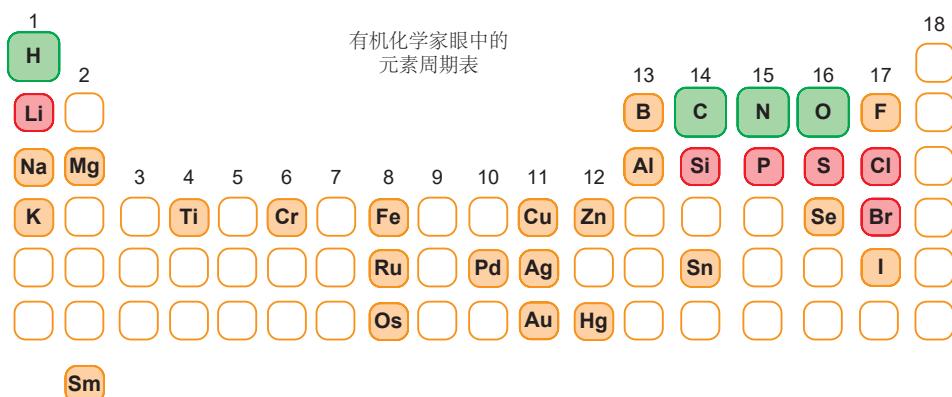
但有机化学有时也向元素周期表的其他部分探索。硅、硼、锂、锡、酮、锌的有机化学也被研究地很好，同时这些“有机”试剂也成为了实验室中的常用试剂。在本书中您也会遇到它们中的许多，例如三丁基氯硅烷、三甲基氯硅烷，三正丁基锡氢，二乙基锌，二甲基铜锂。



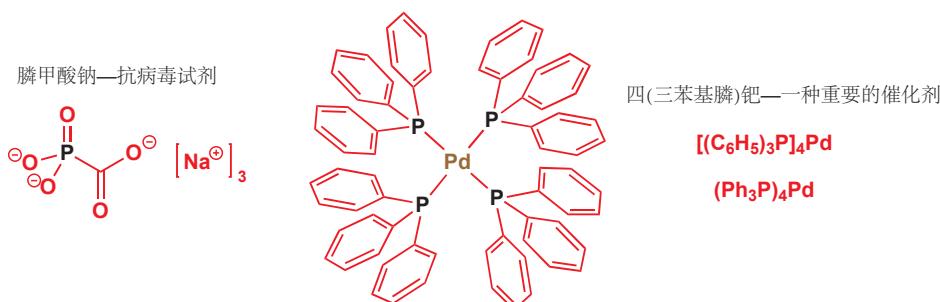
卤素经常出现在一些救命的药物中。抗病毒药物例如非阿尿苷(既包含 F 原子和 I 原子，还包含 N 和 O)都是对抗 HIV 与 AIDS 的基础性药物。它们以核酸中产生的天然化合物为模型。从红藻中提取的天然抗肿瘤试剂 halomon，含有 Br 原子和 Cl 原子。

我们将花费一整章来讨论 S, P, 和 Si 元素的有机化学 (Chapter 27) 并且还会讨论过渡金属，尤其是 Pd (Chapter 40)。

您可能在从前的化学学习中了解过元素周期表。本书的 1184–1185 页将完整的展示元素周期表，有关族，哪些元素是金属，元素在周期表中的位置等等的基础知识，会对您未来的学习有所帮助。



所以无机化学的结束和有机化学的开始在哪里呢？你会说抗病毒化合物膦甲酸钠 (foscarnet) 是有机物吗？它含有碳，分子式为  $\text{CPO}_5\text{Na}_3$ ，但它并没有 C–H 键。那重要的试剂四(三苯基膦)钯呢？它包含很多烃类—事实上有 12 个苯环—但是苯环都在包围钯原子的一圈磷原子上，所以这个分子仅仅依靠 C–P 和 P–Pd 键来结合，并不是靠碳氢骨架支撑。虽然它的分子式  $\text{C}_{72}\text{H}_{60}\text{P}_4\text{Pd}$  看起来十分像一个有机物，很多人却说它是无机的。事实是怎么样的？



答案是：我们不知道，我们也不在乎。传统规则中严格的学科界限是不可取的，也是毫无意义的。化学将继续跨越有机化学与无机化学的，有机化学与物理化学、材料学的，有机化学与生物化学的旧界限。很高兴这些边界本来就是模糊的，因此化学更加丰富。这个可爱的分子  $(\text{Ph}_3\text{P})_4\text{Pd}$  只属于化学。

## 有机化学与本书

我们已经告诉了您有机化学的历史、有机化合物的类型、有机化学所生产的东西，和有机化学需要用到的元素。今天的有机化学是研究自然界中化合物的结构和反应的学问，是研究化石原料如煤和石油可以合成的化合物的学问。这些化合物通常采用碳氢骨架作为支撑，并通常有 O, N, S, P, Si, B, 卤素以及金属原子附着在框架的上面。有机化学被用于生产塑料、颜料、染料、衣服、药物、农用化工品和其他许多东西。现在我们可以用一种不同的方式总结它们。

### ● 有机化学研究方向的几个主要部分：

- 结构的确定—准确地得到一个新化合物的分子结构，即使那个化合物只存在于微量；
- 理论有机化学—从原子、电子的结合方式等方面理解有机结构；
- 反应机理—了解分子之间如何发生反应，并预测未知反应的发生；
- 合成—设计新的分子，然后合成它们
- 生物化学—了解大自然的行为，具有生物活性的分子的结构与功能间的关系。

这本书是所有关于这些事情的。它涉及有机分子的结构，和它们组合这些结构的原因。它是关于分子的形状，和这些形状与它们功能间的联系，特别是在有关生物化学部分中。它解释如何发现这些结构和形状。它告诉您这些分子的反应过程，更重要的是，它们如何、为什么这样反应。它告诉您自然和工业。它告诉您分子如何被制造，以及在合成分子时该考虑什么。

这是您即将进入的旅程中的风景。而且，与其他旅程相同，当您进入一个新的、令人兴奋的、具有挑战性的地方时，首要的事情是先了解有关当地语言的一些知识。幸运的是，有机化学的语言再简单不过了：它们都是图片。下一章我们将具体交流。

## 延伸阅读

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一本您可能感兴趣的，很有意思的书：B. Selinger, *Chemistry in the Marketplace*, 5th edn, Harcourt Brace, Sydney, 2001.

## Check your understanding

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To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 有机结构

## 联系

### 基础

- 本章并不建立于 Chapter 1

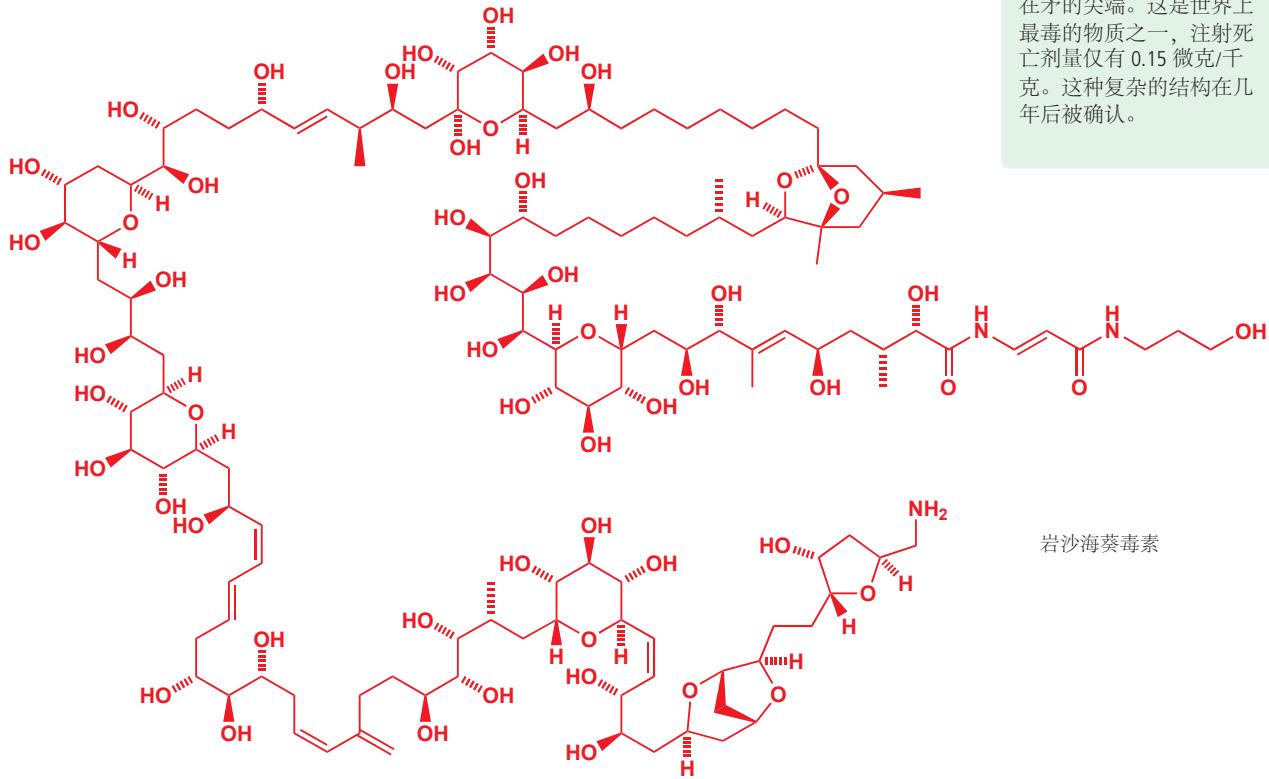
### 目标

- 书的其余部分所使用的图表
- 使用这些图表的原因
- 有机化学家如何在写作和演讲中命名分子
- 什么是有机分子的骨架
- 什么是官能团
- 所有有机化学家都使用的一些缩写
- 以易于理解的形式真实地绘制有机分子

### 展望

- 用光谱法测定有机分子 ch3
- 什么决定了一个分子的结构 ch4

元素周期表中共有一百多个元素。而很多有机分子可以包含一百多个原子——例如岩沙海葵毒素 palytoxin (一种有潜在抗癌活性的天然分子)，就包含129个碳原子，221个氢原子，54个氧原子和3个氮原子。很容易看出来，化学结构可以表现出极大的多样性，最复杂的生物都可以由足够的分子构建出来。



■ 岩沙海葵毒素最早在1971年于Hawaii从*Limu make o Hane*(意为“致命的哈纳海藻 deadly seaweed of Han-a”)中获得，当地人将它涂在矛的尖端。这是世界上最毒的物质之一，注射死亡剂量仅有0.15微克/千克。这种复杂的结构在几年后被确认。

但是我们如何理解一个这样混乱的结构呢？面对由原子构成的分子，我们如何理解呢？本章将教您如何理解和诠释分子结构。这同时也会教会您通过绘制有机结构图，简洁地传达信息。

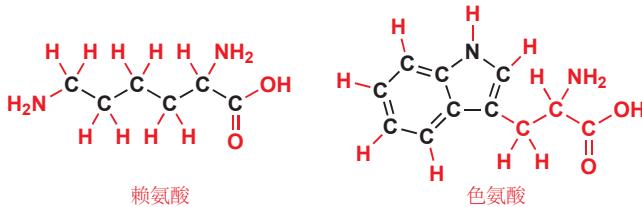
## 碳氢骨架与官能团

正像我们在 Chapter 1 中所介绍的，有机化学是研究含碳化合物的科学。另外，几乎所有的有机化合物也都包含氢原子，大多数还包含氧原子，氮原子，和其他杂原子。有机化学关注的重点是，这些原子如何成键并结合成一个稳定的结构，和这些结构在化学反应中如何变化。

下面是一些分子的结构。包括氨基酸，组成蛋白质的基本单位。看看每个分子中碳原子的数量，和它们的成键方式。即使是如此小的一类分子，它们仍然表现出十足的多样性——甘氨酸和丙氨酸只有两到三个碳原子，而苯丙氨酸有九个。



赖氨酸分子中的原子是链状排列的；色氨酸分子中有一个环。



蛋氨酸 (甲硫氨酸) 分子中的原子排列成一条直链；亮氨酸分子中的原子则有分支。在脯氨酸中，链弯曲形成了一个环。

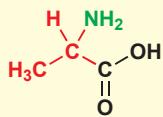


Interactive amino acid structures

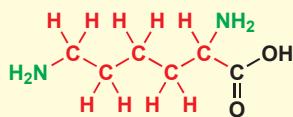
► 我们将在本章中多次用氨基酸举例子，但是关于氨基酸如何聚合形成肽、蛋白质的知识我们将在 Chapters 23 和 42 具体讨论。

尽管如此，这些分子也有它们共同的特点——它们都溶于水，它们都既有酸性又有碱性(两性的)，它们都可以和其他氨基酸结合形成蛋白质。这是因为相比于杂原子 ( $\text{O}$ ,  $\text{N}$ ,  $\text{S}$ ,  $\text{P}$ ,  $\text{Si}$ ...)，有机化学并不十分注重碳原子的个数和排列方式。我们将分子中比较看重的这一小部分称为一个官能团 (functional group)，因为实际上分子的大多数性质都是由它们决定的。所有的氨基酸都包含两个官能团：一个氨基 ( $\text{NH}_2$  或  $\text{NH}$ ) 和一个羧基 ( $\text{CO}_2\text{H}$ ) (当然其中一些也包含其他官能团)。

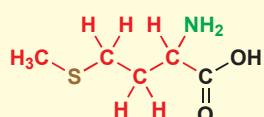
- 官能团决定分子在化学和生物学上的运作方式。



丙氨酸  
仅包含氨基和羧基



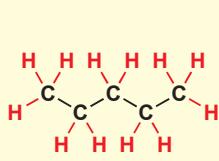
赖氨酸  
有一个额外的氨基



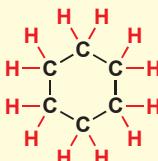
蛋氨酸  
有一个额外的硫醚键

这并不是说碳原子不重要；碳原子只是扮演了一个与附于其上的杂原子不同的角色。我们可以把碳原子组成的链或环想象成分子的骨架。就像我们的骨头支撑着内脏正常工作并彼此交互一样，分子骨架的作用也是支撑官能团，并允许它们参与化学反应。

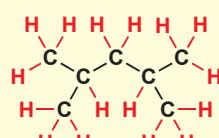
- 碳氢化合物的框架由碳原子构成的链或环组成，它作为官能团的支撑。



链  
(chain)



环  
(ring)



带分支的 (branched)  
链

稍后我们将看到“碳氢化合物作为分子的骨架 (hydrocarbon framework/skeleton)，支撑附着于其上的官能团”的这种解释如何帮助我们更好地理解和诠释有机反应。它也能帮助我们在纸上以清楚的方式表示有机分子的结构。在 Chapter 1 中您已经看到了不少有机分子的结构图了，下面我将教您如何画它们。这一节十分重要，因为清晰地画出结构，简明扼要的交流是作为有机化学家的首要技能。

## 绘制分子

### 实事求是

下面是另一种有机结构。您也许很熟悉它，它是一种脂肪酸，俗称亚油酸。



亚油酸

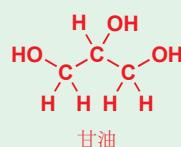
我们也可以将其画成这样



或者这样



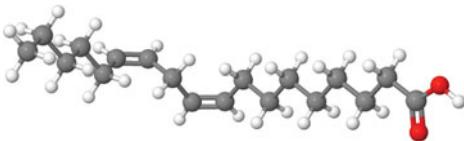
■ 脂肪由三个脂肪酸分子和一个甘油分子组合而成，可以用来储存能量，构成细胞膜。亚油酸，这种特殊的脂肪酸，不能在人体中合成，必须通过必要的饮食补充，例如葵花子油中。脂肪酸间的差异主要是所含碳原子数的不同，但由于都含有羧基，它们的化学性质十分相似。我们会在 Chapter 42 中继续讨论脂肪酸。



甘油

后两种结构通常出现在一些旧书上——因为所有的原子都排列在一条直线上，这样做比较容易印刷（在计算机尚未普及的时候）。所有的键角都是 $90^\circ$ ，这样现实吗？在 Chapter 3 中我们会详细讨论如何确定分子结构和形状的，下图是用 X-射线晶体学（X-ray crystallography）测定的亚油酸结构。

■ X-射线 晶体学通过观察 X-射线 在晶体中原子上的回声得到分子结构。（经过处理，）它能给出清晰的分子结构图示，其中球表示原子，棍表示连接它们的键。



X-射线 测定的亚油酸结构

您可以看到碳原子并非呈直线形排列，而是锯齿状的。即使我们在绘制时必须将三维图像抽象到二维，但我们现在习惯画成锯齿状仍然是有原因的。

 Interactive linoleic acid structure



这是我们绘制有机结构的第一个准则。

### ● 准则 1

将碳链画成锯齿状。

我们想要做到完全的实事求是是困难的——X射线测定的结构表明，亚油酸分子中双键两侧的键角和单键两侧的键角并不相同，前者只是稍稍弯曲，但我们仍然可以忽略这些细节，将整个链表示成锯齿状。晶体结构的研究表明当一个碳原子不是双键的一部分时，它的键角是 $109^\circ$ ；反之，当它是双键的一部分时，则是 $120^\circ$ 。 $109^\circ$  是“四面体角”，即从四面体的中心看两个顶点之间的角度。在 Chapter 4 中我们会考察为什么碳原子会采取这种特殊的排列方式。不管怎么说，我们的绘图是将三维结构投影在纸上得到的，即使再逼真，我们也要做一些妥协。

## 简明扼要

虽然我们应该尽量追求实事求是，但是过多的考虑一些冗余的细节中是不划算的。看下面三张图。



1



2

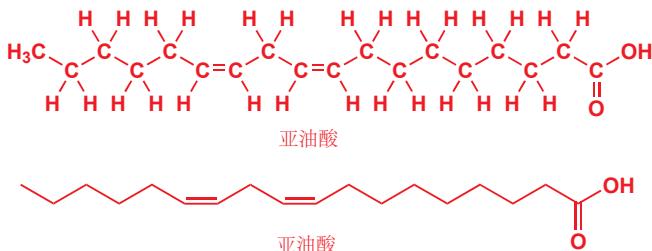


3

图(1) 十分明显，就是达芬奇的蒙娜丽莎。您也许认不出来图(2)——它其实也是蒙娜丽莎，但这幅图是从画框的顶部看的。您能看出画框十分的华美，但它带给您的信息仅此而已，就像只告诉您脂

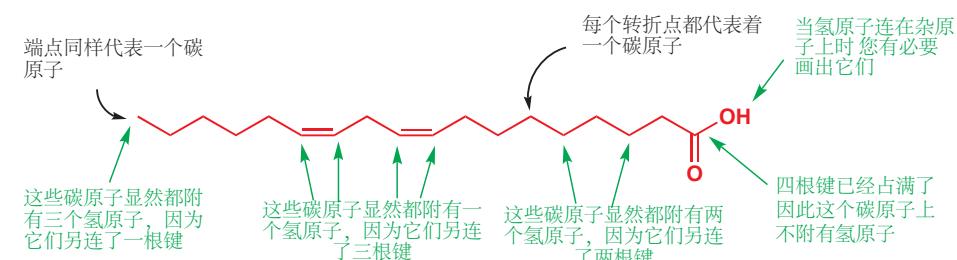
是链状结构一样。它确实是正确的，但它也是没用的。我们绘制分子结构的时候采用的是类似图(3)的方法。它了解原作的想法，包含能让我们辨认出它的全部细节，但是把其余的删去了。这张简明扼要的图片让我们能够快速表达——只花费了 10 分钟：我们没有时间把分子结构画得像一幅伟大的艺术作品！

分子性质的关键是官能团，因此我们必须在绘制的结构中突出官能团，并淡化碳氢骨架。比较如下两种画法：



第二种结构是大多数有机化学家绘制亚油酸的常用方式。瞧瞧我们如何淡化碳链骨架，而让羧基官能团脱颖而出。这个结构比往常任何一个结构都更加清晰，而且画起来更加方便！

为了从原始的结构图得到简化版的结构图，我们做了两件事。第一，我们将与碳原子直接成键的氢原子以及碳氢键都省略了。即使不画出来，我们也可以知道氢原子在哪——通常一个碳原子上连有四根键。第二，我们将整个碳骨架省略成了一条折线，这条折线的端点和转折点都代表着一个碳原子。



即以下两条准则：

### ● 准则 2

省略附着在碳原子上的氢原子和碳氢键 (除非您有理由不这样做)。

### ● 准则 3

省略大写字母 C，仅用折点代表碳原子 (除非您有理由不这样做)。

■ 什么样的理由可以让您不这样做？比如碳氢作为官能团的一部分，或者当您需要将它们突出表示的任何情况（本书中也有很多例子）。请不要将这些准则想的过于僵化，它只是帮助您理解和表述的工具。要注意的一点是，如果您决定写出大写字母 C，您必须将上面的 H 表示出来。

## 一目了然

四面体构型的碳原子，键角实际为  $109^\circ$ ，我们需要尽可能画出  $109^\circ$  在平面上投影的样子！ $120^\circ$  是一个很好的选择，这让结构图也很简洁)

从亮氨酸开始——我们早些时候将其画成右侧的结构。请拿出一张纸，尝试用上述的三条准则画一个简洁的结构。画完之后，再翻开下一页来检验您画的是否正确，并且思考我的建议。

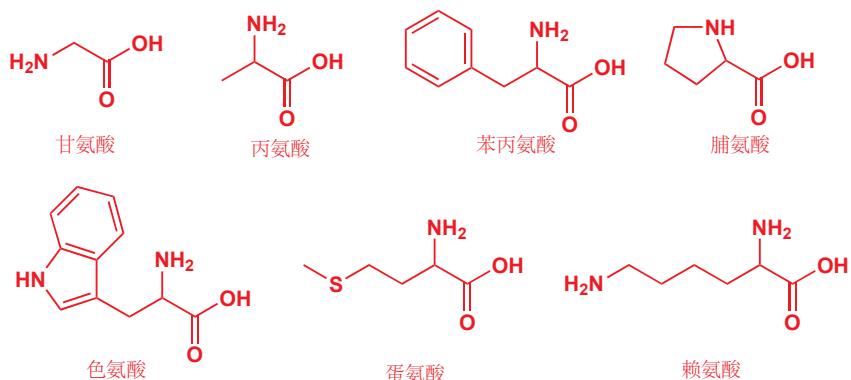


您也许画出了以下几种结构中的一种，它们都是正确的。

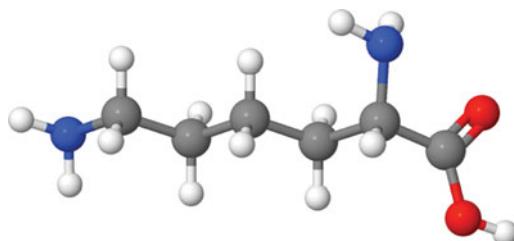


我们给出的准则只是起到指引作用，并不是原则、规矩，无论您是否采用都是可以的。我们的目的是为了淡化作为背景的碳骨架，突显官能团。因此我们认为后两种结构更加优秀——仅有羧基中的碳原子以字母 C 表现出来，这显然是脱颖而出的。

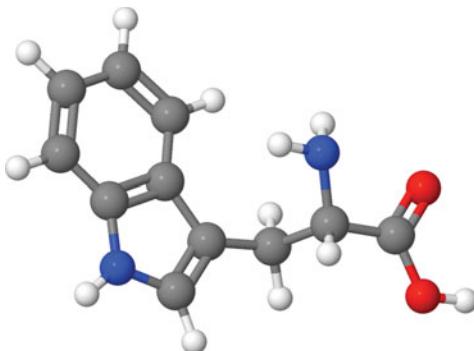
下面您可以继续尝试运用我们给出的准则，画出 p. 16 中提到的氨基酸们。在您画完之前请不要参考我们的建议！



再次提醒，请记住我们只是希望结构式在保证官能团清晰的情况下尽可能简洁。此外，您应该注意到上面这些图也在保持真实性上下了功夫——您可以例如拿赖氨酸、色氨酸与下面的晶体结构进行对比。



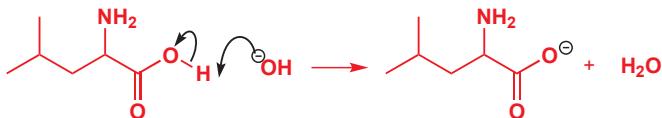
赖氨酸的 X 射线晶体结构



色氨酸的 X 射线晶体结构

## 结构式可以随需要作必要的修改

有些场合，您也许想要强调相同结构中的不同位置，这时结构式可以做必要的修改。我们提到过氨基酸既可以作为酸又可以作为碱。例如亮氨酸做酸时可以与碱（例如氢氧根离子， $\text{OH}^-$ ）反应，碱从羧基上夺取  $\text{H}^+$  的过程用如下方式表示：



这个反应的产物使氧带上了负电荷。为了清晰，我们将它放在一个圆圈里；我们也建议您这样做：因为人们时常忘记给原子标上 + 或 -。我们将来会探讨这类反应，表示时用到的“弯曲的箭头”，我们也会在 Chapter 5 中详细讲述它的含义。现在唯一要注意的是，我们将羧基的框架也表示了出来，这是因为我们想展示在碱的进攻下  $\text{O}-\text{H}$  键如何断裂。这就是在适应我们目的的时候对结构式做的必要修改。

当亮氨酸作为一个碱的时候，涉及的官能团应当是氨基 ( $\text{NH}_2$ )。氮原子将自己附着在一个质子上，用自己的孤对电子形成一根新的共价键。我们可以用如下方式表示：



请注意，由于我们想展示反应机理，因此我们还将氮上的孤对电子标了出来。羧基中的两个氧原子也都带有孤对电子，但我们并没有必要把它们都表示出来，这仍然是取决于场合和需求。甚至由于讨论亮氨酸碱性与羧基无关，我们直接将羧基缩写成了  $\text{CO}_2\text{H}$ 。

## 在纸面表示立体结构

当然，我们刚刚画出的全部结构式都只描述了分子结构的一个方面，即原子的排列顺序。但例如亮氨酸上连有氨基和羧基的碳原子，有四面体的构型，因此四种基团的排列方式可能是不同的，这一点是我们忽略了的。

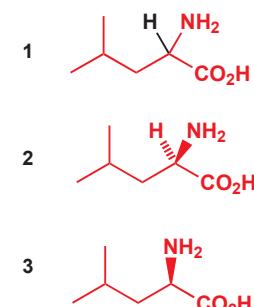
对于碳四面体的排列，观察右侧的结构 1. 如果最长的碳链作为平面，那么我们可以知道，氢原子与氨基这两个基团中，一个朝向我们，在纸平面的上方；另一个背向我们，在纸平面的下方。

对于限定构型的氨基酸，我们可以如结构 2 这样画出。我们约定，普通的直线连接的是在纸平面上的基团；实楔形线连接的是朝向我们，在纸平面上方的基团；虚楔形线连接的是背向我们，在纸平面下方的基团。图中所示的就是一种氢原子背向我们，氨基朝向我们的亮氨酸。

我们亦可以省略氢原子，画成如结构 3 所示的更简单的样子，虽然看起来不太现。由于碳是四面体的构型，而除了平面上的两个基团外我们还要一个朝向我们、在纸面上方的氨基，很容易地想到氨基会处于唯一缺陷的位置，背向我们、在平面的下方。要注意的是，如果您使用以上这种方式表示分子的三维结构，我们通常将碳链摆放在平面上，使分支与取代基位于或朝向我们，或背向我们的位置。

■ 并不是所有的有机化学家都将形式电荷放在圆圈里——这是个人的选择。

■ 孤对电子是原子上的未成键电子配对形成的。我们会在 Chapter 4 讨论。另外现在也不需要知道弯曲的箭头代表什么，我们会在 Chapter 5 讨论。



► 我们将在 Chapter 14 中具体地讨论分子的三维结构——立体化学。

### ● 回顾

绘制有机化学结构要求实事求是，简明扼要，一目了然。

我们给您了三个准则：

- 准则 1：将碳链画成锯齿状。
- 准则 2：省略附着在碳原子上的氢原子和碳氢键。
- 准则 3：省略大写字母 C，仅用折点代表碳原子。

三条准则以及对于立体化学表示的公约以及成长了几十年。它们不是一些人随意的声明，而是有机化学家的通用语言！我们保证在本书接下来的章节中遵守这些规则，我们希望当您在绘制分子结构时，也遵守它们。当您写下大字母 C 或 H 的时候，问问自己是不是有必要而为之的。

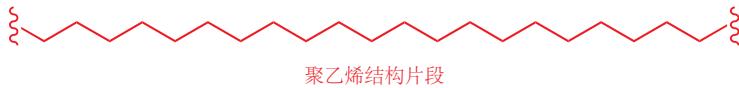
了解了如何绘制分子结构，我们将回到对结构类型的讨论。在接下来的节中，我们将首先讨论碳氢骨架，然后讨论官能团。

## 碳氢骨架

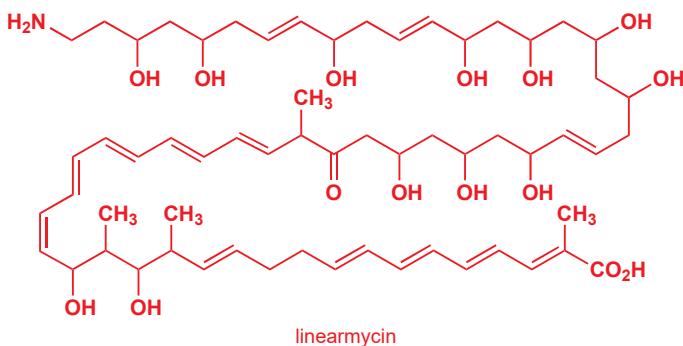
碳可以形成的化合物极为广泛。最特别的一点是它可以与元素周期表中绝大部分元素形成稳定的化学键，包括和它自己。正是碳与碳形成稳定共价键的能力，造就了有机化合物种类的丰富，甚至让生物的存在变得可能。虽然碳元素在地壳中的含量只有0.2%，但它仍然值得我们为它单独设立一个化学分支。

### 碳链

最简单的一类碳氢骨架仅包含原子链。例如，我们之前见过的脂肪酸分子就是由锯齿状的原子链构成的碳氢骨架。聚乙烯是完全由碳氢链构成的聚合物，下图中我们在两端画了波浪线 (wiggly line)，以表明我们画的是不完整的片段。



除了简单的聚乙烯，还有一些相对复杂的原子链构成的分子。下图这种抗生素在 1995 年从真菌中提取，并由于它的线性长链被恰如其分地被命名为 linearmycin。这种抗生素的结构太长了，因此我们在纸面上画的时候，不得不画两个折角。另外，我们没有表示出  $\text{CH}_3$  和 OH 基团的立体构型，因为在写这本书的时候，linearmycin 的立体化学还是未知的。



■ 注意到我们将三个甲基表示成了  $\text{CH}_3$  的形式——因为我们不想让它们在如此长的结构中被忽略。它们只是一根蜿蜒的树干上的几根小小的树枝。

## 烷基的命名

用碳原子个数指代碳原子链是在方便不过的方法了。您可能早就看到过一些比较简单的有机分子，例如取代的烯烃，用过这些名字。不论是在文字表达还是用结构式表达的时候，它们都是十分常见的，我们会在不久后多次看到。

### 烷基的命名和缩写

碳原子数	烷基的命名	结构式 <sup>†</sup>	缩写	对应的烷烃 (= 烷基 + H)
1	甲基 methyl	$-\text{CH}_3$	Me	甲烷 methane
2	乙基 ethyl	$-\text{CH}_2\text{CH}_3$	Et	乙烷 ethane
3	丙基 propyl	$-\text{CH}_2\text{CH}_2\text{CH}_3$	Pr	丙烷 propane
4	丁基 butyl	$-(\text{CH}_2)_3\text{CH}_3$	Bu	丁烷 butane
5	戊基 pentyl	$-(\text{CH}_2)_4\text{CH}_3$	— <sup>‡</sup>	戊烷 pentane
6	己基 hexyl	$-(\text{CH}_2)_5\text{CH}_3$	— <sup>‡</sup>	己烷 hexane
7	庚基 heptyl	$-(\text{CH}_2)_6\text{CH}_3$	— <sup>‡</sup>	庚烷 heptane
8	辛基 octyl	$-(\text{CH}_2)_7\text{CH}_3$	— <sup>‡</sup>	辛烷 octane
9	壬基 nonyl	$-(\text{CH}_2)_8\text{CH}_3$	— <sup>‡</sup>	壬烷 nonane
10	癸基 decyl	$-(\text{CH}_2)_9\text{CH}_3$	— <sup>‡</sup>	癸烷 decane

<sup>†</sup> 不建议使用此形式表示，除了  $\text{CH}_3$ 。 <sup>‡</sup> 较长链的烷基通常不缩写。

■ (针对英文命名) 比较短烷基的名字取决于历史原因，您必须额外了解；五个碳原子及以上长度的烷基的名字来源于希腊数字。

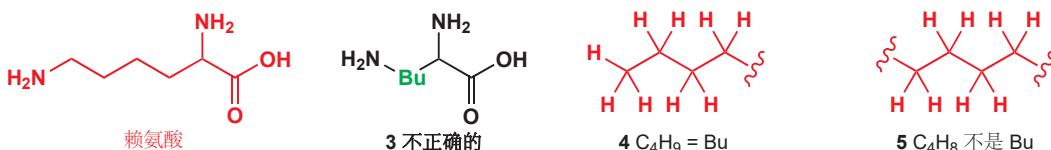
## 有机元素

你可能会注意到，一些烷基的缩写很像元素符号：这是有意而为之的，我们可以叫它们“有机元素”。在绘制分子结构时，它们可以像化学元素一样被使用。使用“有机元素符号 (organic element symbols)”来表示碳链的片段可以让整张图十分整洁。下面是一些例子。结构 1 是我们在第 20 页曾画过的蛋氨酸结构。最左侧的一根棍代表与硫原子相连的一个甲基，不过，这种方法看起来太奇怪了。大多数的化学家更喜欢绘制出结构 2 的样子，用“Me”代替  $\text{CH}_3$  (甲基) 基团。四乙基铅过去曾被添加到汽油中，防止发动机“爆震”，后来因有发现健康危害而被废止。它的结构(您可以从名字中猜出) 可以直接被写作  $\text{PbEt}_4$  或  $\text{Et}_4\text{Pb}$ 。

请注意，这些符号(或者名称)只能在表示端基基团时使用。例如，我们不能将赖氨酸的结构缩写成 3 的样子，因为 Bu 代表的是 4 而不是 5.



四乙基铅



在离开对于碳链的讲解前，我们必须提到一个非常有用的有机符号 R。在结构中，符号 R 可以表示任何基团—这是一张“万用卡”。例如结构 6 可以指代任何氨基酸，如果  $R = H$  则它是甘氨酸，如果  $R = Me$  则它是丙氨酸... 就像我们之前提到过的，有机分子的反应性取决于它们的官能团，而余下的部分是无关紧要的。在这种情况下，我们可以选择用 R 指代它们。



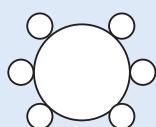
### 碳环



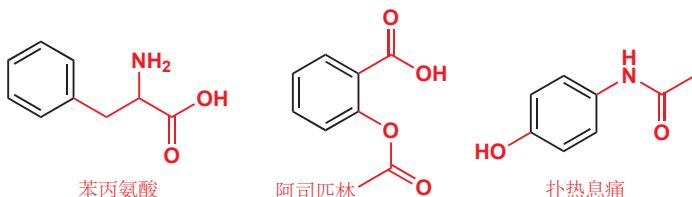
原子环在有机结构中也很常见。您也许听说过奥古斯特·凯库勒 (Auguste Kekulé) 的著名故事，他做了个梦，梦中的蛇在咬它们自己的尾巴，于是他首次意识到苯有一个环状结构。您已经在苯丙氨酸和阿司匹林的结构上见过苯环了，扑热息痛的结构上也有一个苯环。

#### 苯的环状结构

1865年，凯库勒在巴黎向法国科学院提交了一篇论文，文中提出了苯的环状结构，他把这种想法归结于自己的一个梦。然而，凯库勒是第一个提出苯的环状结构的吗？有些人不相信，他们认为那是奥地利教师约瑟夫·劳施密特 (Josef Loschmidt) 的功劳。1861年，凯库勒做梦前4年，劳施密特出版了一本书并在其中用环表示苯。目前尚未确定到底是他们谁，或是一位斯科特·库珀 (Archibald Couper) 的人第一个发现的。



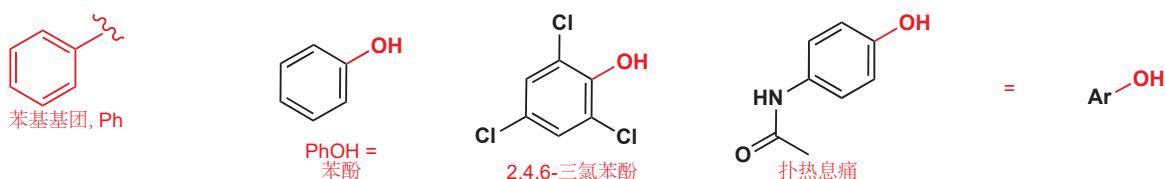
劳施密特绘制的苯的结构



当苯环值由其中一个碳原子附着到分子上/作为端基出现时（像苯丙氨酸，而不是阿司匹林、扑热息痛中的），我们可以叫它“苯基 (phenyl)” 基团，并且用符号 Ph 表示。



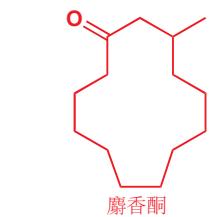
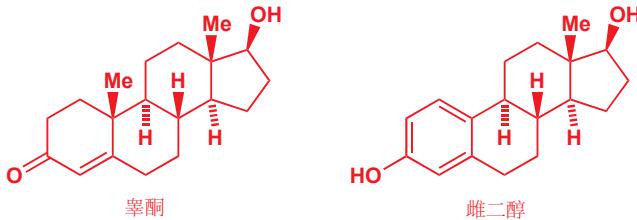
任何含有苯环或其衍生环 (Chapter 7) 的体系被称为“芳香的 (aromatic)”，与 Ph 相关的另一个实用的有机符号是 Ar (来自“芳基 aryl”)。Ph 通常表示  $C_6H_5$ ，而 Ar 可以表示任何被取代的苯环，也就是苯环上任意数量的氢被其他基团所取代的结果。当然 Ar 也用来表示氩，但您并不需要担心，有机化合物中并不会出现氩原子。



例如,  $\text{PhOH}$  只能指苯酚, 而  $\text{ArOH}$  可以指代苯酚, 2,4,6-三氯苯酚 (TCP 防腐剂), 扑热息痛或者阿司匹林 (也包括很多其他的取代苯酚)。类似于  $\text{R}$  是烷基的“万用卡”而  $\text{Ar}$  是芳香基团的“万用卡”。

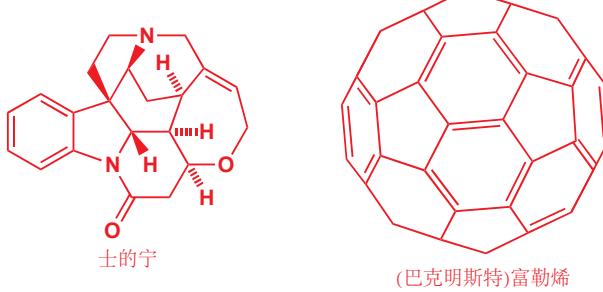
这种被称为麝香酮的化合物是最近在实验室中合成出来的。它的香味被用作香水的底味。在化学家确定它的结构并设计出实验室合成路线前, 麝香的唯一来源是麝鹿, 由于这个原因麝鹿现在已经开始稀有了。麝香酮的骨架是一个 13 给碳原子围成的环。

甾体/类固醇激素有多个(通常是四个)环稠合在一起。下面的两个激素是睾酮 (testosterone) 和雌二醇 (oestradiol), 分别是男性和女性人类重要的性激素。



■ 提醒: 实楔形 (wedged bonds) 朝向纸面前方, 指向我们, 虚楔形键 (hashed bonds) 朝向纸面后方, 远离我们。

有些环状结构要比这些复杂得多。强效毒药士的宁是一团互相连接的环纠缠在一起构成的。



Interactive structures of testosterone, oestradiol, strychnine, and buckminsterfullerene

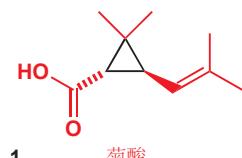
### 巴克明斯特富勒烯

以美国发明家和建筑师理查德·巴克明斯特·富勒 (Richard Buckminster Fuller), “穹顶建筑”的设计者的名字命名。

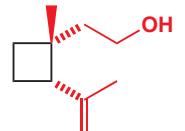


史上最优雅的环状结构之一是上面展示的巴克明斯特富勒烯 (buckminsterfullerene)。它仅由 60 个碳原子构成, 这些碳原子构成环, 弯曲并回到自己的另一侧, 构成一个足球状的笼子。计算任何交点处碳原子的成键数, 你会发现它们都是四, 因此不需要额外添加氢原子。这个化合物的分子式是  $\text{C}_{60}$ 。注意您不能看到全部原子, 因为其中一些在球体的后面。

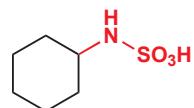
碳原子环的命名以“环 (cyclo)”开始, 然后是根据碳原子数写出的碳链名称。结构 1 展示的是菊酸, 一种名叫除虫菊酯的天然杀虫剂的一部分 (Chapter 1 中有一个例子), 这个分子中含有一个环丙烷结构。丙烷 (Propane) 有三个碳原子, 环丙烷 (cyclopropane) 同样表示具有三个碳原子的脂肪环。诱杀烯醇 (结构 2), 是雄性棉铃象吸引雌性使用的一种昆虫信息素, 这个分子中含有一个环丁烷结构。丁烷 (Butane) 有四个碳原子, 环丁烷 (cyclobutane) 同样表示具有四个碳原子的脂肪环。甜蜜素 (结构 3), 从前被用作人工甜味剂, 含有一个环己烷结果。己烷 (Hexane) 有六个碳原子, 环己烷 (cyclohexane) 是有六个碳原子的脂肪环。



1 菊酸



2 诱杀烯醇

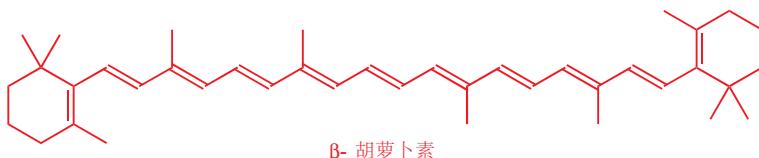


3 甜蜜素

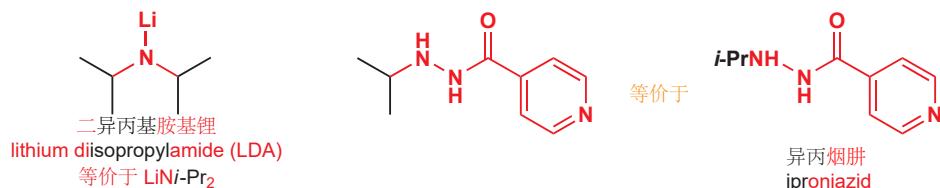
### 支链

碳氢骨架很少只有环和链组成, 它们大多数都存在支链 (branches)。环、链、支链同时存在于许多化合物中, 例如在本章开始时提到的岩沙海葵毒素便是如此, 再比如聚苯乙烯是由碳链和挂在上面的六元环构成的, 还有让胡萝卜显橙色的化合物  $\beta$ -胡萝卜素中。

 Interactive structure of polystyrene



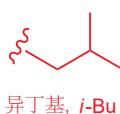
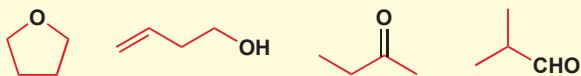
与普通的直链烷基类似，一部分含有支链的烷基也被赋予了专用的名字与“有机元素符号”。最常见的是异丙基 (isopropyl)。二异丙基胺基锂 (Lithium diisopropylamide, LDA) 是有机化学中常用的碱。



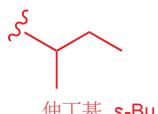
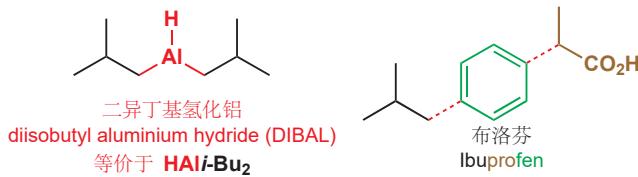
请注意我们之前提到的“丙基 (propyl)”和“异丙基 (isopropyl)”之间的差别；它们表达的是不同的基团——换种说法，异丙基是直链的丙基的一种异构体 (*isomer*)。有些时候为了避免混淆，我们将直链的烷基称作“正烷基 *n*-alkyl”(例如 *n*-Pr, *n*-Bu)——*n* 代表“normal”——这种方法用来区别它们与它们含支链的异构体。异丙烟肼是一种抗抑郁药物，结构中我们使用了 *i*-Pr 表示异丙基，在英文名称上也是类似。“异丙基”可以缩写成 *i*-Pr, *i*Pr 或 *Pr*<sup>i</sup>。这是我们在本书中第一次使用这一写法，而您在今后的阅读中会看到更多。

● 异构体表示各原子数量相同，但排列顺序不同的几种分子。

正丙醇 (*n*-propanol), *n*-PrOH, 和异丙醇 (isopropanol), *i*-PrOH, 就是一对异构体。异构体间不一定含有相同的集团——例如下面的这些化合物就都是 C<sub>4</sub>H<sub>8</sub>O 的异构体：



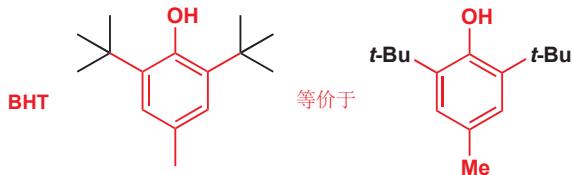
异丁基 (isobutyl, *i*-Bu) 是在 *i*-Pr 基团中加入 CH<sub>2</sub> 基团获得的。等价于 *i*-PrCH<sub>2</sub>-。还原剂二异丁基氢化铝 (diisobutyl aluminium hydride, DIBAL) 中就包含两个异丁基。止痛药布洛芬 (ibupro-fen, 商品名 Nurofen®) 中也包含异丁基。注意布洛芬的名字实际上是由“ibu”(来自异丁基 *i*-sobutyl, *i*-Bu) + “pro我”(来自丙 propyl, 指棕色部分划出的三个碳) + “fen”(来自苯环 phen-yl ring) 拼凑而成的。我们将在本章的最后一部分讲述化合物的命名。



丁基还有两个异构体，它们也都有常用的名字和缩写。仲丁基 (*sec*-butyl, 缩写作 *s*-butyl 或 *s*-Bu) 是取代基碳原子上连有一个甲基和一个乙基的基团。它出现在一个有机锂化合物 (organolithium compound) 仲丁基锂 (*sec*-butyl lithium) 中，这种试剂常用于在有机分子中引入锂原子。

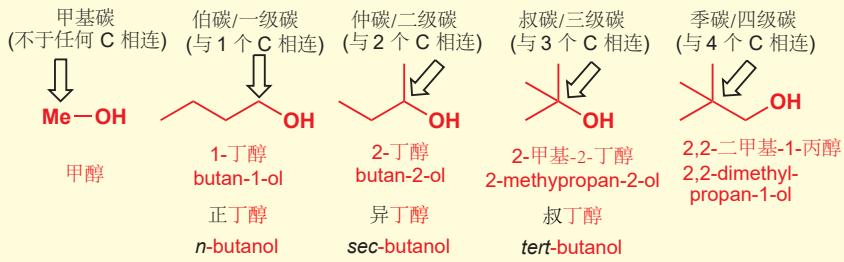


叔丁基/特丁基 (*tert*-butyl, 缩写作 *t*-butyl 或 *t*-Bu) 是取代基碳原子上连有三个甲基的基团。一种添加进包装食品中的抗氧化剂，丁基羟基甲苯 (butylated hydroxy toluene, BHT E321) 中就含有两个 *t*-Bu基团。



### ● 伯 (primary), 仲 (secondary), 叔 (tertiary), 季 (quaternary)

前缀 *sec* 和 *tert* 分别是 仲 (secondary) 和 叔 (tertiary) 的简写，是一种阐释与所指碳原子相连的其他基团数量的术语。(注: 中文的俗称命名不完全依此，但指示碳原子时可采用。)



伯碳指的是只与一个其他 C 原子相连的碳原子，仲碳指与两个其他 C 原子相连的碳原子，等等。这表明碳原子共存在五种不同的类型。这些碳氢骨架的名称不仅是在书写和交流化学时的便利手段。它们还告诉我们分子中的一些基本性质，我们将在讨论反应时使用到。

我们快速而简略地参观了自然和人类构筑出的分子大厦，它们只是作为本章节的其他部分和本书其他章节的引入。然而，幸运的是，无论碳氢骨架有多复杂，它们仍然只是作为官能团的支撑。而且，从大体上说，同一个官能团在不同分子中作用的方式基本数相同。我们在下一节中将要做的，是告诉您一些官能团，并且告诉您为什么它们的属性是理解有机化学的钥匙。

## 官能团

如果您将乙烷 ( $\text{CH}_3\text{CH}_3$ , 或 EtH) 通入酸、碱、氧化剂，还原剂——事实上任何您能想到的试剂中——它都不会发生变化。您唯一能做的就是燃烧它。然而乙醇 ( $\text{CH}_3\text{CH}_2\text{OH}$ , 最好写成 EtOH—旁边有它的结构) 不仅可以燃烧，它还可以与酸、碱、氧化剂反应。

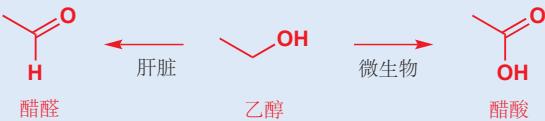
乙醇和乙烷的区别就在于前者的官能团上——即 OH, 羟基 (hydroxyl). 我们知道上述这些化学性质 (可以和酸、碱、氧化剂反应) 是羟基的性质，而不仅仅是乙醇的性质；因为其他包含 OH 官能团的化合物 (换句话说，其他醇类)，不论它的碳氢骨架是什么样的，也具有相似的性质。

您对于官能团的理解将是您理解有机化学的关键。因此，我们现在要初步了解一些相对重要的官能团。我们不会过多的提及它们各自的性质，有关性质的内容会在 Chapter 5 及以后出现。在此阶



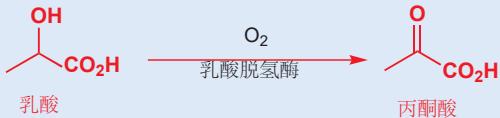
### 乙醇

乙醇与氧化剂的反应使葡萄酒转化为醋，也使人从醉酒变为清醒。在这两种情况中，氧化剂都是空气中的氧气，同时都需要酶催化。在葡萄酒中生长的微生物使乙醇氧化为醋酸（乙酸），而人的肝脏则可以使乙醇氧化为醋醛（乙醛）。

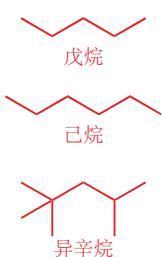


### 人体的代谢与氧化

人体的代谢系统利用醇类的氧化反应将包含 OH 官能团的有害物质，转化为其他化合物。例如，在剧烈运动中肌肉会产生乳酸，在乳酸脱氢酶的催化下，乳酸可以转化为一种在代谢上有用的化合物丙酮酸。



段，您的任务是学习如何在这些官能团在一个结构中出现时，识别它们，所以您需要确保知道它们的名字。包含某种官能团的一类化合物也有它们的名字，例如含有羟基官能团的一类化合物被称为醇，同时学习这些名字比学习单个化合物的系统命名更为重要。我们会介绍这些官能团的知识的一些片段，以帮助您理解它们各自的角色。

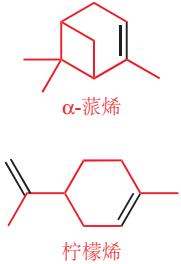


### 烷烃不包含官能团

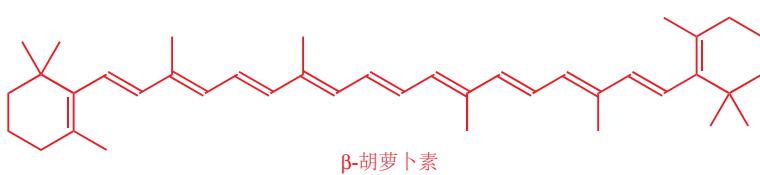
烷烃 (alkanes) 是最简单的一类有机分子，因为它们不包含任何官能团。它们非常不活泼，因此就有机化学家关心的那些内容来说，烷烃可谓相当的无聊。不过，这种不活泼性也可以作为一种优势，戊烷和己烷等等烷烃常被用作溶剂，尤其是在有机化合物的提纯上。对于烷烃的化学，唯一能做的就是燃烧——甲烷、丙烷和丁烷是家庭燃料，汽油也是包括大量异辛烷在内，多种烷烃的混合物。

### 烯烃包含 C=C 双键

将一种键作为一类官能团也许看上去很奇怪，但接下来您就会看到 C=C 双键 (double bond) 赋予有机分子的反应性和其他的官能团，比如氧原子、氮原子的效果是相似的。很多烯烃 (alkenes/olefin) 由植物产生，并且被调香师使用（见 Chapter 1）。例如，蒎烯有着能让人唤起松叶林般感觉的气味，而柠檬烯有着柑橘类果实的味道。



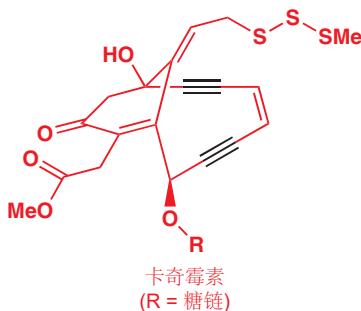
您之前见过的橘黄色色素  $\beta$ -胡萝卜素的主体部分就是由十一根 C=C 双键构成的。带有颜色的有机化合物通常类似地包含带有 C=C 双键的碳链或碳环。在 Chapter 7 中您会了解到为什么会这样。



### 炔烃包含 C≡C 三键

类似 C=C 双键，C≡C 三键也与一类特殊的反应性相关，因此将 C≡C 三键 (triple bond) 称作一种官能团也是十分有必要的。炔烃 (alkynes) 通常是直线形的，因此我们也习惯于将这四个碳

原子画在一条直线上。炔烃在自然界中的分布并不及烯烃广泛，最迷人的一类含有  $C\equiv C$  三键的化合物是在1980年代发现的抗肿瘤剂。卡奇霉素 (Calicheamicin) 是这类药物中的一种，其分子中官能团的组合使其拥有高反应性，可以进攻DNA并且阻止癌细胞的迅速繁殖。下图是我们第一次以三维视图绘制分子，其中两条键穿过了另一条——您能感受到它的形状吗？



### 饱和与不饱和

在烷烃中，每个碳原子都与其他四个原子 (C或H) 成键。它没有继续成键的可能，因此这是**饱和的** (saturated)。在烯烃中，组成  $C=C$  双键两端的碳原子至于其他三个原子相连。它们有继续成键的潜力，因此这是**不饱和的**。普遍上，与四个其他原子相连的碳原子是饱和的；与三个、两个，甚至一个其他原子相连的是**不饱和的** (unsaturated)。记得 R 可能代表任意烷基。

### 醇 ( $R-OH$ ) 包含羟基 ( $OH$ )

我们已经探讨过在乙醇和其他醇类 (alcohol) 中的羟基 (hydroxyl)。碳水化合物就是一种富含羟基的化合物，例如在蔗糖中就有八个 (在 Chapter 1, p.3 中我们展示过它的三维画法)。



Interactive structure of sucrose

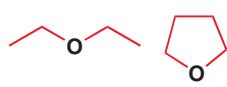
含有羟基的分子通常可溶于水，生命体就通常使用这种性质，将含有羟基官能团的糖，附在其他不溶性的有机化合物上，并且让它们可以留在细胞液中。我们刚刚提到的卡奇霉素中包含的糖链也是为了这个目的。肝脏也是通过反复羟基化那些不需要的有机物，直至它们可溶于水，然后通过胆汁或尿液排出体外的。

### 醚 ( $R^1-O-R^2$ ) 包含烷氧基 ( $OR$ )

醚 (ether) 指的是通过氧原子连接两个烷基的化合物，命名时可以将烷氧基 (alkoxy group) 作为取代基。(英文中) “ether” 一词同样可以作为乙醚 (二乙基醚,  $Et_2O$ ) 的俗称。这类似于 “alcohol” 一词也常被用作指乙醇 (ethanol)。乙醚是一种高度易挥发的溶剂，它的沸点仅有  $35^\circ C$ ，它曾经被用作麻醉剂。四氢呋喃 (tetrahydrofuran, THF) 是另一种常用的溶剂，它是一个环状的醚。

短裸甲藻毒素 B (图片在下一页) 是一种迷人的天然产物，并且于 1995 年在实验室中合成。它的结构中充满了包含醚类官能团/醚键的六元环和八元环。

■ 如果我们想在一个结构中使用多个 “R”，我们通常给予它们编号，如  $R^1$ ,  $R^2\dots$  因此  $R^1-O-R^2$  表示包含两个不同的未指定烷基的醚 (不能写成  $R_1$ ,  $R_2\dots$  那样会意味着  $1 \times R$ ,  $2 \times R\dots$ )



### 胺 ( $R-NH_2$ ) 包含氨基 ( $NH_2$ )

我们在讨论氨基酸的时候见过了氨基 (amino group)：我们提到了正是这个官能团给了这些化合物它们基本的性质。胺类 (amine) 通常有浓重的鱼腥味：丁二胺/腐胺的味道尤其难闻。它们在肉类腐烂时生成。许多神经活性物质也是胺类：安非他明是一种臭名昭著的兴奋剂。



## 短裸甲藻毒素 B

短裸甲藻毒素 B (Brevetoxin B) 是从海洋生物 (来自一种鞭毛藻/甲藻, 称为短裸甲藻 *Gymnodinium breve*, 因此得名) 中提取的一种聚醚。这种海洋生物有时会以惊人的速度繁殖, 造成墨西哥湾沿岸的“赤潮 (red tides)”。鱼类无法在这种赤潮中生存; 同时, 如果人食用在这种赤潮中生长的贝类也会中毒。短裸甲藻毒素是这其中真正的杀手, 因为醚键中的氧原子会干扰钠离子 ( $\text{Na}^+$ ) 的代谢。



硝基化合物 ( $\text{R-NO}_2$ ) 包含硝基 ( $\text{NO}_2$ )



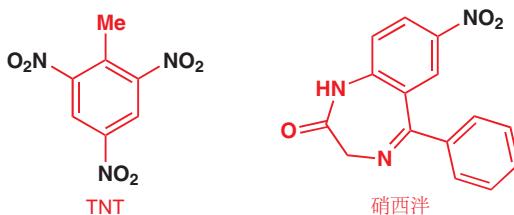
硝基 (nitro group,  $\text{NO}_2$ ) 有时会被画成左边的错误形式，氮原子与其他原子成五跟键，Chapter 4 中您会明白为什么这是不可能的。当您需要将硝基展开来画时，确保您画了正确的结构。如果您直接表示成  $\text{NO}_2$ ，那么无论如何您都是对的！

氮不能  
成五根键!



## 硝基的错误画法

分子中包含硝基的化合物被称为硝基化合物 (nitro compound)，这些分子很不稳定甚至易爆。著名的炸药三硝基甲苯 (trinitrotoluene, TNT) 中就包含三个硝基。当然，官能团的性质也并不是千篇一律的。硝西洋分子中就包含一个硝基，但这个化合物以 Mogadon® 作为安眠药出售。



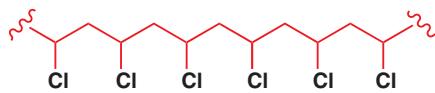
卤代烃 ( $\text{R-F}$ ,  $\text{R-Cl}$ ,  $\text{R-Br}$ ,  $\text{R-I}$ ) 包含卤原子

卤代烃 (alkyl halide/haloalkane) 的四种官能团 (卤原子, 英文命名时采用类似“卤基”说法 fluoro, chloro, bromo, iodo) 性质相似, 其中碘代烃最活泼, 氟代烃最不活泼。聚氯乙烯 (PVC) 是使用最稳广泛的聚合物之一——它是在直链碳骨架上每隔一个碳取代一个氯原子的化合物。另一方面, 碘甲烷 ( $\text{MeI}$ ) 是一种危险的致癌物质, 因为它可以与 DNA 反应, 并且会导致基因序列变化。



 Interactive structure of PVC

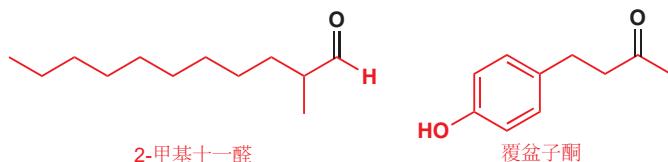
由于卤代烃之间的性质相似，化学家用另一个更为广泛的符号X，方便地代替指Cl, Br, I, 有时也代替F: 例如R-X代表任何卤代烃。



## PVC 结构的一个片段

醛 ( $\text{R}-\text{CHO}$ ) 和酮 ( $\text{R}^1-\text{CO}-\text{R}^2$ ) 包含羰基 ( $\text{C}=\text{O}$ )

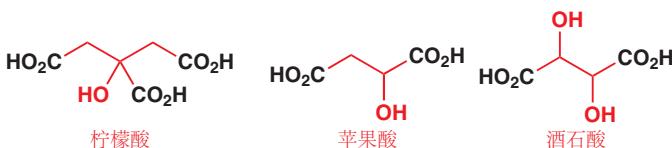
醛(aldehyde)和酮(ketone)可以由醇的氧化反应得到——在人体中，肝脏就是通过这种方式，将血液中的乙醇氧化为乙醛( $\text{CH}_3\text{CHO}$ ) (见 p. 28)以解毒的。如果乙醛停留在血液中不被继续代谢，则会引起宿醉。醛、酮通常有令人愉悦的气味——2-甲基十一醛是“香奈儿五号(Chanel No. 5)”香水的关键化合物，“覆盆子酮(raspberry ketone)”是构成一些香水中覆盆子气味的主要化合物。



■ -CHO 代表



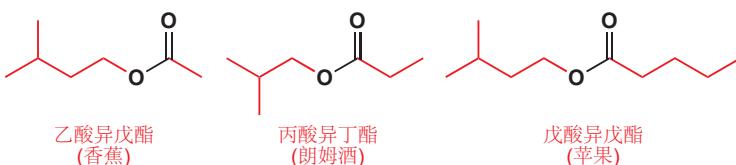
在表示醛的结构时，我们不得不忽视绘制结构的准则 3，而写作 R-CHO——将 C 和 H 单独用字母写出来，这是因为它是我们要突出的官能团的一部分。另一点要说明的：我们通常写作 R-CHO 而不是 R-COH，这是因为后者看上去更像一个醇。



### 羧酸 ( $\text{R}-\text{CO}_2\text{H}$ ) 包含羧基 ( $\text{CO}_2\text{H}$ )

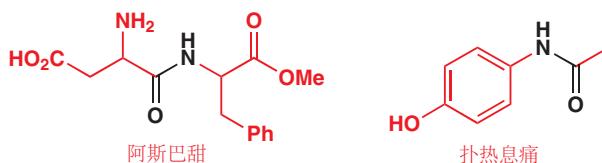
正如其名字所暗示的，包含羧基 (carboxyl group,  $\text{CO}_2\text{H}$ ) 的化合物羧酸 (carboxylic acid) 可以与碱反应，失去一个质子生成羧酸盐 (carboxylate salt)。可食用的羧酸有浓烈的气味，其中不少存在于水果中——柠檬、苹果和葡萄中分别含有柠檬酸、苹果酸和酒石酸。

■ 常常听到的术语“饱和脂肪”和“不饱和脂肪”——分别表示 R 基团是饱和（不含  $\text{C}=\text{C}$  双键）还是不饱和（含有  $\text{C}=\text{C}$  双键）——见 p. 29 的文本框。R 基团含有多个双键的脂肪（例如本章开头的亚油酸形成的酯）被称为“多不饱和的 (polyunsaturated)”。



### 酰胺 ( $\text{R}-\text{CONH}_2$ , $\text{R}^1-\text{CONHR}^2$ , 或 $\text{R}^1-\text{CONR}^2\text{R}^3$ )

蛋白质都是酰胺 (amide)：一个氨基酸中的羧基可以与另一氨基酸中的氨基形成酰胺键 (amide bond, 有时也被叫做肽键 peptide bond)，蛋白质就是这样缩合形成的。每个蛋白质分子都可以包含成百上千个酰胺键。另一方面，以 NutraSweet® 为名称销售的甜味剂阿斯巴甜，也是通过酰胺键连接两个氨基酸形成的酰胺，两个氨基酸分别是天冬氨酸与苯丙氨酸。扑热息痛同时也是一个酰胺。



### 腈 ( $\text{R}-\text{CN}$ ) 包含氰基 ( $\text{C}\equiv\text{N}$ )

卤代烃与氰化钾的反应可以向分子中引入氰基 (cyano) 从而获得腈 (nitrile)。有机上的氰基与无机上的致命氰化物有着大不相同的性质：例如从杏仁中提取的腈类，苦杏仁苷 (laetile)，曾经被开发为抗癌药物。



### 酰氯 ( $\text{R}-\text{COCl}$ )

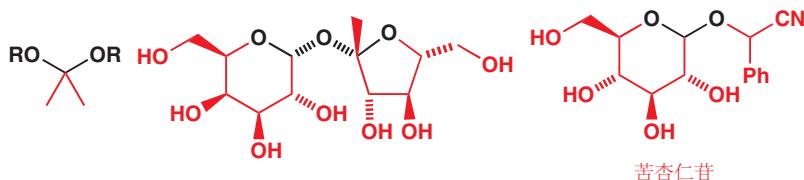
酰氯 (Acyl chloride) 是最活泼的羧酸衍生物 (derivatives of carboxylic acids)，由羧酸中的 $-\text{OH}$  被  $-\text{Cl}$  取代获得，可以用来制备酯或酰胺，由于太过活泼在自然界中几乎找不到。



注：国内常用缩酮 (ketal) 指中心碳连接的另两个基团均为烷基的缩醛（缩酮为缩醛之子集），本书并无此概念。相似的还有半缩醛/半缩酮，p.136.

## 缩醛

缩醛 (acetal) 是同一个碳与两个烷氧基相连的化合物。很多糖类都是缩醛。



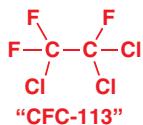
### 杂原子指除去 C 和 H 的原子

如您所见，官能团基本都是对烷烃结构的偏离，要么含有的氢原子比烷少（烯、炔），要么是含有不是 C 和 H 的其他原子。有一个实用的术语描述这些原子：杂原子。杂原子指在有机分子中除去 C 和 H 的任何原子。

## 携带官能团的碳原子可以按氧化程度分类

官能团虽都是不同的，但它们的差异也有大有小。例如，羧酸、酯、酰胺的结构就非常相近：它们官能团中的碳原子，都与两个杂原子 (heteroatoms) 成键，其中一个以双键连接，一个以单键连接。在 Chapter 10 中您会看到，结构上的相似性也在它们反应方式的相似性上有所反映。另外，羧酸、酯和酰胺可以通过简单的试剂，如水、醇、胺以及合适的催化剂，实现相互转化。但若想将它们转化为醛或醇，则需要特殊试剂，一种还原剂 reducing agent (加氢的试剂)。如果两种官能团间的转化，只需要简单试剂，不需要还原剂 (或氧化剂 oxidizing agent)，我们就称携带它们的碳原子有相同的氧化程度 (oxidation level)——对于上述例子，我们称它们均为“羧酸氧化程度”。

### ● 羧酸氧化程度



■ 不要将氧化程度 (oxidation level) 与氧化态 (oxidation state) 混淆。氧化程度由碳与杂原子的成键数决定，而氧化态则由碳所有的成键数决定，包含与 C 和 H 成键的个数。在上述化合物中，碳始终成四根键，因而氧化态均为 +4. (注：这个说法或许有一些问题)

事实上，酰胺可以相当容易地通过脱水 dehydration (水的脱除) 转化为腈，因此我们必须说氰基碳原子与羧酸、酯、酰胺有相同的氧化程度。也许您开始发现能帮您判断它们氧化程度的，这四种结构的相似性了？四种情况中，碳原子都与杂原子成三根键，与 C 或 H 原子成一根键。有几个杂原子并不重要，重要的是与杂原子共成了几根键。注意到这一点后，我们还可以将“CFC-113”，一种对环境不友好，会损害大气臭氧层的气溶胶推进剂和制冷剂中的每个碳原子，都归入羧酸氧化程度中。

### ● 醛氧化程度



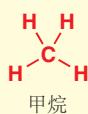
醛和酮都包含与杂原子成两根键的碳原子；它们处于“醛氧化程度”中。实验室常见的溶剂二氯甲烷  $\text{CH}_2\text{Cl}_2$  也含有与杂原子成两根键的碳原子，因此它也含有处于醛氧化等级的碳原子，缩醛中的亦然。

### ● 醇氧化程度



醇、醚和卤代烷都含有一个只与杂原子成一根键的碳。我们将它们标记为“醇氧化程度”，它们之间的转化不需要氧化剂、还原剂，也很容易完成。

### ● 烷烃氧化程度



简单的烷烃，不与杂原子子成键，为“烷烃氧化程度”。

### ● 二氧化碳氧化程度

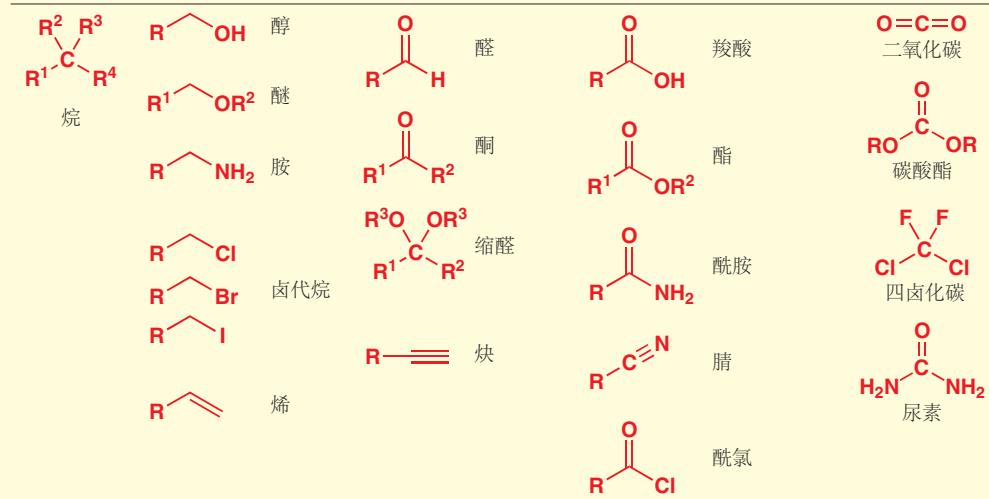


还要一小类与  $\text{CO}_2$  相关的化合物，其中的碳与杂原子成四根键，最好将其描述为“二氧化碳氧化程度”。

很明显，烯和炔并不能轻易地划归到其中一类，因为它们与杂原子不成键（但又与烷不同）。烯烃可以通过醇的脱水制备，不需要氧化剂、还原剂，而炔与醛也存在水化/脱水的关系，它们分别被归入醇氧化程度和醛氧化程度。

### ● 总结: 重要的官能团与氧化程度

与杂原子 不成键: 烷氧化程度	与杂原子成 一根键: 醇氧化程度	与杂原子成 两根键: 醚氧化程度	与杂原子成 三根键: 醛氧化程度	与杂原子成 四根键: 羧酸氧化程度	与杂原子成 四根键: 二氧化碳氧化程度
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## 化合物命名

到目前为止，我们已经用名字讨论了很多混合物。其中很多名字（岩沙海葵毒素，麝香酮，裸藻毒素）都是给予复杂分子的简单名称，并不考虑分子的真实结构、功能——这三种化合物的名称都来

源于它们被首次分离时所来源的有机体的名称。这样的名称叫做**俗称 (trivial names, trivial)**意为“微不足道”，“琐碎”），并不是因为他们不重要，而是因为它们会在日常的科学交流中用到。

这样的名字对于熟悉的，在化学家、生物学家、医生、护士、香水师中应用广泛的化合物是可取的。但目前有 1600 种已知的有机化合物，我们无法一一给它们取名，而且也没人能够全记得住。因为这点原因，国际纯粹与应用化学联合会 (International Union of Pure and Applied Chemistry, IUPAC) 发展了一套**系统命名法 (systematic nomenclature)**，这是一套可以给予任意一个化合物一个唯一的名称的规则，这种名称可以直接地从其化学结构上推导出来。反过来，从系统名称也可以推出一个分子的结构。

系统命名的问题在于，除了最简单的分子外，其他分子的名称都荒诞地不能读出来。在日常的演或写作中，化学家往往会漠视它们，使用系统和俗称命名法的混合。尽管如此，知道这些规则如何操作也是很重要的。接下来，我们将在看向真正的化学语言前，先着眼于系统命名法。

### 系统命名法

这里并没有机会，介绍全部系统命名的规则——它们填满了几卷极其无聊的书，而且有电脑的帮助，您也没有必要知道它们。我们将要做的，是阐明系统命名法的原则。您应当理解这些原则，因为它们是化学家的基础，能够帮您解决绝大多数没有俗称的化合物。

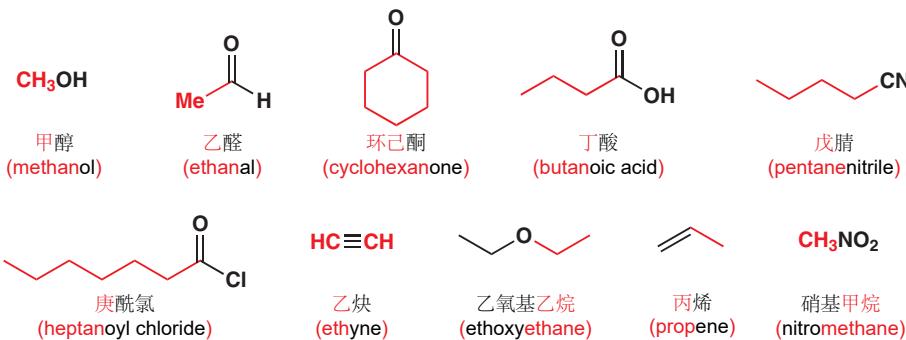
系统名称可以分为三个部分：其一描述了碳氢骨架，其二描述了官能团，还有一个阐释了官能团在碳氢骨架上的位置。

您已经遇到过一些简单的碳氢骨架片段的名称 (甲基、乙基、丙基)。在这些烷基片段上添加一个氢原子，得到对应的烷烃，名称中的“-基”也随之变为“-烷” (-yl 变为 -ane)。它们的结构不言而喻：

#### 碳氢骨架的名称

一个碳	甲烷 (methane)	$\text{CH}_4$	
两个碳	乙烷 (ethane)	$\text{H}_3\text{C}-\text{CH}_3$	
三个碳	丙烷 (propane)	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_3$	环丙烷 (cyclopropane) 
四个碳	丁烷 (butane)	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_3$	环丁烷 (cyclobutane) 
五个碳	戊烷 (pentane)	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$	环戊烷 (cyclopentane) 
六个碳	己烷 (hexane)	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$	环己烷 (cyclohexane) 
七个碳	庚烷 (heptane)	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$	环庚烷 (cycloheptane) 
八个碳	辛烷 (octane)	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$	环辛烷 (cyclooctane) 
九个碳	壬烷 (nonane)	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$	环壬烷 (cyclononane) 
十个碳	癸烷 (decane)	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$	环癸烷 (cyclodecane) 

在碳氢骨架名称中，可以加入官能团的名称，既可以是前缀，也可以是后缀。下面是一些例子。  
数清楚链上碳原子的总数是很重要的，有时官能团内会包含碳原子：戊腈事实上是 BuCN 吧。

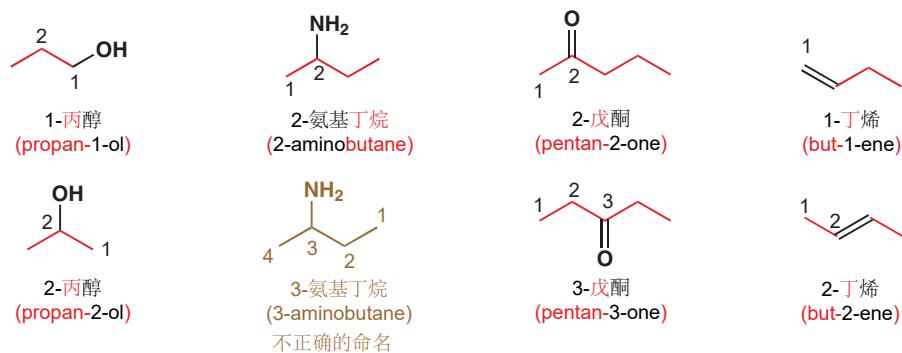


有官能团连接在苯环上的化合物，以相似的方式命名。

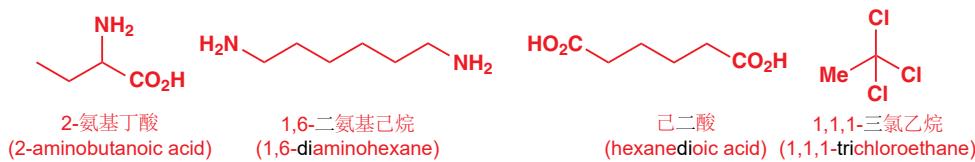


### 用编号定位官能团

有时，名称中会加入编号，用来确定官能团附着的碳原子。上文展示过的那些化合物都不需要编号——检查您是否清楚每一个为什么不需要编号。使用编号时，需要从一端开始数碳原子。在大多数情况下，从任意一端开始数得到的两组编号都可以使用。一些例子会说明这一点。再次注意，一些官能团用前缀表示，一些用后缀表示，编号往往就在官能团名称的前面（注：中文命名中，做后缀的官能团的编号位于碳氢骨架名称的前面，其他与英文相同）。



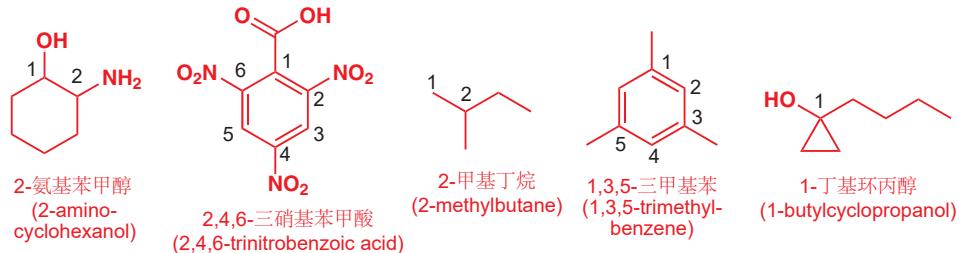
一个碳上最多可以带有四个官能团：在四溴甲烷 (*tetrabromomethane*)， $\text{CBr}_4$  的例子中达到了这一极限。下面是一些其他的多于一个官能团的例子。



编号说明了官能团距碳链一端的距离。同一个化合物中各个官能团在数编号时，都要从相同的一端开始。注意如果有两个以上的相同官能团时，我们使用二、三、四 (di-, tri-, tetra-) 来说明。

对于环状化合物，并没有链端，但我们可以用编号显示两个基团间的距离——从带有其中一个官能团的碳原子开始，沿环计数。这个规则在碳氢骨架是链状或环状时可使用，但很多骨架还带有分

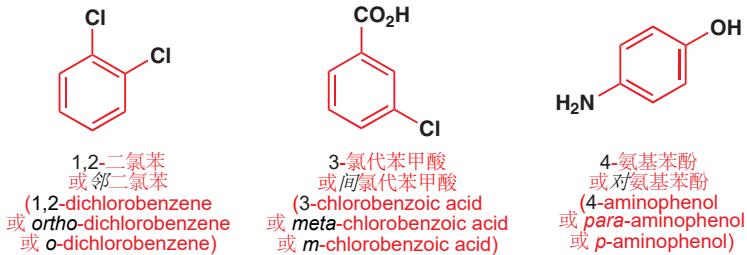
支。我们可以将支链视作官能团处理。



### 邻、间、对 (Ortho, meta, para)

■ *ortho*, *meta*, *para* 常缩写作 o, m, p.

对于取代的苯环，确认取代基位置的另一种方式是选用术语“邻”、“间”和“对”。邻化合物是 1,2-二取代的，间位化合物是 1,3-二取代的，而对化合物是 1,4-二取代的。下面的一些例子说明得更加清晰。



当心！*Ortho*, *meta*, 和 *para* (英文) 在化学中还有其他意思：您可能会遇到正磷酸 (orthophosphoric acid)、亚稳态 (metastable states)、多聚甲醛 (paraformaldehyde) 等名称——这些都与苯环的取代模式无关。

## 化学家真正是如何称呼分子的？

给化合物命名的目的是便于同其他化学家的交流。大多数化学家喜欢用结构图交流，因为结构远比任何种类的化学命名重要。这就是为什么我们详细介绍了结构图的画法，而只泛论了化合物命名。图示的好处在于便于理解，可快速绘制，而且不易误解。

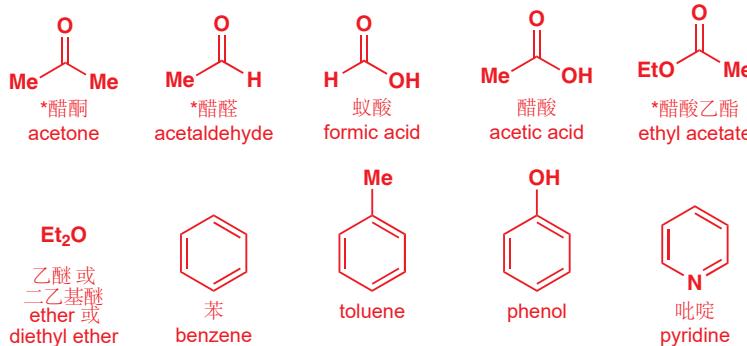
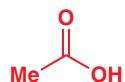
- 永远要在名称的旁边给出图示，除非是非常简单的化合物，如乙醇。

但我们在演讲时，还需要一种能与写作时的图示一样清晰的交流方法。原则上，我们可以用系统命名。然而在实践上，除了最简单的分子外，其他任何物种完整的系统名称都太过笨拙，因而难以用于日常化学演讲。因此有很多替代方法出现了，大多数基于俗称和系统名称的混合。

## 众所周知、广泛使用的简单化合物的名称

一部分化合物被以俗称称呼，不是因为它们的系统名称过于繁琐，而仅仅由于习惯。我们非常了解它们，因此我们使用它们熟悉的名称。

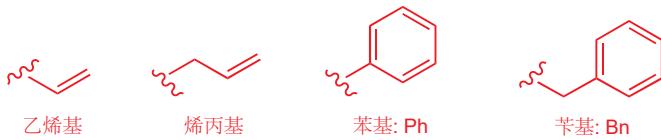
您从前可能见过右侧的化合物，也许它被称作乙酸 (ethanoic acid)，也就是其系统名称。但在化学实验室里，每个人都叫它醋酸 (acetic acid)，也就是它的俗称。下面的几种化合物都具有以上特点（注：多数囿于英文；“\*”指英文俗称常用，但推得的中文俗称并没有其系统名称常用）。



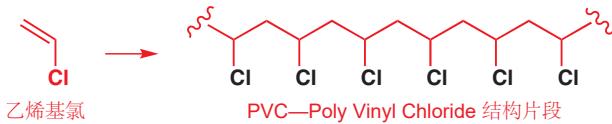
■ 我们还没有要求您去记忆任何分子的俗称，但左侧的 10 个化合物很重要，因此您必须熟记它们（及俗称）。现在就开始记忆。

上述俗称都是长期使用、易于理解的历史名称，它们不像系统命名那样容易混淆。“Acetaldehyde”与“ethanal”都指乙醛，但后者更容易与“ethanol（乙醇）”混淆。

俗称同样拓展到了包含官能团的片段上。丙酮 (Acetone), 乙醛 (acetaldehyde), 和醋酸 (acetic acid) 都含的乙酰基 acetyl/ethanoyl ( $\text{MeCO}-$ ) 可简写作 Ac，化学家通常在书写化合物的化学式时用到这个有机元素符号，例如乙酸  $\text{AcOH}$ 、乙酸乙酯  $\text{EtOAc}$ 。下面的四个片段在机理和结构上都有意义，化学家也赋予了它们特别的名称、有机元素符号，即乙烯基 (vinyl)、烯丙基 (allyl，注：中文里类似的俗称有由远及近的不成文规定)、苯基 (phenyl) 和苄基 (benzyl)。



乙烯基的名称允许化学家给例如乙烯基氯 vinyl chloride（中文多用“氯乙烯”）这样的化合物起简单的俗称，乙烯基氯是聚合得到 PVC（聚氯乙烯 polyvinyl chloride）的原料；但这个名字的重要性，更多地体现在乙烯基与烯丙基反应性的差异上（Chapter 15）。

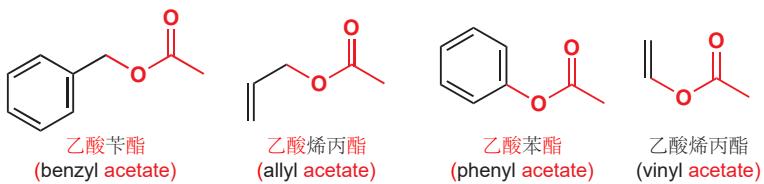


烯丙基的名称来源于大蒜（葱属，*Allium sp.*）。右侧的化合物是大蒜味道和气味的来源，烯丙基构成了它的一部分。

烯丙基和乙烯基是不同的，乙烯基指的是直接与双键  $\text{C}=\text{C}$  碳原子相连，而烯丙基指的是与与  $\text{C}=\text{C}$  双键相邻的碳相连。这种区别极体现在化学反应上：经典的烯丙基化合物非常活泼，而乙烯基化合物相当不活泼。

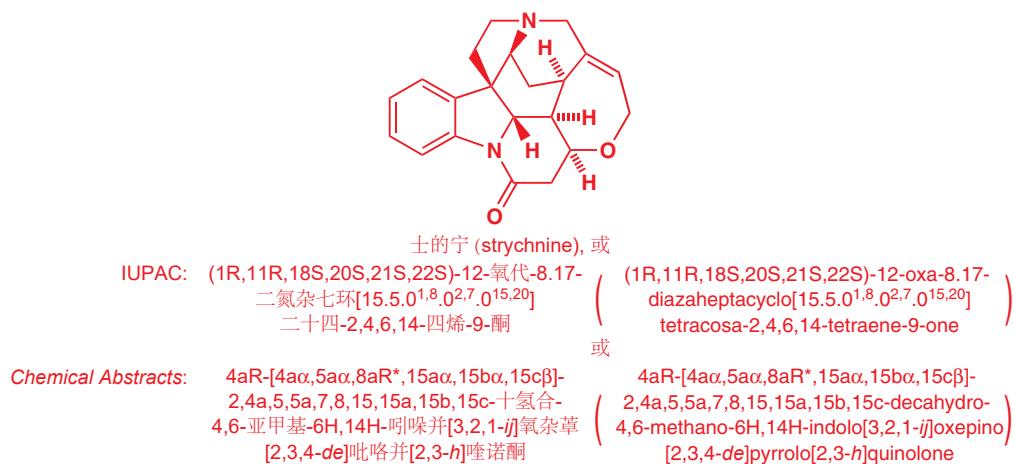
由于一些原因，烯丙基和乙烯基并没有得到有机元素符号，而苄基却有  $\text{Bn}$  作为符号。同样很重要的是不要将苄基与苯基混淆：苯基通过苯上的一个碳原子连接，而苄基通过连接在环上的一个碳原子相连。经典的苯基化合物不活泼，但苄基化合物通常活泼。苯基就像乙烯基，而苄基则像烯丙基。我们将在本章的最后复习您所见过的全部有机元素符号。



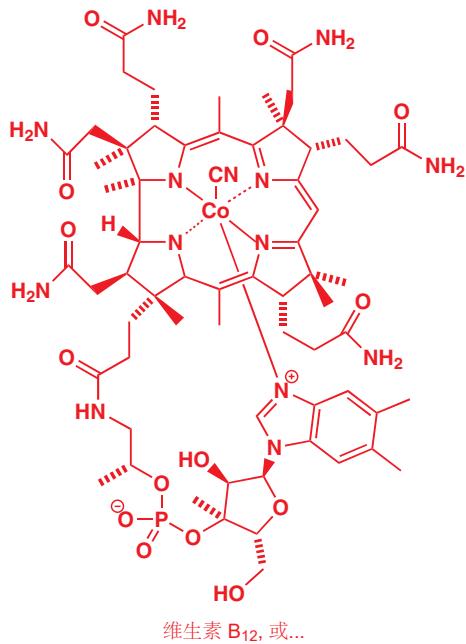


### 更复杂，但仍广为人知的化合物的名称

从自然资源中分离得到的复杂分子通常被赋予俗称，英文这些情况下，系统命名实在不现实！士的宁 (Strychnine) 是一种有漂亮的结构的著名毒药，出现于很多侦探故事中。所有的化学家都称它为士的宁，因为它的系统名称几乎不可读。来自 IUPAC 和 *Chemical Abstracts* (化学文摘) 的两组专家对士的宁的系统命名持有不同的看法。其他类似的还有盘尼西林、DNA，和叶酸。



更离谱的是维生素 B<sub>12</sub>，一种复杂的故络合物，有非常错综复杂的三维结构。不查阅有机化学的高级教科书，没有一个化学家能够背熟它的结构。在查阅时，它所在的索引也应是“维生素 B<sub>12</sub>”，而非它的系统名称。我们甚至还不知道它的系统名称是什么，而且我们也并不很感兴趣。



即使是相当简单的重要分子，例如氨基酸，就有相对容易理解的系统名称，但我们一般还是用其俗称称呼。有一点经验后，俗称很容易记住，也很难搞混。在 Chapter 23 中有完整的氨基酸俗称。



将一点系统命名与俗称混合，是一种获得化合物简单名称的灵活方法。丙氨酸是位于蛋白质中的一种简单氨基酸。苯基取代后，得到的是苯基丙氨酸 (phenylalanine)，是同样位于蛋白质中的一种较复杂的氨基酸。甲苯是通常称呼甲基苯的名称，可以加入三个硝基 (即使命名上的，也是化学反应上可行的) 得到著名的爆炸性三硝基甲苯 (trinitrotoluene) 或 TNT.



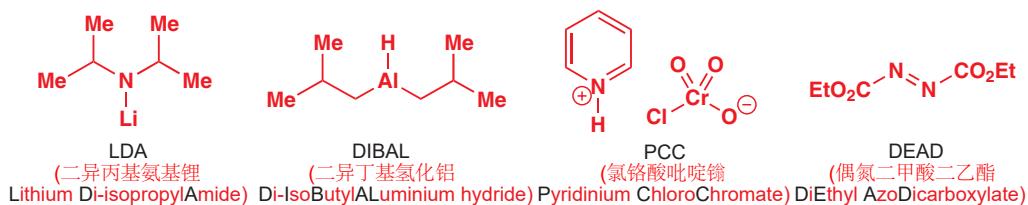
## 用首字母缩略词命名的化合物

一些化合物被我们用首字母缩略词称呼，也就是它们系统名称或俗称的简写。我们刚才看到的 TNT 就是 TriNitroToluene 一词的缩写；首字母缩略词更加常见的用途是定义常用的溶剂或试剂。在本书中，您稍后就会遇到如下溶剂：



■ 这些常用溶剂的名称和结构都需要您记熟。

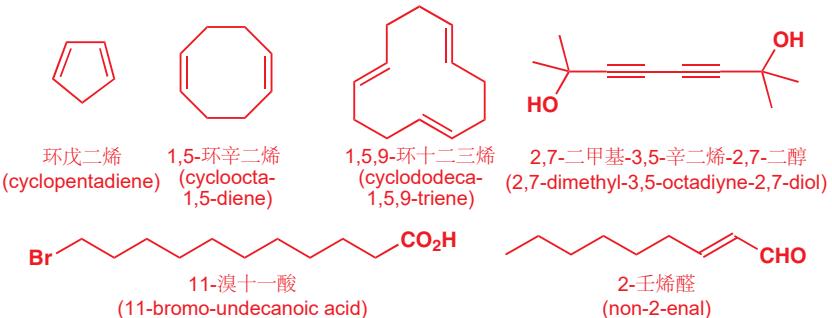
下面的几种试剂通常用首字母缩略词表示，它们的功能会在其他章中向您介绍，您不需要现在知道它们。您可能发现了，首字母缩略词的名称，一些来源于俗称，一些来源于系统名称。



## 化学家使用系统命名称呼的化合物

专业的有机化学家也会使用系统命名，这一点也许会让您奇怪，但事实如此。系统名称真正开始于戊烷

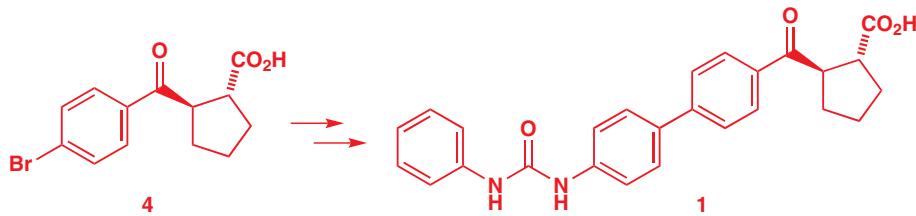
pentane ( $C_5H_{12}$ )，因为前缀 *pent-* 表示的就是五，而 *but-* 并不表示四（中文则开始于十一烷）。对于 5 到 20 个碳的简单的开链，或环状衍生物，如果它们没有正在使用的常用名，化学家就会用系统名称称呼它们。下面是一些例子。



这些名称都包含一个阐述碳氢骨架尺寸的音节：戊 (*penta-*) 指代  $C_5$ ，辛 (*octa-*) 指代  $C_8$ ，壬 (*nona-*) 指代  $C_9$ ，十一 (*undeca-*) 指代  $C_{11}$ ，十二 (*dodeca-*) 指代  $C_{12}$ 。这些名词很容易从结构中的出来，更重要的是，您可以通过名称清楚地知道结构。其中一种可能需要您停下来思考（是哪一种？），但其他几种，当您在没有图示时听到它们，仍能立刻理解。

### 没有俗称的复杂分子

当化学家在实验室合成复杂的新分子，并在一家化学杂志上发表合成方法时，它们会给出完整的系统名称，无论它们可能多长，多笨拙。但在论文的正文部分，或在实验室中讲述他们制得的化合物时，它们会以“那个胺 (the amine)”或“那个烯烃 (the alkene)”称呼。所有人都知道这意味着哪一种胺，哪一种烯烃，因为它们见过那个化合物的化学结构，或多或少都有一些印象。这是谈论几乎任何分子最好的策略：画出结构，并给这个化合物一个“标记”名称，例如“那个胺”、“那个酸”。在书面化学中，最简单的方法是给每个化学结构以“标记”编号。为了说明我们的意思，让我们来谈论一个近期的药物合成。



这个潜在的抗肥胖药物 1，可能能够解决糖尿病患者的胰岛素抵抗，最近，Abbott 实验室由一个简单的中间体 4 合成了它。在已发表的文章中，这个药物被称作“一种选择性的 DGAT-1 抑制剂”，但这对我们的价值并不大。论文的正文部分以“化合物 1”称呼它。这比用它的系统名称明智得多：反-(1*R*,2*R*)-2-(4'-*(3*-苯脲基)联苯甲酰基)环戊基甲酸。对于较简单的中间体，他们根据他们自己想强调的方面曾称作“酮酸 4”、“芳基溴 4”以及“游离酸 4”。注意，最重要的是事先给出它们带有编号的结构图。

### 您该怎样命名分子？

那么您该如何称呼一个分子呢？这其实取决于实际情况，但照着本书中的例子，您不会偏离太

远。本书中我们将使用真正的化学家使用的名称称呼化合物。现在，您并不需要知道所有化合物的常用名词，但您应当在您遇到每一个时，在脑海中留下印象。在传递一个化合物的名称时，您应当先了解它指的是什么结构。

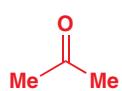
### ● 关于化学名称的建议——按重要性排序的六点

- 先画出结构，然后再考虑名称。
- 熟记官能团的名称（酯、腈，等等）。
- 学习和使用一些化学家常用的简单化合物的名称。
- 在演讲中，用“那个酸”（或其他什么）来称呼，与此同时要指向结构图。
- 掌握系统（IUPAC）命名法的基本原则，并能应用于中等大小的化合物上。
- 找一个笔记本记下您将来会遇到的首字母缩略词、俗称、结构等。

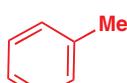
本章中，我们就遇到了很多分子。它们中的大多数是为了阐明观点而引入，因此请不要去背它们的结构！相反，请识别它们包含的官能团的名称。然而，有 14 种简单化合物（其中三种是溶剂）的名称是我们建议您记下的。盖上下表中每列的右侧，并画出这 14 个化合物的结构。

需要熟记的重要结果

丙酮



甲苯



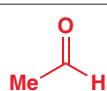
乙醚或二乙基醚



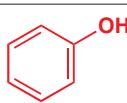
吡啶



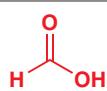
乙醛



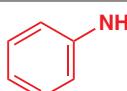
苯酚



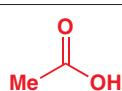
甲酸（蚁酸）



苯胺



醋酸, AcOH



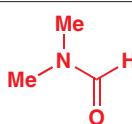
THF, 四氢呋喃



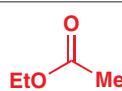
苯



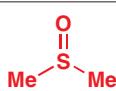
DMF, Me<sub>2</sub>NCHO,  
二甲基甲酰胺



乙酸乙酯, EtOAc



DMSO



这就是命名法这一主题的全部内容——您会发现，在实践中应用这些名称，或听他人谈论这些化合物时，您很快就会记住其中最重要的几个。但我们还要重申，在传递一个化合物名称时，请确保您完完全全知道它指的是什么——画出结构作为检查。

● 回顾：骨架片段名称和“有机元素”

R	烷基		t-Bu	叔丁基	
Me	甲基		Ar	芳基	任何芳香环
Et	乙基		Ph	苯基	
Pr (n-Pr)	丙基		Bn	苄基	
Bu (n-Bu)	丁基		Ac	乙酰基	
i-Pr	异丙基			乙烯基	
i-Bu	异丁基			烯丙基	
s-Bu	仲丁基		X	卤原子	F, Cl, Br 或 I

## 延伸阅读

所有美国的巨本教科书都有涉及结构、形状和分子的绘制的简单章节，但它们倾向于使用 Lewis 结构式（国内称结构简式），所有的原子、键、电子都被画出来，键角则惯用直角。

一个简短而明智的介绍: Oxford Primer *Foundations of Organic Chemistry* by M. Hornby and J. Peach, OUP, Oxford, 1996.

更多关于岩沙海葵毒素的信息: E. M. Suh and Y. Kishi, *J. Am. Chem. Soc.*, 1994, **116**, 11205–11206.

有关苯的环状结构的首次提出的竞争的讨论，见 Alfred Bader 的文章，“Out of the Shadow”刊载于 17 May 1993 发行的 *Chemistry and Industry*.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 有机结构的确定

## 联系

### ► 基础

- 有机分子有哪几种结构 [ch2](#)

### 目标

- 通过 X-射线晶体学 确定结构
- 通过质谱法确定结构
- 通过  $^{13}\text{C}$  NMR 光谱法确定结构
- 对于  $^1\text{H}$  NMR 光谱法的介绍
- 通过红外光谱法确定结构

### ► 展望

- $^{13}\text{C}$  NMR 光谱法是如何帮助定位电子的 [ch7](#)
- 红外光谱法是如何告知我们分子的反应性的 [ch10 & ch11](#)
- 通过  $^1\text{H}$  NMR 光谱法确定结构 [ch13](#)
- 基于光谱法解决未知结构 [ch13](#)

## 概述

### 光谱法可以准确而快速地确定有机结构

您还记得在上一章中，我们曾力劝您将结构建造得符合现实吗？现在我们需要回答这个问题：什么是真实结构？我们如何知道某种分子的真实结构？请您一定要清楚这一点：我们的确知道分子的真实结构。您如果认为现代有机化学最重要的进步是能够快速地，精准地确定分子的结构的话，那么您非常正确。一言以蔽之：光谱法赋予了我们这个能力。

#### ● 什么是光谱法？

与分子相互作用的射线或波	光谱法	能告诉我们什么
X-rays 射线被原子散射	测量散射图案	键长和键角
无线电波使原子核共振	绘制共振频率的图表	碳氢骨架的连接和对称性
红外波使键振动	绘制吸收的图表	分子中的官能团

## 本章的结构

我们首先会考虑以一个整体考虑结构的确定，然后介绍三种不同的方法：

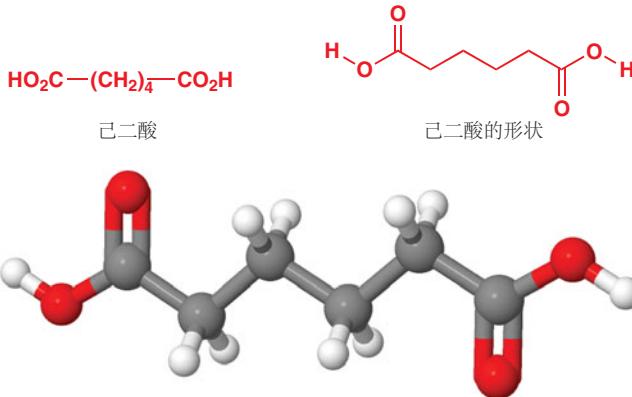
- 质谱法 mass spectrometry (确定分子质量和原子组成)；
- 核磁共振法 nuclear magnetic resonance (NMR) spectroscopy (确定对称性、分子中的支链，和连接方式)；
- 红外光谱法 infrared spectroscopy (决定分子中的官能团)。

如果您想更细致地了解我们讨论的光谱方法中的任何一种，您应当参考本章末尾“延伸阅读”一节中列出的专业书籍。

在这些中，NMR 要比所有其他的加起来都重要，因而我们也将在 Chapter 13 更细致地讨论它。然后，在我们讨论了较广泛的一些分子后，将会在用于综述的 Chapter 18 中将这些观点整合，并向您展示，未知的结构是如何真正被确定的。

### X-射线是分子结构的终审

在 Chapter 2 中，我们建议您以锯齿形(zig-zag)绘制分子，而非以键角为  $90^\circ$  或  $180^\circ$  的直线绘制。这是因为我们知道它们是锯齿形的。“直”链状的二酸的 X-射线晶体结构，如下所示。您可以清晰地看出锯齿形的链，平面的羧基，和朝向您、远离您的氢原子。因而，很明显，如第二种画法那样，将分子画得更加真实，是有意义的。



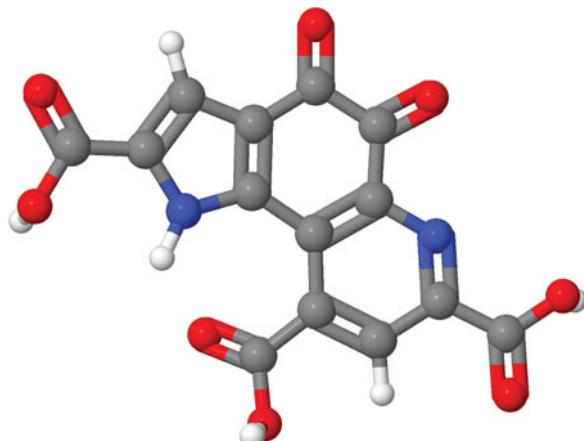
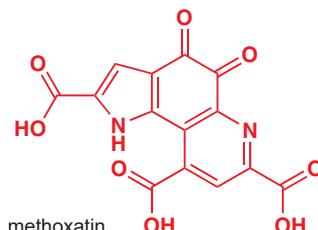
X-射线晶体结构，是通过使化合物的晶体样本衍射 (diffract) X-射线 来确定的。由所得的衍射图案，可以推断出原子在分子中精确的空间排布——这通常不包括氢原子，因为氢原子太轻，无法衍射 X-射线，它们的位置可由结构中其它部分的位置推断出。X-射线 比任何其他方法都能更好地回答的一个问题是：分子采取什么样的形状。它还被用于解决另一个重要的问题，即确定未知化合物的结构。例如，有一些地下细菌 (subterranean bacteria) 用甲烷作为能源，它们可以将甲烷转化为有用的物质，这非常神奇，化学家想知道这一过程是如何完成的。1979 年，他们发现该细菌使用一种被他们称为“methoxatin (吡咯并喹啉醌)”的辅酶 (coenzyme) 使甲烷氧化为甲醇。Methoxatin 是一种新的化合物，结构尚未确定，并且仅能非常少地获得。用 NMR 确定它的结构十分困难，最终是通过 X-射线晶体学确定了它是一种多环三羧酸。

■ 辅酶是一种与酶共同 (hand-in-hand) 催化反应的生化试剂。



Interactive structure of methoxatin

■ 俗名“methoxatin”有其系统表述：4,5-二氢-4,5-二氧代-1H-吡咯并[2,3-f]喹啉-2,7,9-三羧酸。两种都是有效的名称，但常用的名词是哪种则不言而喻。





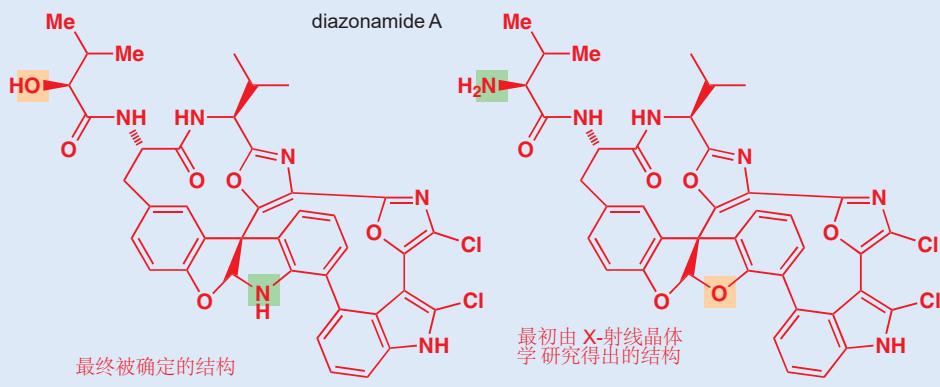
## X-射线晶体学 有其局限性

X-射线晶体学既然如此强大，为什么我们还需要其他方法呢？有两点原因：

- X-射线晶体学通过X-射线通过电子时的衍射得以工作，并且要求样品为晶体。如果一个有机化合物是液体或并不能良好结晶的固体，那么它的结构就不能用这种方式确定。
- X-射线晶体学本身就是一门科学，需要专业技能，并且结构的确定需要较长时间。现代方法将时间缩短到了几小时，或更短，但尽管如此，与之对比的配有机机器人的现代NMR设备，则可以在一夜之间处理超过100份光谱。我们通常会例行使用NMR；而对于较困难的未知结构的确定，和重要分子的具体形状的确定，还会使用X-射线。

### X-射线晶体学 并不是万无一失的

X-射线晶体学通常不能“看到”H原子，因此您要认识到，它并不是万无一失的：它仍可能判断错误。一个著名的例子有关于抗生素 diazonamide A，在1991年（从海洋有机体中分离出该化合物）至2001年（错误被意识到前）之间，人们都认为它的结构是下方右侧的。它与下方左侧的结构质量相同，而X-射线晶体学并不能区分开O和N。但当右侧的化合物被合成出来时，错误才变得明显，它的真实结构于2002年在左侧的结构被合成出来，并被证实与天然产物等价时才得以确定。



## 光谱法结构确定概述

将您自己置身于下面的专业化学家经常遇到的情形：

- 您从化学反应中注意到了一个出乎意料的产物。
- 您从植物提取物中发现了一个先前未知的化合物。

- 您侦察到了一种可疑的食物污染物，并需要确定它是什么。
- 您在药物的批量生产中定期测量它们的纯度。

在这些情形中，也许除去第二个，您都需要一个快速而可靠的答案。假设您正在测量心脏药物普萘洛尔 (propranolol) 的纯度。您会首先想知道分子量 (相对分子质量)，和原子组成，它们可以来源于质谱。普萘洛尔的分子量为 259，原子组成为  $C_{16}H_{21}NO_2$ 。下一步，您需要得知碳骨架——来源于 NMR 对如下所示的三个结构片段的揭示。



■ NMR 不会真的将分子断裂为碎片，但它将分子视作了连接在一起的碳氢碎片。

NMR 观察所得的碎片有很多组合方式，在此阶段，您不能确定氧原子以 OH 基存在，还是以醚存在，不能确定氮原子是否以胺存在，也不能确定 Y 和 Z 是否为同一个原子，例如 N。从强调官能团的红外光谱中，您可以得到更多的信息，它会阐明，分子中有一个 OH，氮原子以 NH 存在而非其他官能团，例如 CN 或  $NO_2$ 。目前仍然剩下很多种可能的结构，它们可以通过  $^1H$  NMR 所揭示的细节区分。在本章中，对于  $^1H$  NMR 的讨论会十分简要，因为它比  $^{13}C$  NMR 更为复杂，我们将在 Chapter 13 中单独讨论。

现在，我们必须逐个研究这些方法，并且了解，它们是如何为我们提供有关普萘洛尔分子的信息的。

### ● 每种光谱方法都能告诉我们什么

光谱方法和它们所做的事	能告诉我们什么	提供的数据类型
质谱可为分子称重	分子量 (相对分子质量) 和原子组成	$259; C_{16}H_{21}NO_2$
$^{13}C$ NMR 可揭示不同的碳原子核	碳骨架	没有 $C=O$ 基；芳环中有十个电子；有两个碳挨着 O；还有三个饱和 C 原子
红外光谱揭示化学键	官能团	没有 $C=O$ 基；有一个 OH；一个 NH
$^1H$ NMR 揭示所以不同的 H 原子核	H 原子的区分	两个甲基；芳环上有六个 H 原子；挨着 O 的碳上有两个 H 原子；挨着 N 的碳上有三个 H 原子

## 质谱法

### 质谱法为分子称重

给中性分子称重并不简单，质谱仪的工作方式，是称量带电的离子：电荷使分子可被电场控制。因此，质谱仪分为以下三个组成部分：

- 使分子汽化并离子化为带电的离子束的部分
- 使相同 质量:电荷比 (质荷比) 的粒子束聚集，比例不同的分开的部分
- 检测离子的部分

■ 质谱法 (Mass spectrometry) 与其他形式的光谱法 (spectroscopy) 不同，这是由于它测量的是质量而不是能量的吸收。

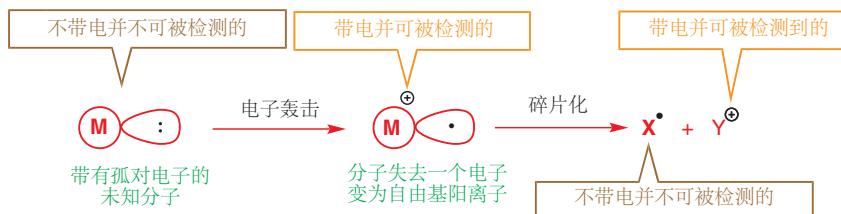
注：此处的“离子化/电离 (ionize)”与电解质的“电离 (dissociate/ionize)”不同，请注意区分。

所有常用种类的质谱仪都在高真空中操作，并用多种方法中的一种，使中性分子转化为离子，最常用的几种是电子轰击 (electron impact)，化学电离 (chemical ionization)，和电喷雾 (electrospray)。



## 电子轰击质谱法

电子轰击 (electron impact, EI) 质谱法中，分子会被高能电子轰击，这会使结合较弱的电子被击离分子。如果您认为不好理解，请想象对着一堵砖墙仍砖块：砖块不会粘在墙上，而是会将松散的砖块从墙的顶部敲下来。失去一个电子的同时会留下另一个未成对电子，和一个正电荷。失去的电子会是能量相对较高的一个 (来自墙的顶部的砖块)，通常是不参与成键的，例如孤对电子。

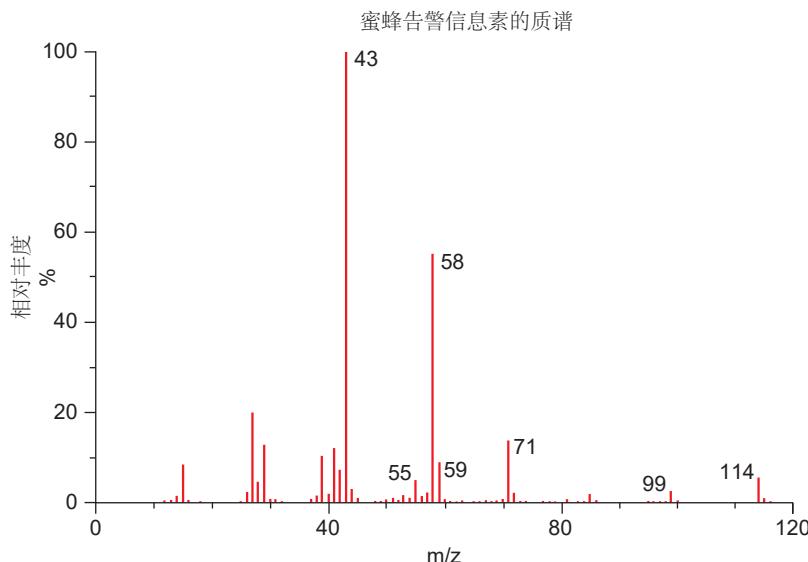


若是氨，则会得到  $\text{NH}_3^{+\bullet}$ ，若是酮，则会得到  $\text{R}_2\text{C}=\text{O}^{+\bullet}$ 。这些不稳定的物种被称为**自由基阳离子 (radical cations)**，带电后，它们便可以被电场加速，并聚集在检测器 (detector) 上，检测器根据离子被电场偏转的距离检测离子。自由基阴离子抵达检测器仅需大约  $20 \mu\text{s}$ ，有时它们仍会在抵达前碎片化，但其他的离子仍可被检测。这些碎片往往比它们的“母体”分子离子 (molecular ion) 质量更低，因此通常，我们关注的是质谱中观测到的最重的离子。

### 自由基阳离子

大多数分子中的电子都是全部成对的，而**自由基 (radicals)** 包含未成对电子。带有负电荷的分子是**阴离子 (anions)**，带有正电荷的分子是**阳离子 (cations)**。**自由基阳离子**和**自由基阴离子**仅仅表示的是既带电荷，又包含未对电子的物种。

有代表性的 EI 质谱图：



这种化合物已被识别是工蜂在觅食时分泌的一种信息素，以防止它的同伴们前去相同的，已被采过的花蜜资源。当然仅有很少量的化合物可用于分析，但这不重要：质谱法对于微克级样本也是成功的。上一页的光谱图表明分子量为 114，即观察到的最大的分子量：事实上这个分子是挥发性酮，2-庚酮。



## 化学电离、电喷雾质谱法和其他方法

■ 如果您对如何根据碎片图案得到结构感兴趣,请查阅本章结尾列出的专业书籍。

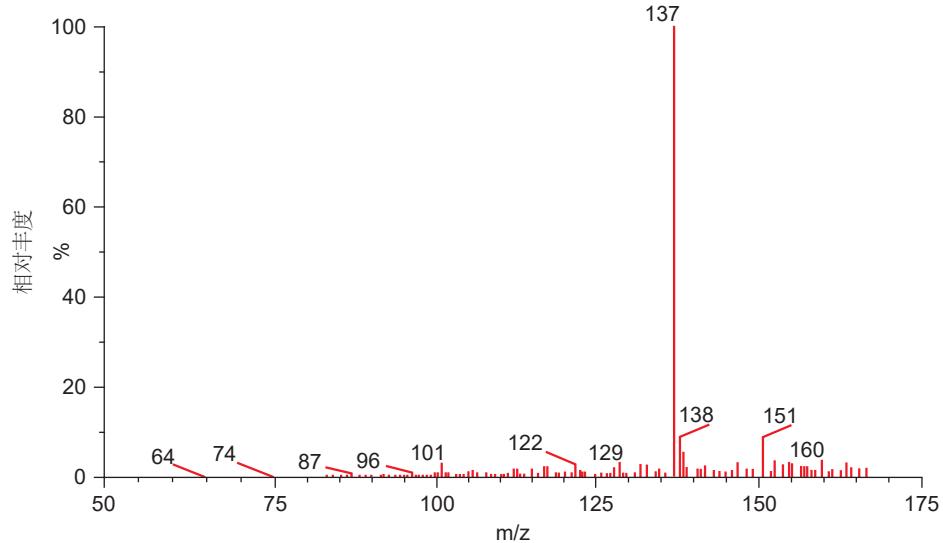
- 我们不会太过详细地讨论离子化技术/电离技术：在此阶段，知道有一些方法能够温和地使分子离子化，并使得质量可被确定就足够了。

碎片化是 EI 质谱法的一个问题，对于不牢固的分子，轰击电子的能量足以使之彻底变为碎片，无法得到任何分子离子。有用的信息可从碎片的图案中得出，但一般来说，以称量一整片分子为目标仍是较有用。用许多其他的技术可以实现这一点，其中最常用的是化学电离 (CI) 和电喷雾 (ES)。

化学电离是通过将一种气体，例如氮气，与质谱仪的底物混合而完成的。电子对  $\text{NH}_3$  的轰击可能导致通过质子转移得到一些  $\text{NH}_4^+$ ，它可以与底物反应得到带电的络合物，并被电场加速。化学电离质谱法测量到的分子量通常相对底物的分子量来说是  $M + 1$  或  $M + 18$  ( $\text{NH}_4^+$  的分子量)。电喷雾质谱仪中，底物会以气溶胶形态 (aerosol) 被离子化 (注：可用于称量一些难挥发的底物)，此时有钠离子的存在，这意味着通常观察到的质量是  $M + 1$  和  $M + 23$ ，如果离子化形成阴离子，则为  $M - 1$ 。

如下是 2-庚酮 的电喷雾质谱图。注意观察，单个分子离子是多么清晰可见啊，但其分子量为 137，比(真正的)分子量 114 多 23(换句话说，所得的质量是  $M + Na^+$ )。

## 2-庚酮的电喷雾质谱图

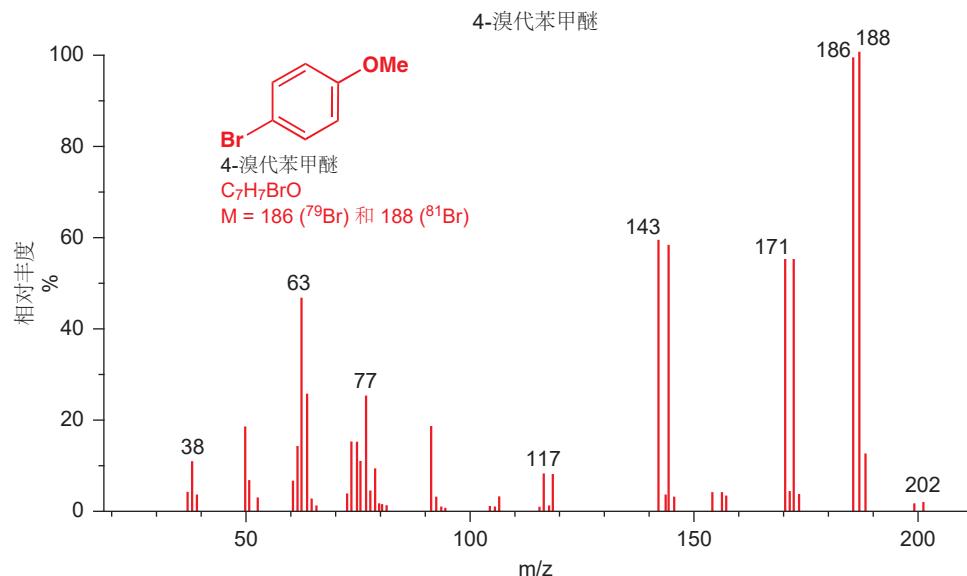


质谱法测定同位素

大多数元素以多于一种同位素 (isotope) 存在。通常，其中一种同位素占该元素原子的绝大部分 (也许是 >99%)。但对于某些元素，几种同位素的原子可能都在样品总体中占据可观的比例。例如氯，

通常是<sup>35</sup>Cl 和<sup>37</sup>Cl 3:1 的混合 (35.5 为氯的平均相对原子质量), 而溴则是<sup>79</sup>Br 和<sup>81</sup>Br 1:1 的混合 (平均原子量 80). 由于质谱仪称量的是孤立的分子, 因此不会包含平均; 相反, 它测得的是每个分子的真实质量, 无论它包含哪种同位素。

例如, 如下的芳基溴的分子离子在 EI 质谱图中, 在 186 和 188 处有两个强度大抵相同的峰。如果检测到两个强度相等, 且间距 2 质量单位的分子离子, 这就暗示分子中含有溴。

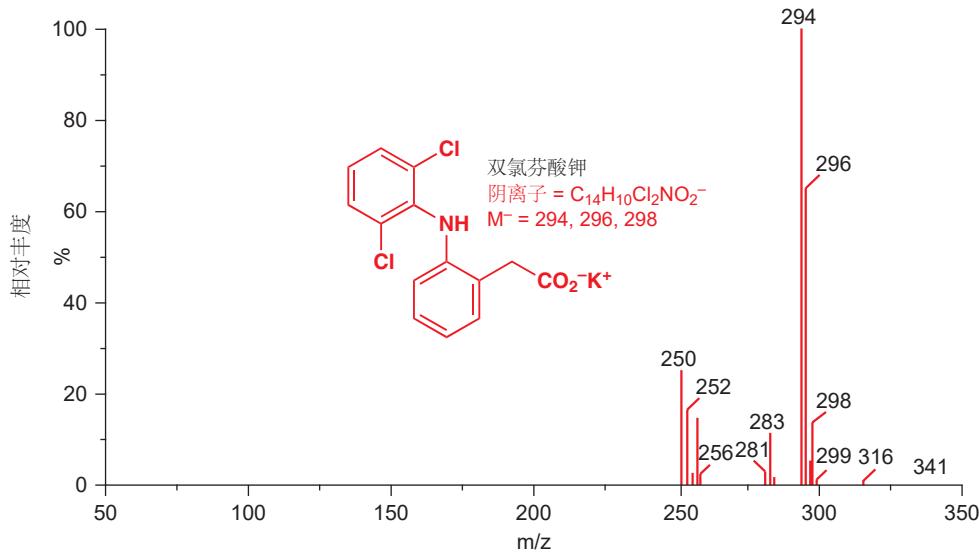


含氯分子的质谱图也可以类似地分辨出来, 同样是两个间距两个质量单位的峰, 但比值为 3:1, 来源于<sup>35</sup>Cl 和<sup>37</sup>Cl 3:1 的同位素比例。

那么若多于一个 Br 或一个 Cl 时会如何呢? 下面是一个例子: 止痛药双氯芬酸 (diclofenac). 该光谱由市面上出售的药片中获得, 药片中含有活性成分的钾盐 (并会在胃的酸性环境中被质子化为活性成分)。

■ 双氯芬酸在这方面与水溶性阿司匹林很相似: 见 Chapter 8, p. 163.

ES 光谱图以三个峰显示羧酸根阴离子, 位于 294, 296, 和 298. 峰的相对大小可以由每个 Cl 原子可为<sup>35</sup>Cl 的 75% 可能性, 和为<sup>37</sup>Cl 的 25% 可能性得出。比例因此为  $\frac{3}{4} \times \frac{3}{4} : 2 \times \frac{3}{4} \times \frac{1}{4} : \frac{1}{4} \times \frac{1}{4}$  即 9:6:1.



关于常见的带有多于一种  $>1\%$  风度的同位素的元素的总结

元素	同位素	近似比例	确切比例
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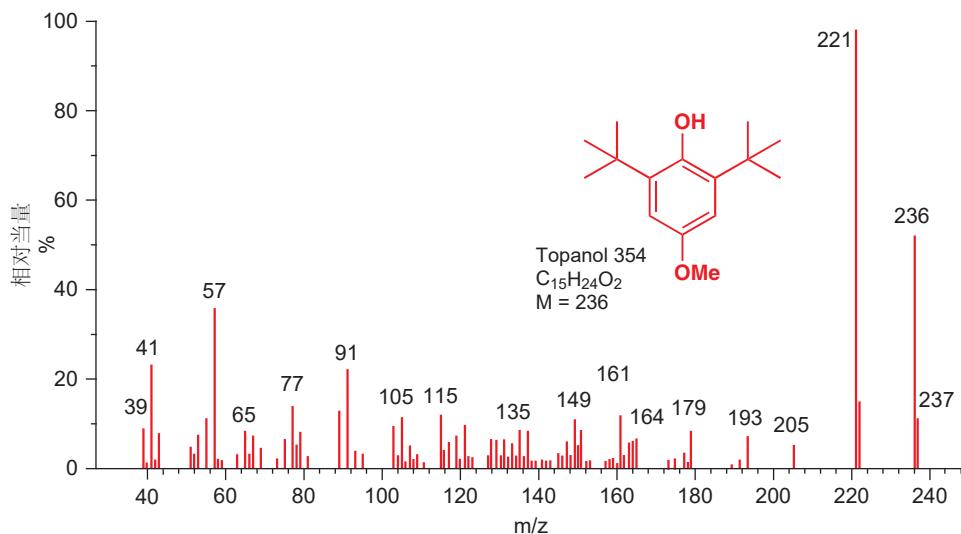
碳	$^{12}\text{C}$ , $^{13}\text{C}$	98.9:1.1	
氯	$^{35}\text{Cl}$ , $^{37}\text{Cl}$	3:1	75.8:24.2
溴	$^{79}\text{Br}$ , $^{81}\text{Br}$	1:1	50.5:49.5

H, N, O, S, P, F 和 I 中不同于  $^1\text{H}$ ,  $^{14}\text{N}$ ,  $^{16}\text{O}$ ,  $^{31}\text{P}$ ,  $^{32}\text{S}$ , 和  $^{128}\text{I}$  的同位素数量都很少。真正反常的是锡，锡以 10 种不同的稳定同位素的混合存在，主要的几个为  $^{116}\text{Sn}$  (15%),  $^{117}\text{Sn}$  (8%),  $^{118}\text{Sn}$  (24%),  $^{119}\text{Sn}$  (9%),  $^{120}\text{Sn}$  (33%),  $^{122}\text{Sn}$  (5%), 和  $^{124}\text{Sn}$  (6%)。现实中，任何元素贴切准确的同位素比例都因其来源而异，这一事实可以提供有用的方法医信息。

### 碳次要但却重要的同位素 $^{13}\text{C}$

很多元素中次要同位素都低于 1% 水平地出现，因而通常不重要，但我们不能忽略了普通碳中出现的 1.1% 的  $^{13}\text{C}$ ，主要同位素当然为  $^{12}\text{C}$ 。另一种同位素， $^{14}\text{C}$ ，有放射性，可用于碳定年法 (carbon dating)，但它的天然风度很微小。稳定的同位素  $^{13}\text{C}$  还是 NMR 活性的 (NMR active)，我们稍后会考察。如果您仔细观察本章目前为止出现过的全部质谱图，您就会发现每一个峰旁边都会有一个小峰比其高出一个质量单位：它们来源于包含  $^{13}\text{C}$  而不是  $^{12}\text{C}$  的分子。这些峰的确切高度是实用的，它们可以暗示分子中碳原子的数目。每个碳都有 1.1% 的几率是  $^{13}\text{C}$  而非  $^{12}\text{C}$ ，因此 C 原子数越多，几率会越大。如果一个分子离子中含有  $n$  个碳原子，则  $\text{M}^+$  比  $[\text{M} + 1]^+$  的比例应为  $100:(1.1 \times n)$ 。

观察如下的燃料添加剂 Topanol 354 的谱图，结构与分子式已经给出。它包含 15 个碳原子，因此每个分子有 16.5% 的几率包含一个  $^{13}\text{C}$  原子，您可以清晰地看出位于 237 处相当大的  $\text{M} + 1$  峰。我们可以忽略带有两个  $^{13}\text{C}$  原子的可能性，因为这种可能性很小。



- 对于任何质谱图，往往首先观察最重的峰。注意分子中是否有氯或溴，并检查  $\text{M}^+$  比  $[\text{M} + 1]^+$  的比例是否与您预期的碳原子数大致匹配。

### 高分辨率质谱法可以确定原子组成

普通质谱可以告诉我们分子的分子量 (MW)：例如，对于 p. 48 的蜜蜂信息素，即使我们不知道它的结构，也可以轻易地知道它的 MW 为 114。在此基础上，如果我们想推断出  $\text{C}_7\text{H}_{14}\text{O}$ ，那么我们需要更多的信息，因为 114 可以表示其他很多事物，例如  $\text{C}_8\text{H}_{18}$  或  $\text{C}_6\text{H}_{10}\text{O}_2$  或  $\text{C}_6\text{H}_{14}\text{N}_2$ 。尽管如此，对于这些“同一”分子量的不同原子组成方式，如果我们知道确切的分子量，我们仍然可以区分它们，因为单个同位素的原子量并非整数（除了用作定义的  $^{12}\text{C}$ ）。下表给出了一些精确到五位小数的原子量，五位小数是您获得有意义的结果所需要的精确度。通过被称为高分辨率质谱法 (high-resolution mass spectrometry) 的技术可以获得这样精确的分子量测量值。

确切原子量不是整数，是因为质子 ( $1.67262 \times 10^{-27} \text{ kg}$ ) 和中子 ( $1.67493 \times 10^{-27} \text{ kg}$ ) 在质量上有细微的区别，事实上电子也有质量 ( $9.10956 \times 10^{-31} \text{ kg}$ )。

## 常见核素的确切原子量

元素	同位素	原子量	确切原子量
氢	<sup>1</sup> H	1	1.00783
碳	<sup>12</sup> C	12	12.00000
碳	<sup>13</sup> C	13	13.00335
氮	<sup>14</sup> N	14	14.00307
氧	<sup>16</sup> O	16	15.99492
氟	<sup>19</sup> F	19	18.99840
磷	<sup>31</sup> P	31	30.97376
硫	<sup>32</sup> S	32	31.97207
氯	<sup>35</sup> Cl	35	34.96886
氯	<sup>37</sup> Cl	37	36.96590
溴	<sup>79</sup> Br	79	78.91835
溴	<sup>81</sup> Br	81	80.91635

对于 p. 48 上的蜜蜂信息素，精确的分子量为 114.1039。如下的表格对比了 MW 近似值为 114 的几种可能原子组成，因而结果是确定的。被确定了。在精确到三位小数的分子量中，仅有  $\text{C}_7\text{H}_{14}\text{O}$  这一组成符合观察值。看到这两个数字时，您可能认为匹配得并不好，但请注意观察这四者以百万分之一级表示的误差，仅有一个答案脱颖而出。注意，即使精确到两位小数，对于区分这四种化合物也是足够的了。

## 蜜蜂告警信息素确切质量确定

组成	计算所得的 $\text{M}^+$	观察所得的 $\text{M}^+$	ppm 级误差
$\text{C}_6\text{H}_{10}\text{O}_2$	114.068075	114.1039	358
$\text{C}_6\text{H}_{14}\text{N}_2$	114.115693	114.1039	118
$\text{C}_7\text{H}_{14}\text{O}$	<b>114.104457</b>	<b>114.1039</b>	5
$\text{C}_8\text{H}_{18}$	114.140844	114.1039	369

- 在本书的其余部分，每当我们声明一个分子具有一定的原子组成时，您便可以假定它是通过分子离子的高分辨率质谱确定的。

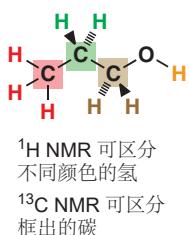
上表中您可能没有注意到的一件事是，没有一项只包含一个氮原子。两个氮原子的，有；一个氮原子的，没有！这是因为，任何同 C, H, O, S 组成的完整分子，若仅有一个氮原子，则分子量必定为奇数。这是因为 C, O, S, 和 N 的原子量均为偶数——只有 H 的原子量为奇数。C, O, S, 和 N 中，只有氮可以形成奇数根键 (3)。带有一个氮原子的分子中氢原子的数目必定为奇数，因而分子量也为奇数。

## ● 快速数氮 (对于仅包含 C, H, N, O, 和 S 中的元素的分子)

分子量为奇数的分子必定含有奇数个数的氮原子。分子量为偶数的分子必定含有偶数个数的氮原子，或不含氮原子。

## 核磁共振法

### 它能做什么？



核磁共振 (NMR) 让我们能检测原子核，并了解它们在分子中所处的环境的种类。在例如丙醇的分子中，羟基中的氢原子明显地与碳骨架上的氢原子不同——例如它可以被金属钠移去。NMR ( $^1\text{H}$ , 或质子 NMR) 可以容易地通过见侧氢原子处在的环境以区分这两种类型的氢。此外，它还可以区分其他所有存在的不同种类的氢原子。同样，碳 (更确切地说是  $^{13}\text{C}$ ) NMR 可以容易地区分三种不同的氢原子。NMR 是的作用极为广泛：它可以扫描人体大脑 (见图片)，原理仍是相同的：检测不同环境中的原子核 (由此检验原子)。



■ 医学上使用的 NMR 通常被称为磁共振成像 (magnetic resonance imaging, MRI)，为了担心患者警惕有关核的事。

### NMR 使用强磁场

想象我们能“关闭”地球磁场的时候。导航的制作将更加困难，因为任何罗盘都没有用了，它们的指针会随机地指向任何方向。然而，一旦我们重新打开磁场，它们便都会指向北方——它们的最低能量状态。现在，如果我们想强迫指针指向南方，那么我们会需要耗费能量，并且当然，一旦我们放开手，指针会重新回到它的最低能状态，指向北方。

类似的，当一些原子核被放置在磁场中时，它们会像微小的罗盘指针一样，根据它们的“指向”持有不同的能级。(我们稍后会阐释原子核如何“指向”某个位置。)一个真正的指南针可以在 $360^\circ$ 间旋转，并且应有无限个数目的不同能级，它们在能量上都比“基态 (ground state)”(指向北方)能量高。幸运的是，对于原子核则简单多了：它的能级，就像电子的能级一样 (您将在下一张了解的)，是量子化的 (quantized)，它仅可采取特定的能级。这就像一个只能指向，比如南、北的指南针，或者是一个只能指向东、西、南、北的指南针，在这四种情况之间什么都没有。正如指南针，若想感受地球磁场的影响，则必须由磁性材料制成一样，只有某些原子核是“磁性的”。很多 (包括“一般的”碳-12,  $^{12}\text{C}$ ) 原子核根本不与磁场相互作用，因而不能被 NMR 设备观察到。对于本章来说重要的，是表现出磁性的，碳的次要同位素  $^{13}\text{C}$ , 氢在地球上风度最大的同位素  $^1\text{H}$  也有这种性质。当将  $^{13}\text{C}$  或  $^1\text{H}$  原子置于磁场中时，它会有两种可行的能量状态：它既可以与磁场一致 (aligned with) 地摆放 (您可能会说，“向北”)，这会是最低能状态，也可以与磁场相反 (aligned against) 地摆放 (“向南”)，较高能。



■ 左侧的图片是一台有代表性的 NMR 仪。胖胖的圆柱体是过冷的磁铁。悬挂在其上的设备是一个自动进样器 (automatic sample changer), 前面的控制台用于控制器。

原子核允许磁相互作用的性质,  $^{13}\text{C}$  和  $^1\text{H}$  拥有, 而  $^{12}\text{C}$  没有的性质, 是自旋 (*spin*)。如果您设想  $^{13}\text{C}$  和  $^1\text{H}$  原子核自我旋转, 您便可了解到, 原子核是如何朝向一个方向的——是它自旋的轴 (*axis*) 的方向与磁场方向一致或相反。

让我们暂时回到罗盘的例子上。如果您想让一个罗盘指针偏离指北, 那么您必须推动它——此时会消耗能量。如果您将罗盘放在一个条形磁铁旁, 那么向磁铁的吸引力要远大于向北极的吸引力, 指针现在会指向磁铁。此时若想推动它, 则也要困难得多。推动罗盘指针的困难程度, 取决于磁场的强度, 也取决于指南针的磁化程度——如果它仅被弱磁化, 那么推动它就容易得多; 而如果它根本没有被磁化, 它就可以自由旋转。

同样, 对于在磁场中的原子核, 核自旋 (*nuclear spin*) 与磁场一致和与磁场相反的两种状态的能量差, 取决于:

- 磁场有多强,
- 原子核本身的磁性。

磁场越强, 两种原子核的排列方式的能量差就越大。现在我们要说明, 关于 NMR 有一个不幸的事情: 核自旋与磁场一致, 或与磁场相反的能量差真的非常小——如此小, 使得我们需要一个非常非常强的磁场, 以观察区别。

**核自旋是量子化的, 并有其符号  $I$ 。**原子核可采取的不同能级的个数由特定核素的  $I$  值决定。核自旋  $I$  可以有多种值, 例如  $0, \frac{1}{2}, 1, \frac{3}{2}, \dots$  能级的数目由  $2I + 1$  得到。例如  $^1\text{H}, I = \frac{1}{2}; ^2\text{H} (= \text{D}), I = 1; ^1\text{B}, I = \frac{5}{2}; ^{12}\text{C}, I = 0.$

## NMR 也使用无线电波

磁场中的  $^1\text{H}$  或  $^{13}\text{C}$  原子核可以有两种能级, 将原子核从较稳定的状态翻转 (*flip*) 到较不稳定的状态需要能量。所需的能量很小, 可以由无线电波频率的低能电磁辐射提供。无线电波将原子核从较低能状态转到较高能状态。关掉无限脉冲, 原子核又回到较低能状态。它这一过程发生时, 能量会重新释放, 而这 (微小的无线电频率的电磁辐射脉冲) 便是我们要检测的。

我们现在可以总结 NMR 光谱仪工作的原理。

1. 未知化合物的样本被溶解在合适的溶剂中, 装入一个窄管中, 并放入一个非常强的电磁铁。

为了使样品中的缺陷 (*imperfections*) 均匀, 用快速气流使管子高速旋转。在磁场中, 任何

**NMR 光谱仪中包含非常强的电磁铁。**地球磁场的场强在 30 到 60 微特斯拉之间。而 NMR 中使用的有代表性的磁铁的场强在 2 到 10 特斯拉之间, 比地磁场强约  $10^5$  倍。这些磁铁是危险的, 不能将任何金属物件带入它所处的房间: 糊涂的工人将金属工具箱牢固地吸在 NMR 磁铁上的故事有很多。即使是使用了非常强的磁铁, 能量差仍然很小, 原子核对较低能状态的偏好也很小。幸运的是, 我们可以检测这种小偏好。

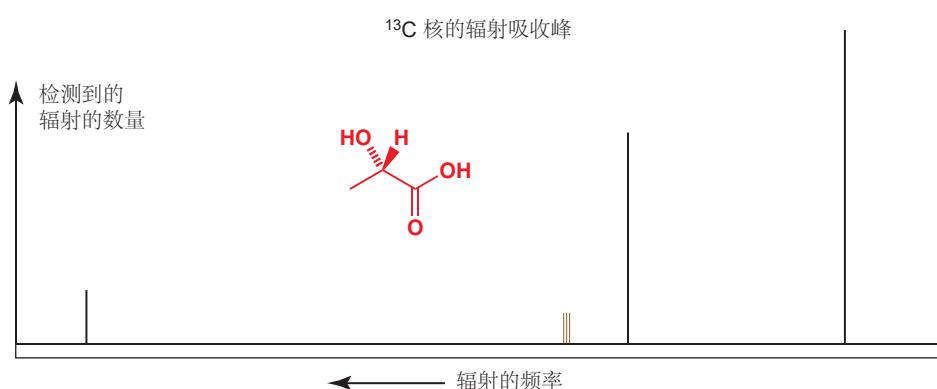
无线电波的能量非常非常低。您可能知道——如果不知道，将来也需要知道的——与电磁辐射相关的能量有关于波长  $\lambda$  的关系式为：

$$E = hc/\lambda$$

当  $h$  和  $c$  (普朗克常数和光速) 是常量时。波长以米为单位的无线电波，比波长在 380 nm (紫) 和 750 nm (红) 的可见光的能量低数百万倍。

带有核自旋的原子核都会拥有几种不同的能级，确切个数取决于核自旋的数值。对于  $^1\text{H}$  和  $^{13}\text{C}$  NMR，存在两个能级。

2. 用无线电频率能量的短脉冲照射样品。这会扰乱两个能级间的平衡：一些吸收了能量的原子核会被激发到较高能级。
3. 脉冲结束后，原子落回低能级时释放的辐射会被检测，使用一种复杂的无线电接收器。
4. 经过大量的计算机运算，结果会以强度 (intensity, 即吸收的数量) 与频率 (frequency) 的形式被显示出来。下面是一个例子，我们将在后面详细讨论。



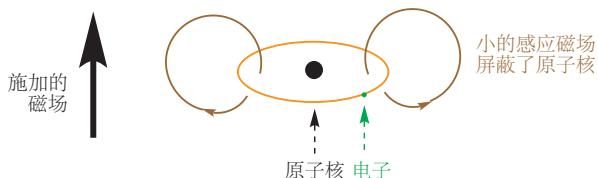
■ 这里的“共振”是一个很好的比喻。如果您有一架钢琴，您按下一个按键以释放一根琴弦，然后用力敲击琴盖，那么您就会听到您按下的那个音符，并且仅有它会持续地发出声响——它发生了共振。敲击声涵盖很多频率，但只有合适的频率会被琴弦吸收，并重新发出。化学上，“共振”一词还有另一种用法，将在 Chapter 7 涉及，那种用法没有这种用法贴切：这两者没有关系。

### 为什么化学环境不同的原子核吸收不同频率的能量？

上方的光谱中，每个峰都代表一种不同种类的碳原子：每个都在不同的频率吸收能量（吸收能量，即共振 **resonates**——因而称为“核磁共振”）。但为什么碳原子会“不同”呢？我们已告诉您，有两个因素影响能量差（因而影响频率）——磁场强度，和所研究的原子核的种类。所以您可能认为所有的  $^{13}\text{C}$  原子核都在同一特定的频率共振，所有质子 ( $^1\text{H}$ ) 都应该在同一（与碳不同的）频率共振。但事实并非如此。

不同类型的碳原子在频率上的变化，意味它们与磁场由“核一致”到“核平行”跳跃的能量差不同。原因在于，问题中的  $^{13}\text{C}$  原子核感受到的磁场，与我们施加的磁场并不是完全一样的。每个原子核都被电子环绕，在磁场中，它们都会阐释微小的电流。这些电流会产生它们自己的磁场（感应磁场，**induced magnetic field**，如同螺线管或线圈中流动的电流产生的磁场一样），这些磁场会与我们施加的磁场方向相反。我们称这些电子在外加磁场中**屏蔽**（**shield**）了原子核。如果一个  $^{13}\text{C}$  原子和另一个  $^{13}\text{C}$  原子的电子分布不同，那么它们的原子核感受到的局部磁场也是不同的，因此对应的共振频率就也不同了。

电子在施加的磁场中屏蔽了原子核  
(shielding of nuclei from an applied magnetic field by electrons):



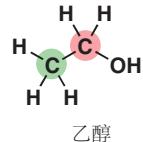
● 原子核周围电子排布的变化会影响:

- 原子核感受到的局部磁场
- 原子核共振的频率
- 分子在该原子上的化学性质

这种在频率上的变化被称作化学位移 (chemical shift). 它的符号是  $\delta$ .

作为例子, 请考虑如有所示的乙醇。红色的与 OH 基相连的碳, 相比于绿色的碳, 周围供享用的电子较少, 这是因为氧原子更加负电性, 会将电子拉向氧的一侧, 远离红色碳原子。

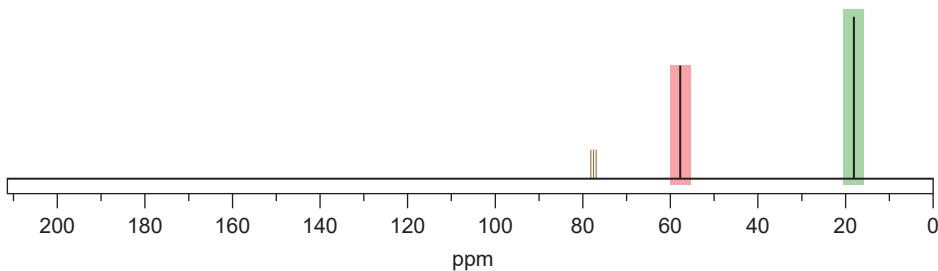
因而, 红色碳原子核感受到的磁场会稍比绿色碳的大, 它比绿色碳原子享有的电子少, 因而在外加磁场中被屏蔽得也少——换句话说, 它被去屏蔽 (deshielded) 了。由于连有氧的碳感受到的磁场更强 (由于它缺少了一部分电子屏蔽, 它在磁场中更“暴露”), 它两种排列方式的能量差就更大。能量差更大了, 共振的频率也就更高了 (能量与频率成正比)。因此, 对于乙醇, 我们应当料到, 红色的带有 OH 基的碳共振的频率比绿色的碳高, 这也确实被  $^{13}\text{C}$  NMR 光谱所表现出来了。



乙醇

■ 我们通常当然不会画出全部的 Cs 和 Hs, 但在此由于我们就是要讨论它们, 因而我们把它们画出来了。

乙醇的  $^{13}\text{C}$  NMR 光谱图

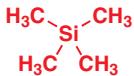


■ 在 77 ppm 处棕色表示的峰, 来自常见溶剂 ( $\text{CDCl}_3$ ), 我们暂时可以忽略。我们将将在 Chapter 13 解释它们。

## 化学位移的刻度

当您观察一幅真正的 NMR 光谱图时, 您就会发现刻度并不以磁场的单位出现的, 也不以频率、能量的单位, 而是以“百万分之一 (parts per million)” (ppm) 表示的。对此有一个很好的理由。原子核共振的确切频率取决于外加磁场。这意味着一份样品在两台磁场不同的光谱仪上运行时, 它会在不同的频率共振。如果我们不能准确地说明信号在哪, 这会使工作进行得非常困难, 因而我们的解决办法是, 选取一种反映仪器工作频率 (operating frequency) 的标准样品 (reference/standard sample), 并用待测样品的频率到标准样品的距离表示它。我们知道, 在一个给定的磁场中, 所有的质子都在近似相同的频率共振, 确切频率取决于它们所处的是哪种化学环境, 化学环境又继而取决于它的电子。因此我们选取标准样品 (具体是什么会在后文提及) 中质子的共振频率作为仪器工作频率, 它仅取决于磁场强度——磁场越强, 工作频率越大。在日常生活中, 化学家提及选用的磁场强度时, 不会以特斯拉为单位, 而是会以它的工作频率 (即标准样品中质子的共振频率) 表达。一台 9.4 T NMR 仪会被表述为一台 400 MHz 光谱仪。其他原子核, 例如  $^{13}\text{C}$ , 会在不同频率共振, 其强度也会以质子工作频率表述。

### 标准样品—四甲基硅烷, TMS



四甲基硅烷, TMS

■ 硅与氧对于邻位碳原子有相反的效应：正电性的硅起屏蔽作用；负电性的氧起去屏蔽作用。电负性: Si: 1.8; C: 2.5; O: 3.5.

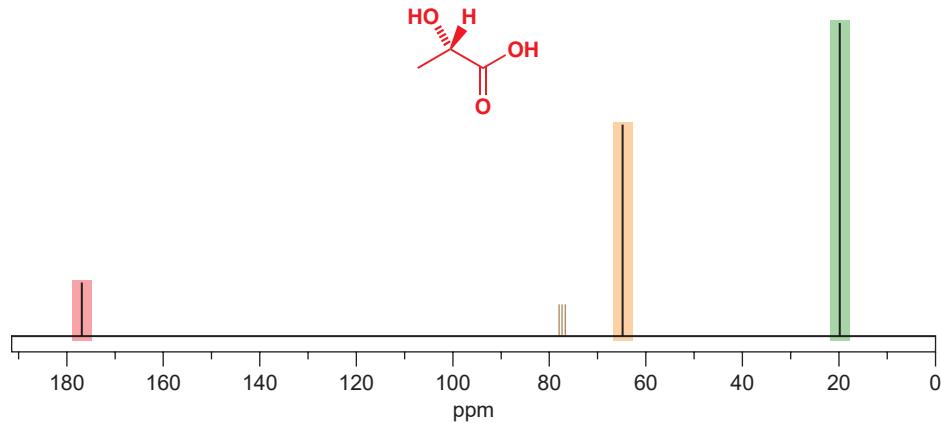
我们通常用作标准样品的化合物是四甲基硅烷 (tetramethylsilane), TMS. 这是一种将硅烷 ( $\text{SiH}_4$ ) 中的四个氢都用甲基替代的化合物，即  $\text{Si}(\text{CH}_3)_4$ . 与硅相连的四个碳原子都是完全等价的，并且，由于硅比碳更加正电性，这四个碳原子也都很富电子（或被屏蔽得多），这意味着它共振的频率小于大多数有机化合物。这样，标准样品的共振峰就不会出现在整张光谱的中央，这是有用的！

样品中给定原子核以百万分之一 (ppm) 计的化学位移， $\delta$ ，被定义为与其共振频率有关的下式：

$$\delta = \frac{\text{频率 (Hz)} - \text{TMS 的频率 (Hz)}}{\text{TMS 的频率 (MHz)}}$$

无论 NMR 仪的工作频率（即磁场强度）为多少，同一给定样品（例如乙醇）都往往会在同一化学位移上。乙醇中（红色的）与 OH 相连的碳在 57.8 ppm 处共振，而甲基的（绿色的）碳在 18.2 ppm 处共振。注意，根据定义，TMS 本身在 0 ppm 处共振。大部分有机化合物中的碳原子核，都会在较大的化学位移处共振，一般在 0 到 200 ppm 之间。

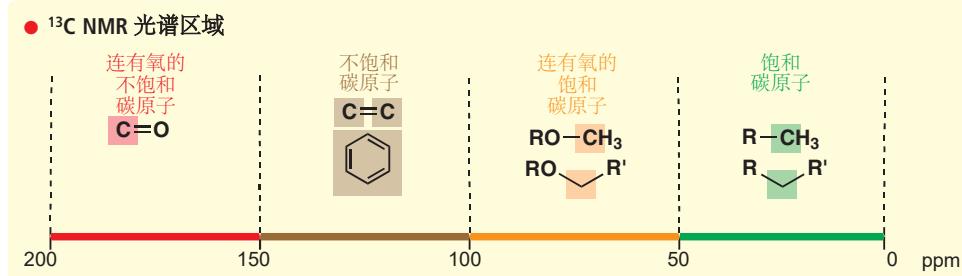
现在，让我们回到您在 p. 54 见过的样品光谱，下图是它的正确表述，您可以从中看出我们已讨论完的细节。这是一个 100 MHz 光谱；横轴是频率，但通常以磁场的 ppm 表述，每个单位是 100 MHz 的一个 ppm，即 100 Hz. 我们可以很快看到，176.8, 66.0, 和 19.9 ppm 处有三个峰，分别是分子中的三种类型的碳原子。

乳酸的  $^{13}\text{C}$  NMR 光谱

■ 再次说明，请忽略 77 ppm 处棕色的峰——这对目前的我们没有意义。您同样无需关注峰的强度。这是光谱记录方式产生的结果，在  $^{13}\text{C}$  光谱中，信号强度通常无关紧要。

### $^{13}\text{C}$ NMR 光谱区域

除了观察到峰的数量，我们还可以更进一步：弄清楚碳原子所处的化学环境。所有  $^{13}\text{C}$  光谱都可分为四个主要区域 (regions): 饱和碳原子 (0–50 ppm), 连有氧的饱和碳原子 (50–100 ppm), 不饱和碳原子 (100–150 ppm), 连有氧的不饱和碳原子，即  $\text{C}=\text{O}$  基 (150 到大约 200 ppm).



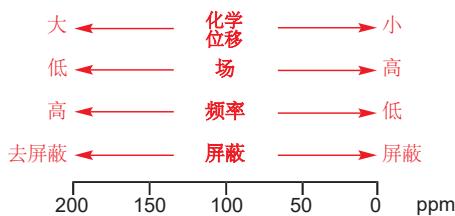
方才您见到的光谱来自于乳酸 (2-羟基丙酸)。当您翻页时，手臂肌肉中便会有葡萄糖被合成为乳酸——这是无氧呼吸中葡萄糖的分解产物 (breakdown product)。乳酸中的碳原子的光谱峰所处的区域各不相同。

但等一下，您可能会说——我们难道不是只能看到 碳-13 原子核的信号，而看不到组成任何乳酸的一般样中大部分碳原子的 碳-12 原子核的吗？答案是肯定的，确实，任何样品中都只有 1.1% ( $^{13}\text{C}$  的天然丰度) 的 C 原子在  $^{13}\text{C}$  NMR 中“可见”。但由于这些  $^{13}\text{C}$  原子会在样品中或多或少地随机分布，丰度的问题并不会对光谱的外观造成任何影响。它真正的影响在于，例如， $^{13}\text{C}$  NMR 不如  $^1\text{H}$  NMR 灵敏，因为样品中基本所有的 H 原子都是“可见的”。

## 描述化学位移的多种方式

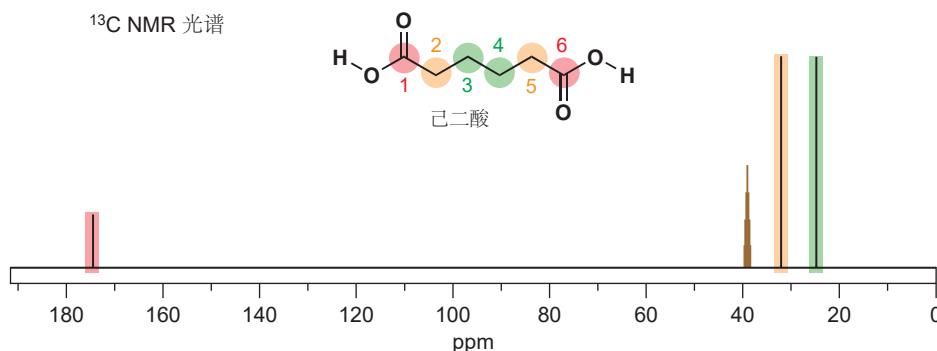
化学位移的刻度由零 (TMS 共振的位置) 向左发展，和通常的横坐标取法是相反的。在零附近的化学位移显然很小，但却被称为“高场区”，这是易混的，其原因在于，这里是原子核感受到的磁场较高的一端。我们建议您用“大的 (large)”或“小的 (small)”描述化学位移， $\delta$ ，用“高的 (high)”或“低的 (low)”描述磁场以避免混淆，磁场描述的另一方式是“高场区 (upfield)”(小  $\delta$ ) 和“低场区 (downfield)”(大  $\delta$ )。

我们已用过的一种有用的描述方式是屏蔽。每个碳原子核都被在磁场中屏蔽它们的电子所环绕。简单的饱和碳原子受到的屏蔽较多：它们的化学位移较小 (0–50 ppm) 并且在高场区共振。负电性氧原子的加入使化学位移向低场区变化至 (downfield into) 50–100 ppm 区域。原子核被去屏蔽了。不饱和碳原子感受到的屏蔽更小 (100–150 ppm)，这是由于其电子分布在原子核周围的方式不同所致。如果它们同样与氧成键 (最常见的与氧成键的不饱和碳原子是羧基碳)，那么原子核就会更加被去屏蔽，并使化学位移达到最大的 200 ppm. 下面的图示总结了这些谈论 NMR 光谱的方式。



## 一些简单分子 $^{13}\text{C}$ NMR 光谱的导览

现在，来看一些真实的  $^{13}\text{C}$  NMR 光谱。我们的第一种化合物是己二酸，它简单的 NMR 光谱如下所示。第一个问题是这样的：为什么六个原子仅出现三个峰？这是由于分子的对称性导致的，两个羧基是完全相同的，它们的峰出现在 174.2 ppm. 同样，C2 和 C5 是完全相同的，C3 和 C4 也是完全相同的。它们都位于饱和区域，0–50 ppm，其中与吸电子  $\text{CO}_2\text{H}$  基相连的被去屏蔽的更多，因此我们分配 C2/C5 为 33.2 ppm 处的峰，C3/C4 为 24.0 ppm 处的峰。



■ 事实上，自然碳中  $^{13}\text{C}$  的低丰度使得  $^{13}\text{C}$  光谱更简单了——我们会在 Chapter 13 中深入讨论这一问题。

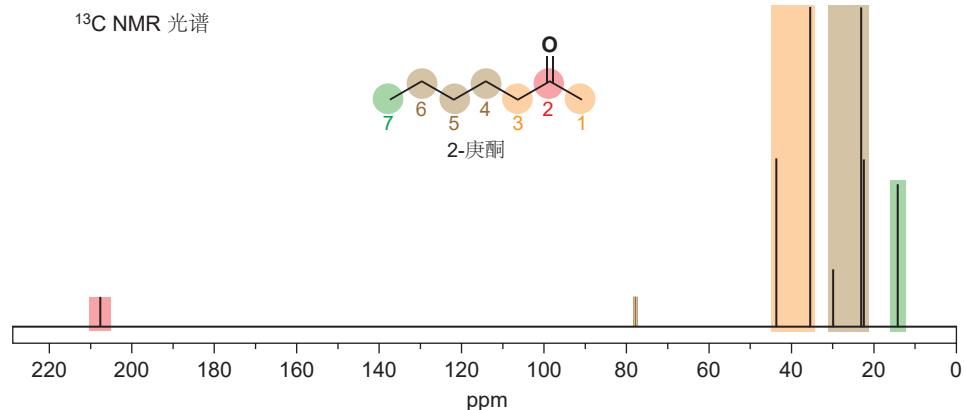
■ NMR 光谱最初是通常变换外加场强记录的 (扫场)。现在，则是通过改变辐射脉冲产生的无线电波的频率完成的 (扫频)。“高场”和“低场”是扫场时代遗留下的术语。

如果您在读过 Chapter 4 后再回顾这一掌，您就会知道为什么不饱和 C 原子比饱和碳原子更加去屏蔽，这是由于  $\pi$  键有一个节面 (nodal plane)，即一个不会有电子出现于其中的平面。 $\pi$  键中的电子在对原子核的屏蔽上没有  $\sigma$  键电子有效。

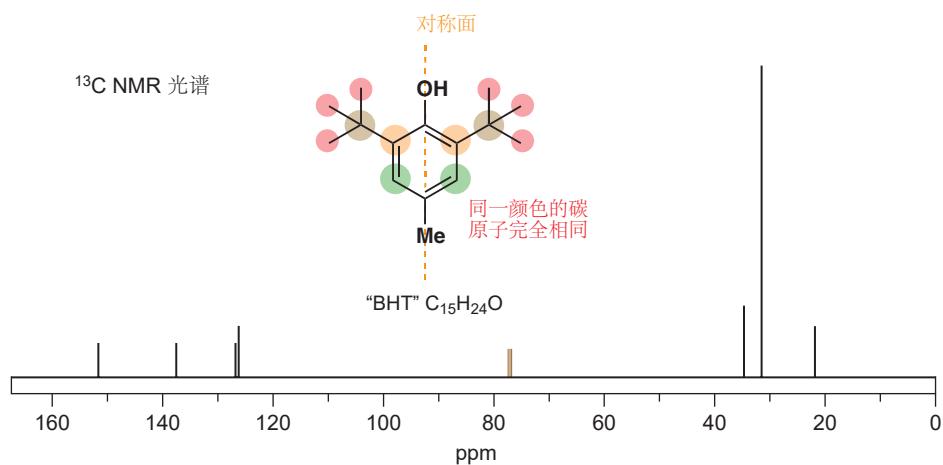
■ 为什么这个化合物没必要叫做“1,6-己二酸”呢？嗯，这是因为羧基只能位于链的末尾，因此只有一种己二酸是可能出现的：1 和 6 是冗余的。

■ 这个光谱是在一种不同的溶剂，DMSO (二甲亚砜 dimethylsulfoxide) 下得到的，因而棕色峰在不同区域，形式也不同。我们将在 Chapter 13 中处理这个问题。

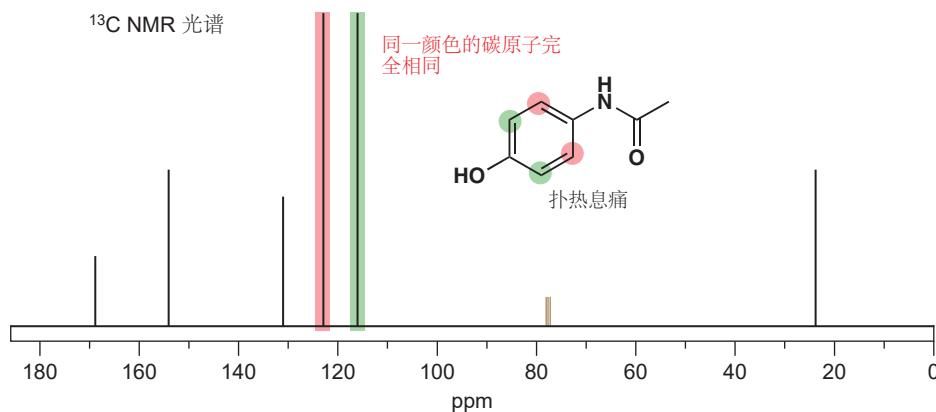
2-庚酮是在 p. 48 涉及过的蜜蜂信息素。它没有对称性，因此全部的七个碳原子都是不同的。羰基很容易识别 (208.8 ppm), 但剩余部分的识别却较困难。连有羰基的两个碳原子在最低场区出现，而 C7 则应是最高场区 (13.9 ppm). 在正确的化学位移处有正确数目的信号出现是重要的。如果这一点满足了，我们便没必要担心我们能否将它们准确地分配给每个碳原子 (例如对于 4, 5, 6 之间). 如我们之前所说，不要关心峰的强度。



您在 p. 8 曾见过了 BHT: 它的分子式是  $C_{15}H_{24}O$ , 第一个令人惊讶的内容是，它有 15 个原子，却在 NMR 光谱上仅显示七个峰。很明显分子中有很多对称性；事实上，垂直于苯平面，有一个对称面，如图所示，不同颜色的碳分别相互对称，并分别给出一个信号。在  $\delta = 30.4$  ppm 处最强的信号归属于叔丁基上六个完全相同的甲基 (红色)，另两个在 0–50 ppm 范围内的信号是 C4 轴上的甲基和叔丁基的棕色中心碳。芳香区域内，只有四个信号，因为有两对碳是相同的。与上个例子一样，我们不关心它们确切是哪一个——我们只需要检查在正确的化学位移处有没有正确数目的信号。

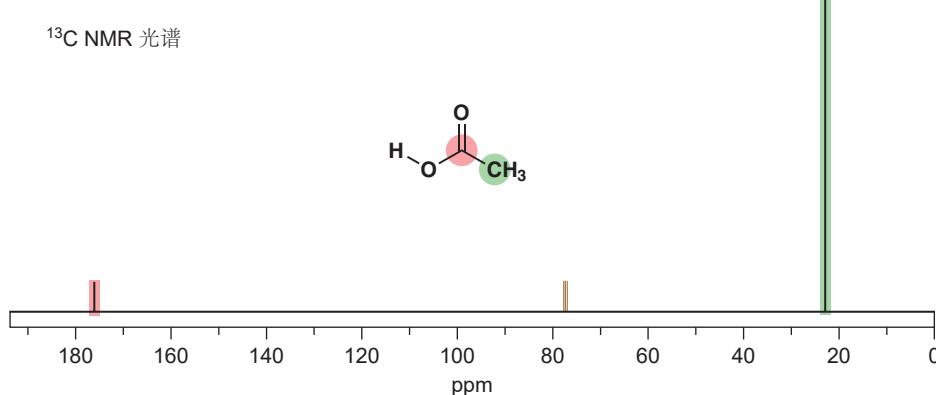
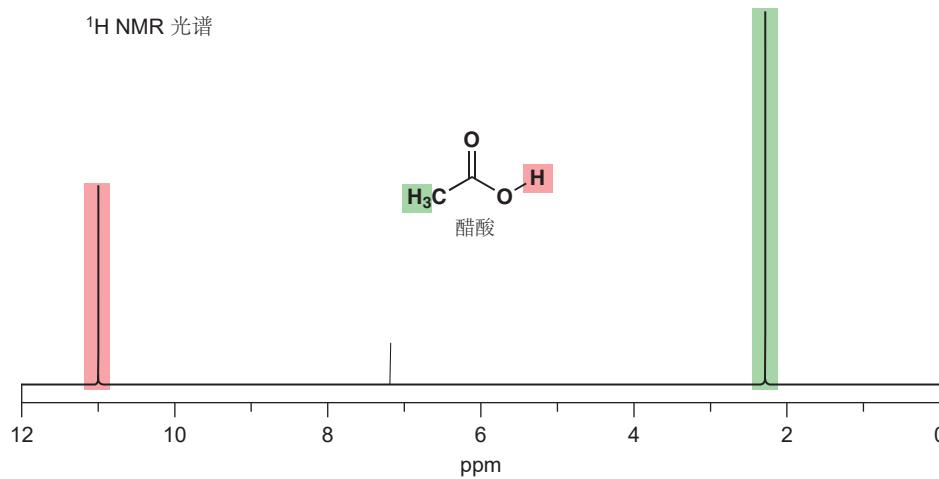


扑热息痛是一种结构简单的常见止痛药——它是一种在苯环上另连有一个酰胺取代基的苯酚。它的 NMR 光谱包含一个在 24 ppm 处的饱和碳原子 (酰胺侧链的甲基)，一个在 168 ppm 处的羰基，和在 115, 122, 132, and 153 ppm 处的四个其他峰，它们是苯环上的碳原子。为什么是四个峰？因为苯环上有两对碳是相同的 (红色和绿色所示的两对都只显示一个峰)，这告诉我们， $NHCOCH_3$  基不会真的像图中所示的那样处于一侧，而是会快速旋转，因此在平均上，环的两侧无法区分，与 BHT 一样。为什么有一个芳环峰出现在位于  $C=O$  区域的 153 ppm 处呢？这会是 C4 轴上与氧相连的原子，回忆一下，与氧相连的不饱和碳原子不一定是羰基碳 (p. 56 图表)，不过它并没有 168 ppm 处真正的  $C=O$  基去屏蔽得多。



## <sup>1</sup>H NMR 光谱

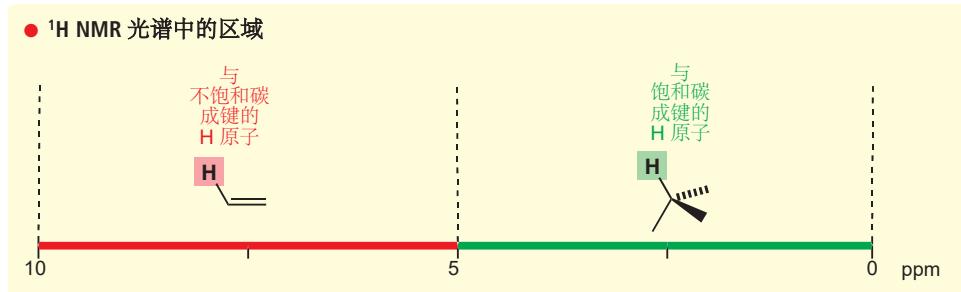
<sup>1</sup>H NMR (或“质子 (proton) NMR”)光谱的记录方式与<sup>13</sup>C NMR 光谱相同：用电磁波研究原子核的能级差。不同的地方是此时用<sup>1</sup>H 替代了<sup>13</sup>C 原子核。与<sup>13</sup>C一样，<sup>1</sup>H 原子核自旋为 1/2，因而也有两个能级：它们既可以与外加磁场排列一致，也可以排列相反。如下是醋(乙)酸, MeCO<sub>2</sub>H 的<sup>1</sup>H NMR 光谱，其下方还有它的<sup>13</sup>C NMR 光谱。



<sup>1</sup>H NMR 光谱与<sup>13</sup>C NMR 光谱有很多相似之处：刻度由右向左增长，零点由相同的标准化合物给出，即由 Me<sub>4</sub>Si 中的质子而非碳原子的共振位置定义为零点。然而，如上方光谱所示，刻度尺寸小得多，一共仅有 10 ppm，而碳谱则需要 200 ppm. 这完全说得通：化学位移的变化，衡量的是原子

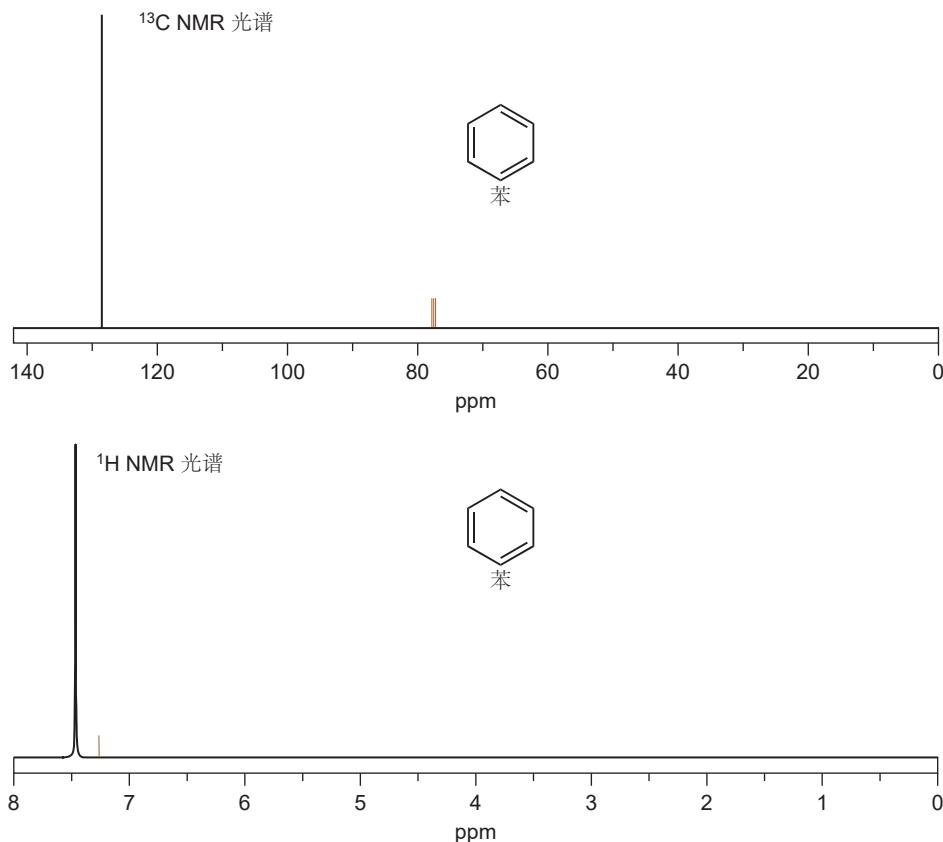
核周围电子屏蔽效应的程度。氢原子核旁仅有两个电子，其可能的分布变化不可避免地比碳原子核周围的八个电子少。尽管如此，屏蔽造成的差别也能体现出来，如您所料，醋酸中羧基上直接与氧相连的 H 原子，受到的屏蔽比甲基上的 H 原子多。

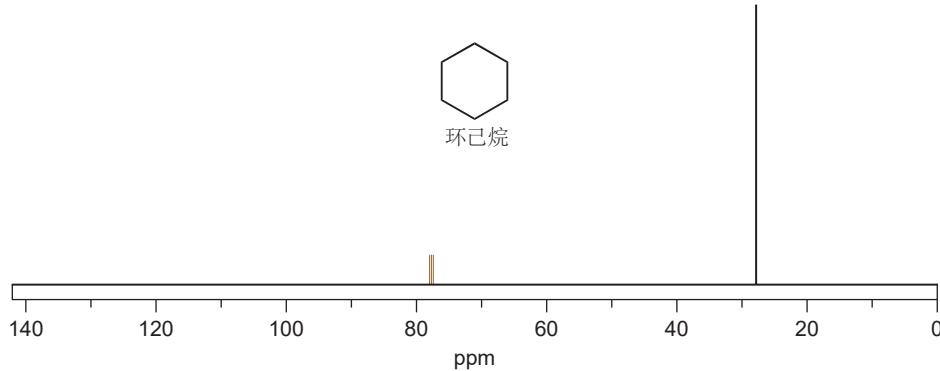
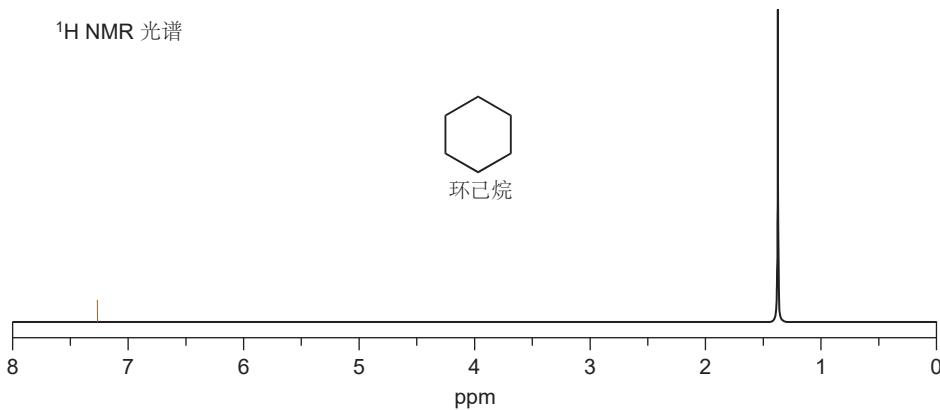
我们同样可以将  $^1\text{H}$  NMR 光谱像  $^{13}\text{C}$  NMR 光谱一样分成区域。与饱和碳原子成键的氢原子在右手边出现，是光谱中屏蔽较强 (5 到 0 ppm 之间) 的区域；而与不饱和碳原子成键 (主要是烯烃、芳烃，或羰基) 的氢原子出现在左手边，是位于 10 到 5 ppm 之间的弱屏蔽区域。和  $^{13}\text{C}$  光谱一样，附近的氧原子也会吸电子密度，使得这些区域内的信号都各自向左手移动。



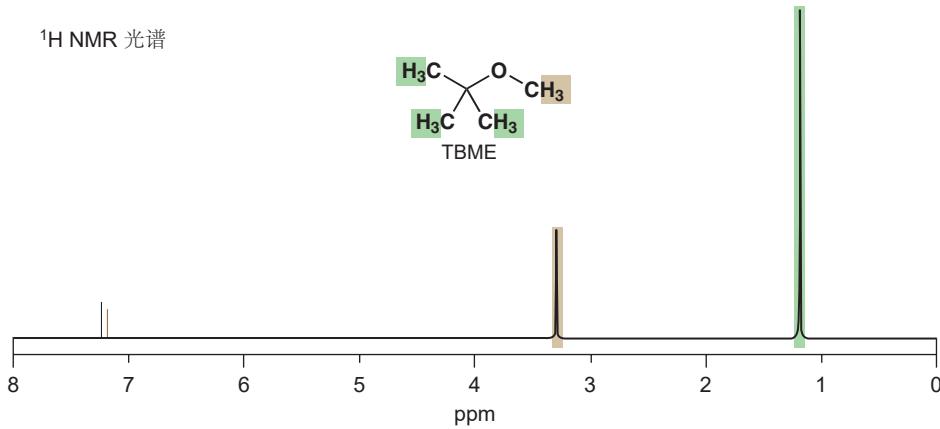
### 一些 $^1\text{H}$ NMR 光谱的例子

在下面的一些光谱中，您可以清楚地了解， $^1\text{H}$  NMR 信号是如何进入这些区域的。前两个光谱，苯和环己烷的例子中，都只含有一个峰，因为它们中的每个质子都是完全相同的。苯中，该峰位于 7.5 ppm，即我们料想的，与不饱和 C 原子相连的氢原子该处在的区域；环己烷中，该峰位于 1.35 ppm 处，这是因为环己烷中全部的质子都与饱和 C 原子相连。为了帮助对比，我们同样也展示了苯和环己烷的  $^{13}\text{C}$  光谱。对于苯，信号位于不饱和 C 区域 (100–150 ppm)，在 129 ppm 处，对于环己烷，则位于饱和 C 区域，在 27 ppm 处。

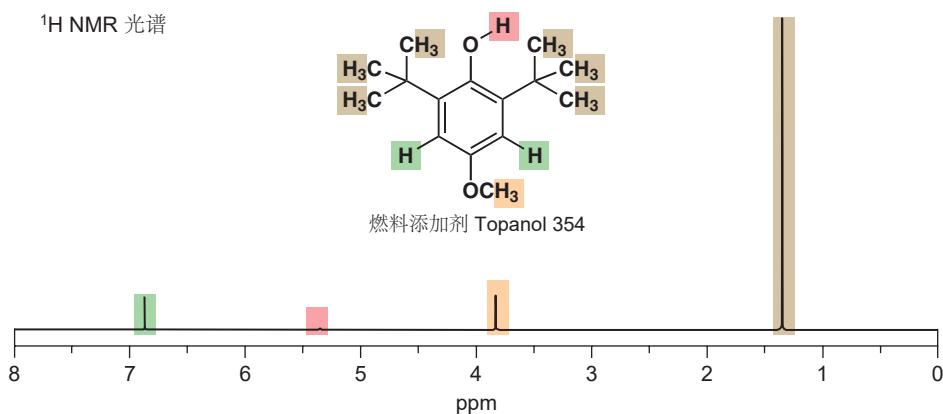


<sup>13</sup>C NMR 光谱<sup>1</sup>H NMR 光谱

叔丁基甲基醚是一种溶剂，也是一种燃料添加剂，它的 <sup>1</sup>H 光谱说明了邻近的氧原子的影响：在 1.1 ppm 处的大峰，来源于组成分子中叔丁基部分的三个完全相同的甲基中的九个 H 原子，醚的甲基部分中的三个 H 原子则处于 3.15 ppm。这三个氢原子所连的 C 原子本身与 O 成键，氧的负电性吸引它们的电子，并去屏蔽 <sup>1</sup>H 原子核，将其转移到较大的化学位移处。

<sup>1</sup>H NMR 光谱

我们在 BHT 的 <sup>13</sup>C NMR 光谱中点出的对称面，也意味着与之相关的化合物 Topanol 354 在 <sup>1</sup>H NMR 光谱中，相比于其他含有 26 个 H 原子的化合物更加简单：在 5 到 0 ppm 间的一个大峰和两个小峰，来自叔丁基的 18 个质子和三个甲基各三个质子；另一个在 5 到 10 ppm 之间的小峰则来源于与芳环相连的两个质子。

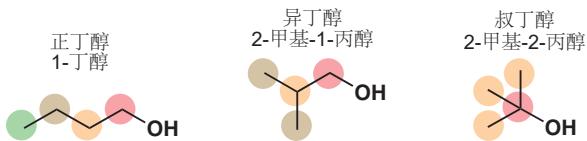


<sup>1</sup>H NMR 还有很多其他的特征，我们会暂且将它们放在一边，毫不夸张地说，它在决定结构的一般路线中，比其他所有方法放在一起都更加重要。我们将对于 <sup>1</sup>H NMR 更加细致的讨论放在了 Chapter 13 中。

### NMR 在解决未知结构上是一个很有力的工具

为了说明 NMR 的强大实力，请考虑下面三种分子式为 C<sub>4</sub>H<sub>10</sub>O 的醇，它们的 <sup>13</sup>C NMR 光谱都很不相同。光谱中峰的数值如下表所示。

▶ 正、异，和叔的含义已在 Chapter 2 (p. 26) 中阐释清楚。

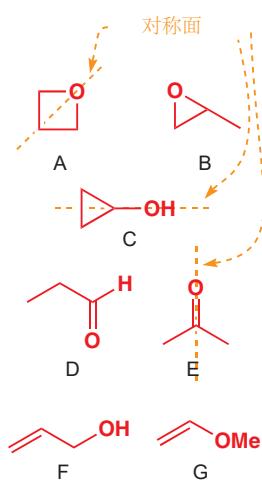


化学位移 ( $\delta$ , ppm)

碳原子	正丁醇	异丁醇	叔丁醇
●	62.9	70.2	69.3
○	36.0	32.0	32.7
■	20.3	20.4	—
▲	15.2	—	—

每个醇都有一个与氧连接的饱和碳原子，它们的信号也都在通常的与氧相连的饱和碳原子的区域出现 (p. 56)。然后，还有与氧隔一个碳原子连接的碳：它们在正常饱和碳原子，0–50 ppm 区域的低场一端——大约 30–35 ppm——由于它们仍被附近的氧去屏蔽。其中两种醇，还有更远的，化学位移更小 (即更高场区，屏蔽更多的) 碳，位于大约 20 ppm；最后，只剩一种正丁醇，还有更远的位于 15.2 处的碳原子。信号的数目和化学位移可以很清楚地辨识分子。

化学家常会遇到这样的情况，它们从例如高分辨率质谱法中，得知了一种未知化合物的分子式，并需要找到一个与 NMR 数据匹配得结构。下面是一个例子：侧边栏的七种合理结构都表现出 C<sub>3</sub>H<sub>6</sub>O 的分子式。下一页将给出三幅 <sup>13</sup>C NMR 光谱，它们可以表达这些化合物中的三种。您的挑战在于，识别出是哪三个。我们会给您一些提示，请您在阅读下一页的答案 (谱图后面的段落为答案) 前自己解决这个问题。

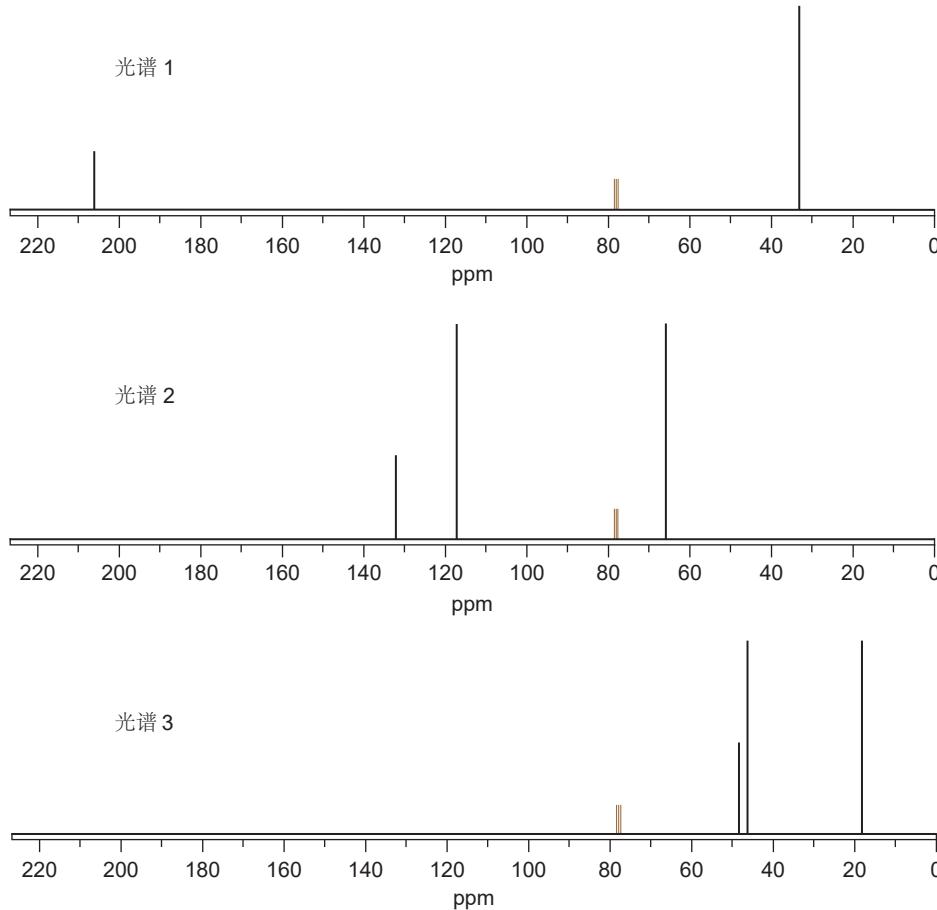


简单的对称性可以从剩下的结构中区分 A, C, 和 E，由于它们只含有两类碳原子。D 和 E 中含有的羰基，将在 150–200 ppm 区域给出一个峰，其中 D 还有两个不同的饱和碳原子，而 E 只含有一个。对于 F 和 G 两种烯烃，它们都含有两种不饱和碳原子 (100–200 ppm)，但在醚 G 中，其中一个不饱和碳与氧相连——您会料想到，它会被去屏蔽，进而在 150 和 200 ppm 处出现峰。

最大的问题存在于三个饱和化合物 (A, B, 和 C) 上。环氧 B, 有两个不同的与氧相连的碳原子 (50–100 ppm) 和一个普通的饱和碳原子 (0–50 ppm). 余下的两个分子则都在 0–50 ppm 区域和 50–100 ppm 区域有一个峰 (注: 由于碳谱的强度无意义, 无法区分峰对应的原子个数), 只有用更强  $^1\text{H}$  NMR 技术, 和达到一定程度的红外光谱法 (我们马上将着眼于的) 才能可靠地区分它们。

■ 环氧指三元环状醚, 如 B.

下面是这些分子中的三种的 NMR 光谱。在继续阅读前, 请看看自己能否将它们分配给前一夜的结构。同样要试着指出哪些峰属于哪些碳原子。



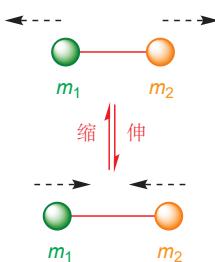
我们希望这并不会给您造成多大的麻烦。唯一的有羰基和两个完全相同的碳原子的化合物是丙酮 (E) 因此光谱 1 便是它。注意, 在非常低场区的信号 (206.6 ppm) 通常术语简单酮  $\text{C}=\text{O}$  碳原子。光谱 2 含有两个不饱和碳原子, 和一个与氧相连的饱和碳原子, 因而一定是 F 或 G. 事实上它需要是 F, 因为两个不饱和碳原子的信号相似 (137 给 116 ppm), 因而它们都不能与氧相连 (>150 ppm). 还剩下光谱 3, 由于所有信号都低于 50 ppm, 因而没有与氧相连的碳原子出现; 但并没有符合这一描述的化合物, 位于 48.0 和 48.2 ppm 处的两个峰疑似接近我们武断地确定的 50 ppm 边界。它们当然都与氧相连, 因而该化合物是 B.

## 红外光谱

### 官能团可通过红外光谱识别

$^{13}\text{C}$  和  $^1\text{H}$  NMR 光谱法可以告诉我们很多关于分子的碳氢骨架的信息, 而质谱法则可以一个整体称量分子。它们都不能很好地揭示官能团。一些官能团, 例如  $\text{C}=\text{O}$  或  $\text{C}=\text{C}$ , 由于含有碳原子, 因而可在  $^{13}\text{C}$  NMR 光谱中观察, 但更多数的官能团, 例如醚键、硝基, 在 NMR 中, 我们只能观测到它们对临近 H 或 C 原子化学位移的影响。

## 红外中键的振动



然而，红外 (IR) 光谱为官能团的观察提供了一种直接的途径，因为它所检测的是键的伸缩 (stretch, 伸 stretch/relax 缩 contract) 和弯曲 (bend)，而非其他关于原子本身的特点。它尤其擅长于检测例如 OH, C=O, NH<sub>2</sub>, 和 NO<sub>2</sub> 等官能团中的不对称双键的伸缩，由于这个原因，IR 光谱法作为另一种实用的结构分析方法，很好地补充了 NMR.

**NMR** 需要光谱中无线电波区域的电磁波，使原子核由一个状态翻转到另一个状态。伸缩和弯曲单个化学键所需的能量，虽然仍然很小，但已经相当大了，因而对应短得多的波长。这些波长处在红外区内，紧贴在可见光 (波长在 10 到 100 mm 之间) 长波长的一侧。当一个分子的碳骨架振动时，所有结合中的键都会伸缩 (stretch, relax)，总的来说，这些吸收都是无用的。然而，一些键可以基本上独立于分子的其余部分地伸缩，我们可以利用这一特点来识别官能团。当化学键满足以下两条中的一条时，会出现该情况：

- 比邻近的键强得多或弱得多，或
- 处于两个比相邻原子重得多或轻得多的原子之间

**胡克定律**描述的是连接在一根弹簧上的两个质点的运动。如果您学习物理，就会遇到它。在此您不需要关注它的推导过程，只需要关注它的结果。如下形式：

$$\nu = \frac{1}{2\pi c} \sqrt{\frac{f}{\mu}}$$

其中  $\nu$  为频率， $f$  为力常数， $\mu$  为约化质量。 $c$  是使单位起作用的常量。

的确，键振动 (vibrate, 包括伸缩和弯曲) 的频率，原子的质量和键的强度的关系，基本上与简单简谐振动的胡克定律/虎克定律 (Hooke's law) 相符。胡克定律显示，振动的频率  $\nu$  与力常数 (force constant)  $f$ ——表示键的强度或多或少——的平方根成正比，并且与约化质量 (reduced mass)  $\mu$ ——即两个原子质量的乘积除以它们的和——的平方根成反比。

$$\mu = \frac{m_1 m_2}{m_1 + m_2}$$

对于我们化学家，精确的数学并没有简单的结果重要。

● 键越强，原子越轻，振动得就越快。

红外光谱是简单的吸收光谱。样品被溶解在溶剂中 (或放在惰性 NaCl 板的表面)，并且暴露于红外辐射下。然后用不同波长扫描，以红外辐射的波长为横坐标，每个波长中可以穿过样品的红外能量的数目为纵坐标作图。为了更好地得出这些数字，IR 光谱通常不指出波长，而是指出一种称为“波数 (wavenumber)”的值，单位为 cm<sup>-1</sup>，指每厘米内波长的数目。对于典型的键，这个值会处于 4000 (短波长，即高频率) 到 500 (长波长，即低频率) 之间。振动迅速的强键、轻原子，如您所料地处于光谱的高波数一侧，通常在左手边。

为了说清楚我们的意思，如下有以两种方式分组的一些典型的键的 IR 频率数值。首先是原子重量递增的一系列键 (D, 氚的质量为 H 的两倍，Cl 的质量约为 O 的两倍)，然后是强度递增的一系列键。

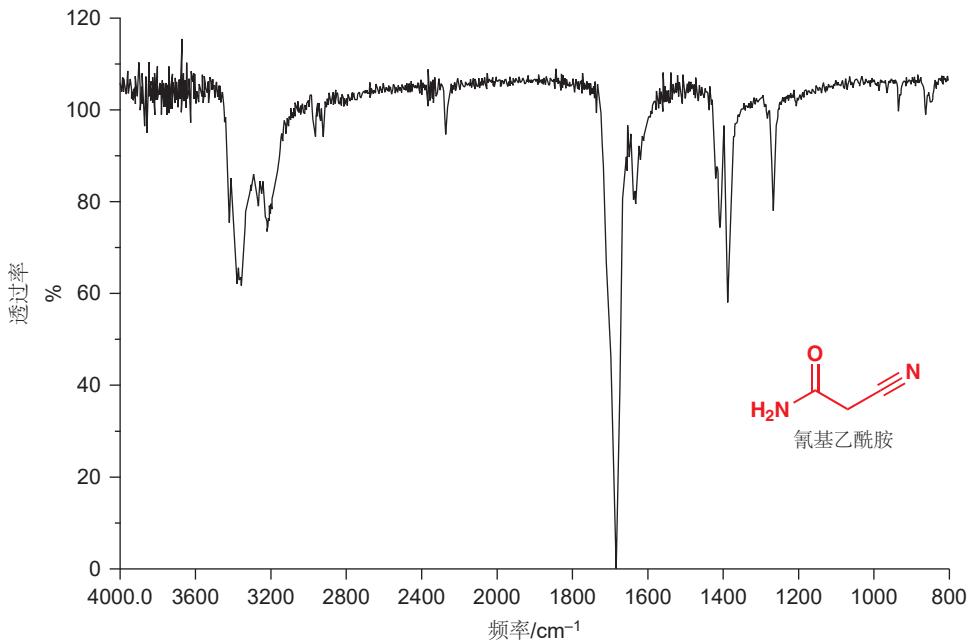
主要受原子质量影响的值 (原子越轻，频率越高)

C—H	C—D	C—O	C—Cl
3000 cm <sup>-1</sup>	2200 cm <sup>-1</sup>	1100 cm <sup>-1</sup>	700 cm <sup>-1</sup>

主要受键的强度影响的值 (键越强，频率越高)

C≡O	C=O	C—O
2143 cm <sup>-1</sup>	1715 cm <sup>-1</sup>	1100 cm <sup>-1</sup>

如下是经典的 IR 光谱真实的样子：注意波数的刻度由高到低排列，吸收的最大值也是颠倒的（IR 谱图的纵坐标为“透过率 transmission”）——您可能会说，IR 谱图上下前后都是颠倒的。如果您仔细观察，您还会发现，刻度的尺寸在中间也发生了变化，这是为了给谱图更为详细的右侧更多的空间。

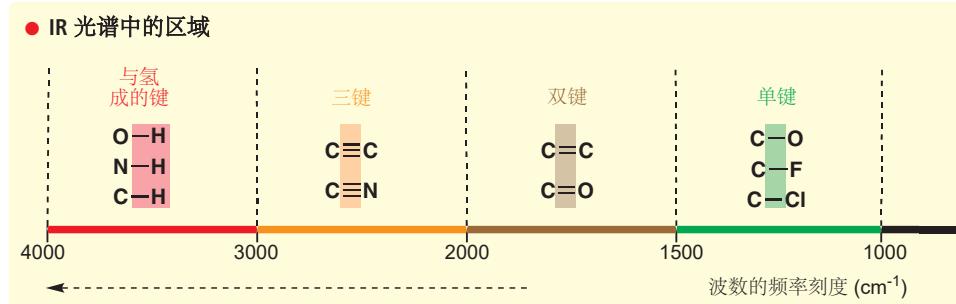


这是氰基乙酰胺 (cyanoacetamide)，右侧所示的化合物的谱图。谱图的整个形状就是这种化合物的特征，但作为化学家，我们需要能够诠释光谱，并且我们可以通过将其分成区域做到这一点，如我们在 NMR 光谱中所做的一样。

## 红外光谱中有四个重要区域

第一个区域，位于  $4000$  到  $2500\text{ cm}^{-1}$  的，是 C—H, N—H, 和 O—H 键伸缩的区域。有机分子中的大多数原子（例如 C, N, O）质量都近乎相同（12, 14, 16...）。氢比这些原子都轻一个数量级，因此它通过对约化质量巨大的影响主宰着伸缩频率，任何与 H 成的键都会来到谱图的左手边。

即使是非-H 原子间所成的最强的键——如 C=C 或 C≡N 中的三键——都在比与氢成的键稍低的频率处吸收：它们处在下一个区域，三键区域，位于  $2500$  到  $2000\text{ cm}^{-1}$ 。这个区域，和剩下的两个区域中，约化质量几乎是相同的，因而区域按键的强度划分：C=C 和 C=O 双键出现于大约  $2000$ – $1500\text{ cm}^{-1}$ ，继续向右，则是单键区域，低于  $1500\text{ cm}^{-1}$ 。下面的图表总结了这些区域，您应当记住。



### 约化质量和原子质量

我们在 p. 64 介绍了约化质量的思路。为了说明 H 在约化质量上的影响，请考虑：一根 C-C 键的约化质量是  $(12 \times 12)/(12 + 12)$ ，即  $144/24 = 6.0$ 。如果我们其中一个原子换为 H，则约化质量也变为  $(12 \times 1)/(12 + 1)$ ，即  $12/13 = 0.92$ ，但如果我们将其变为 F，那么约化质量变为  $(12 \times 19)/(12 + 19)$ ，即  $228/31 = 7.35$ 。当我们增加到 19 (F) 时，引起的变化较小；但若将其减小到 1 (H)，则影响是巨大的。

■ IR 中的吸收经常以“峰 (peaks)”表述——在谱图上, 它们当然表现为“谷 (troughs)”!

回顾 p. 65 中氨基乙酰胺的谱图, 我们可以看到位于大约  $3300$  和  $2950\text{ cm}^{-1}$  之间的 X-H 的峰, 它们是  $\text{NH}_2$  和  $\text{CH}_2$  基中 N-H 和 C-H 的伸缩。还有一个在三键区域 ( $2270\text{ cm}^{-1}$ ) 中相当弱的峰, 是  $\text{C}\equiv\text{N}$  基; 在大约  $1670\text{ cm}^{-1}$  处的强峰则属于  $\text{C}=\text{O}$  基。我们稍后会解释为什么有些 IR 峰比其他的强。光谱的剩余部分在单键区域中。这个区域一般不会被细致地诠释, 但它也是化合物作为一个整体时的特征, 就像同样不能被“诠释”的人类指纹特征一样。它确实被称为指纹区 (fingerprint region)。能从这个谱图中获取的有用信息, 是化合物中存在  $\text{C}\equiv\text{N}$  和  $\text{C}=\text{O}$  基, 也能获得  $\text{C}=\text{O}$  吸收的确切位置。

### X-H 区域 ( $4000\text{--}3000\text{ cm}^{-1}$ ) 用于区分 C-H, N-H, 和 O-H 键

C-H, N-H, 和 O-H 组合的约化质量大约是相同的。这些键的 IR 波段的任何区别都应是由于键的强度所致。实践上, C-H 伸缩发生于  $3000\text{ cm}^{-1}$  周围 (虽然它们在识别化合物上用处很小, 因为很少有有机物不含 C-H 键), N-H 伸缩发生于大约  $3300\text{ cm}^{-1}$ , O-H 伸缩更高, 在  $3500\text{ cm}^{-1}$  周围。我们可以立刻推断, O-H 键比 N-H 键强, 而后者又比 C-H 键强, IR 是一个很好的键的强度的量度。

■ 这可能震惊到您: 您过去可能一直认为 O-H 键比 CH 键更活泼。这当然是对的, 但您会在 Chapter 5 中发现, 除去键的强度, 还有其他因素控制着反应性。当我们在 Chapters 35 和 39 中讨论自由基反应时, 键强会重要得多。

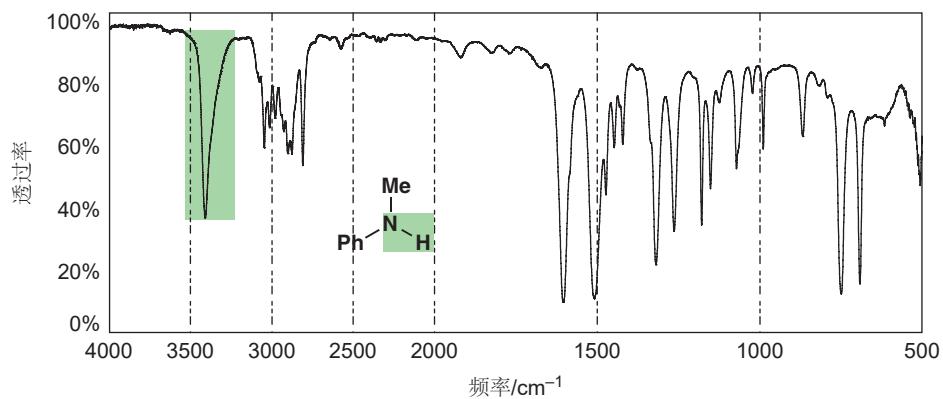
#### 与氢成的键的 IR 波段

键	约化质量, $\mu$	IR 频率, $\text{cm}^{-1}$	经典键的强度, $\text{kJ mol}^{-1}$
C-H	$12/13 = 0.92$	$2900\text{--}3200$	$\text{CH}_4: 440$
N-H	$14/15 = 0.93$	$3300\text{--}3400$	$\text{NH}_3: 450$
O-H	$16/17 = 0.94$	$3500\text{--}3600^{\text{a}}$	$\text{H}_2\text{O}: 500$

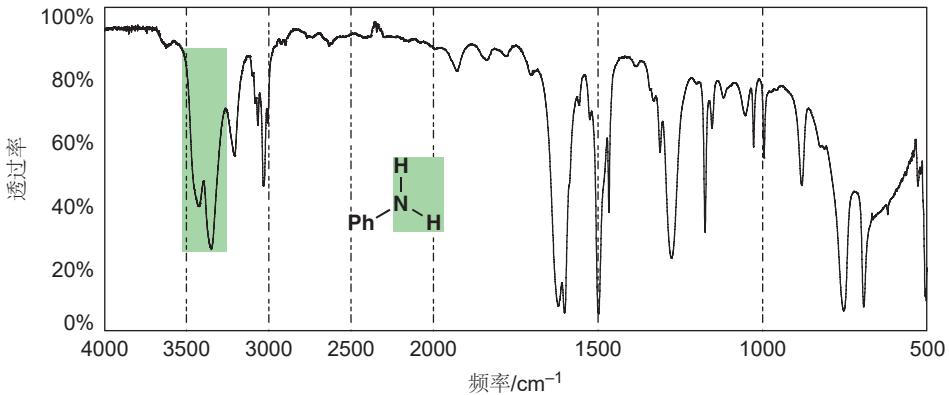
<sup>a</sup>当无氢键键合时: 见下文 (有氢键时在  $3500\text{--}2900$  出现宽峰)。

这四种化合物中, X-H IR 伸缩所得的吸收波段的形式是非常不同的。看看如下光谱的阴影部分。

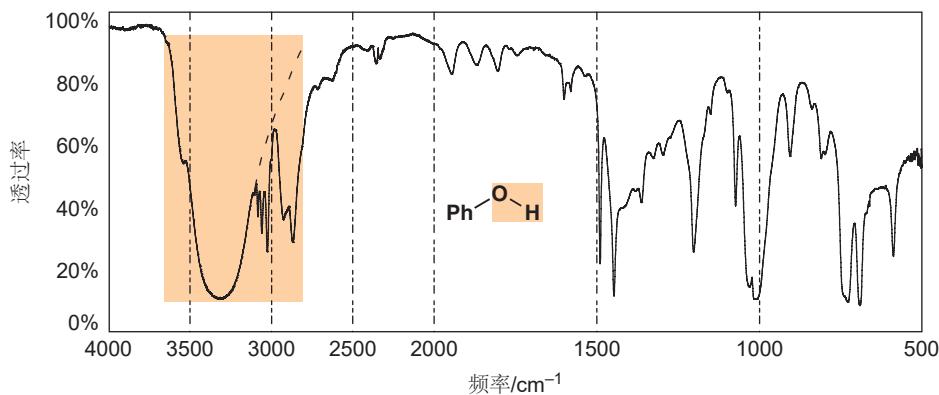
光谱 1



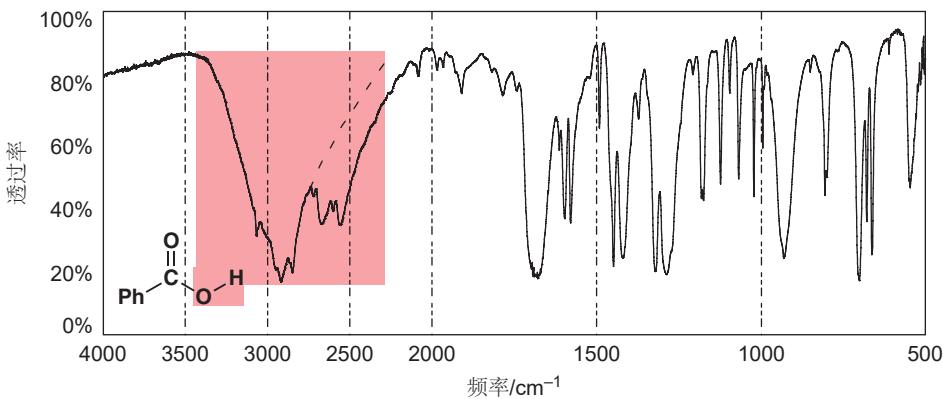
光谱 2



光谱 3



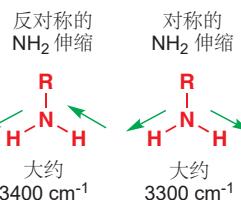
光谱 4



NH 基的 IR 峰 (光谱 1) 看起来与 NH<sub>2</sub> 基的峰不同 (光谱 2). 只有当一根键的强度和约化质量和与之相邻的键有差别时，才可得到独立的振动。在孤立 N—H 基的情境中，无论 NH 基是简单仲胺 (R<sub>2</sub>NH) 的一部分，还是酰胺 (RCONHR) 的一部分，这都很可能是正确的，我们通常在大约 3300 cm<sup>-1</sup> 处得到一个锐利 (sharp) 的峰。NH<sub>2</sub> 基也与分子的其余部分独立，但 NH<sub>2</sub> 基内部的两根 NH 键有完全相同的键常数和约化质量，因而会作为一个简单单元振动。此时出现两种同样强的键波段：一种是两根 N—H 键同相位 (对称 symmetric) 振动，另一种是两根 N—H 键反向振动 (反对称 antisymmetric)。反对称振动需要更多的能量，因而出现在稍高的频率处。

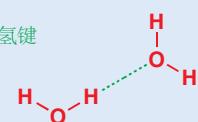
O—H 波段发生于更高的频率，有时以一个锐利的吸收出现在 3600 cm<sup>-1</sup>；而更常见的情况则是像在光谱 3 和 4 中那样，在 3500 到 2900 cm<sup>-1</sup> 之中的任何位置出现一个宽 (broad) 吸收，这是因为 OH 基会形成长度、强度均不同的强氢键。在 3600 cm<sup>-1</sup> 处出现锐利的吸收，则表明这是一个无氢键结合的 OH 基；吸收的频率越低，则 H 键越强。

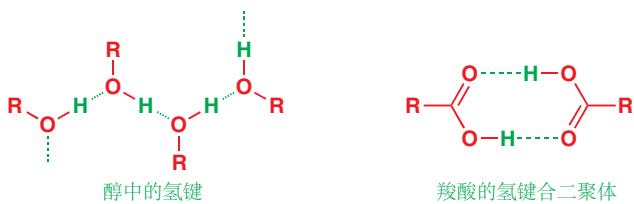
醇会形成一个分子的羟基氧和另一个分子的羟基氢之间的氢键。这些键在长度上不同（虽然它们通常比普通的共价 O—H 键长得多），因而对真正的共价 O—H 键微弱的弱化作用也会不同。当一根键的键长和键强发生变化时，它的伸缩频率便会分布于一个均值附近的范围内。醇，包括光谱 3 所示的苯酚，通常会在大约 3300 cm<sup>-1</sup> 处给出一个圆滑 (rounded) 的吸收（与前面光谱中相同区域内的 N—H 锐利的形状对比）。羧酸 (RCO<sub>2</sub>H) 可以在两分子分别提供的一个羰基氧和一个酸性氢间形成两根强 H 键，进而形成氢键合二聚体 (hydrogen-bonded dimers)。它们在长度和强度上也有相当大的差异，因而通常会得到非常宽的 V型 吸光度 (absorbance)，如您在苯甲酸的光谱 4 中所见。



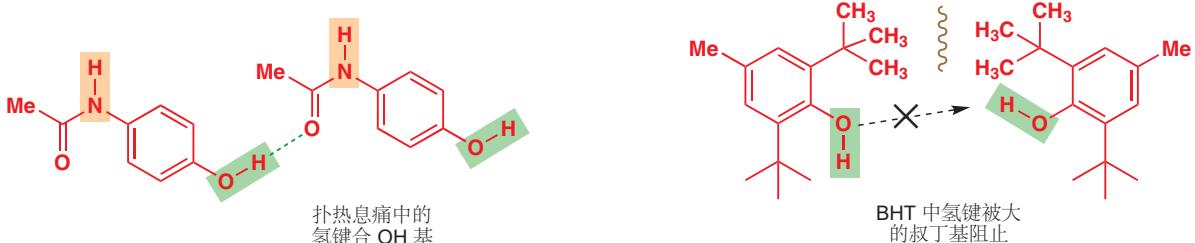
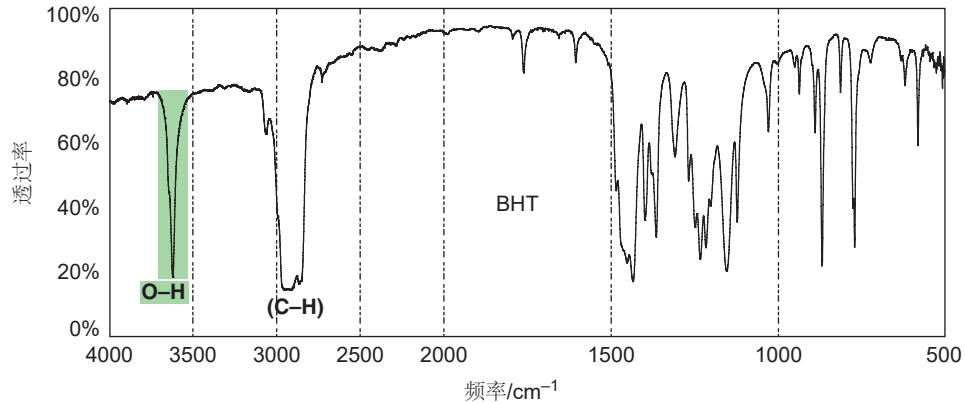
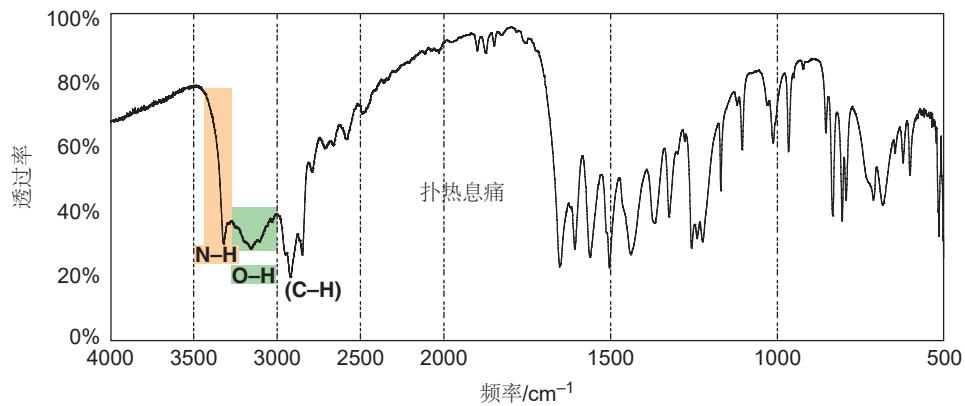
Interactive vibrations of methylamine

氢键 (Hydrogen bonds) 是由富电子原子，如 O 或 N 到同样与这类原子以“一般”键相连的氢原子之间形成的键。下图中是两分子水之间的氢键，实线代表“一般”键，绿色的虚线代表较长的氢键。氢原子处在两个氧原子之间距离的大约三分之一处。



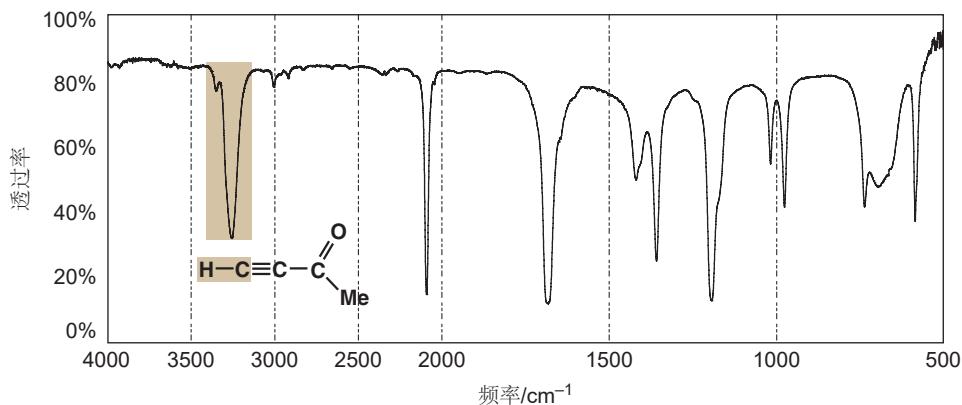


扑热息痛和 BHT (您在 pp. 58–59 所认识的) 的光谱说明了氢键对峰形 (peak shape) 的影响。扑热息痛在  $3330\text{ cm}^{-1}$  处有一个典型的锐利的峰, 它是 N–H 伸缩; 然后, 在 3300 到  $3000\text{ cm}^{-1}$  区域内, N–H 和 C–H 伸缩的缝隙中, 有一个圆滑的吸收, 这是氢键合的 O–H 伸缩。相比之下, BHT 在  $3600\text{ cm}^{-1}$  处有一个锐利的吸收, 这是由于两个大的叔丁基组织了典型氢键的形成。



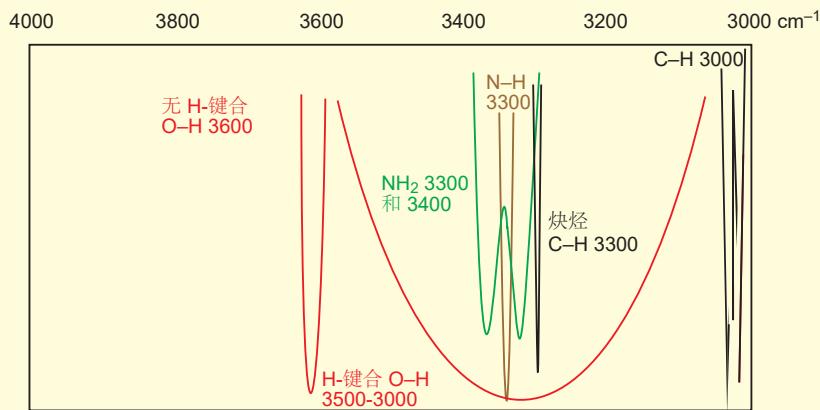
第一次见到末端炔烃,  $\text{R}-\text{C}\equiv\text{C}-\text{H}$ , 的 IR 光谱时, 您可能感到困惑, 因为您会在大约  $3300\text{ cm}^{-1}$  处看到一个像是 N–H 伸缩的相当强的 (strongish) 锐利的峰——下一页中, 甲基丙炔酮/甲基乙炔基酮 (methyl propynoate/propiolate) 的光谱可说明此现象。通常的 C–H 伸缩在大约  $3000\text{ cm}^{-1}$

处，而在炔基中，伸缩峰的位移并不能用约化质量的变化解释，而应当用下图所标出的键的强度的增加解释。炔烃 C—H 键比烷基 C—H 键更短，更强。



在 Chapter 4 中，您会认识到，饱和结构中的碳用  $\text{sp}^3$  轨道成 C—H 键，而末端炔烃则用  $\text{sp}$  轨道成 C—H 键，后者的轨道含有一半 s 成分，而非四分之一的 s 成分。在 s 轨道中的电子，相比于在 p 轨道中的电子，被碳原子核抱得更紧，离其更近，因此  $\text{sp}$  轨道会促成一根更短、更强的 C—H 键。

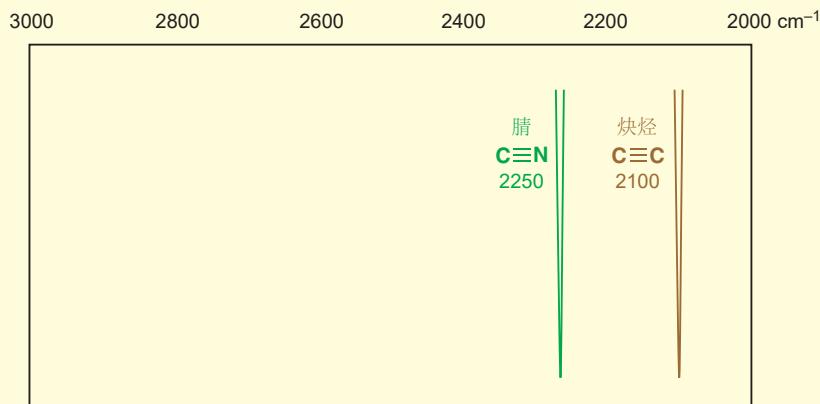
### ● 4000–3000 $\text{cm}^{-1}$ 区域内 X—H 键的典型峰形和频率



### 三键区域 ( $3000$ – $2000 \text{ cm}^{-1}$ )

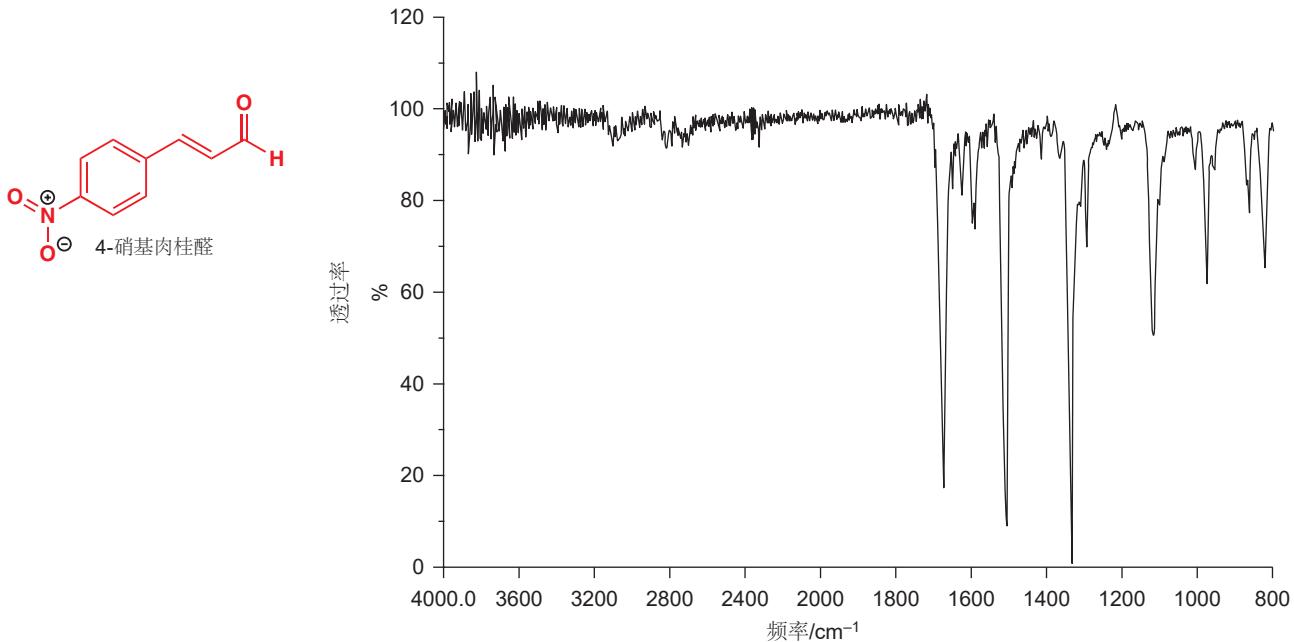
这个区域通常是空的，这就意味着，当您看到处于 2000 到 2500 之间的峰，您便可以绝对地肯定，这个化合物是一个炔烃 (通常在 2100 周围) 或是一个腈 (在  $2250 \text{ cm}^{-1}$  处). p. 65 上文有例子。

### ● 三键区域仅有的两个峰



### 双键区域在 IR 谱图中最为重要

双键区域中最重要的吸收，是羰基 ( $\text{C=O}$ )，烯烃或芳烃 ( $\text{C=C}$ )，和硝基 ( $\text{NO}_2$ ) 的吸收。它们都产生锐利的波段， $\text{C=O}$  会在  $1900$  到  $1500 \text{ cm}^{-1}$  之间的任何位置给出一个强 (strong/intense) 波段；烯烃  $\text{C=C}$  会在大约  $1640 \text{ cm}^{-1}$  处给出一个弱 (weak) 波段，而  $\text{NO}_2$  则在  $1500\text{s}$ -中段 和  $1300\text{s}$ -中段  $\text{cm}^{-1}$  给出两个强波段。芳烃通常在  $1600$ – $1500 \text{ cm}^{-1}$  间给出两个或三个波段。我们可以在下方所示的，4-硝基肉桂酸 (4-nitrocinnamaldehyde) 的谱图中说明其中的几个特征。



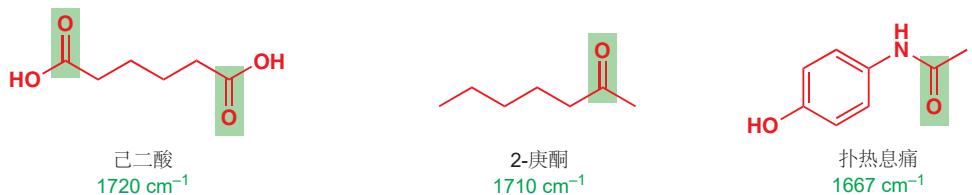
► 我们将在 Chapter 7 中阐明离域现象。此时此刻，请接受两根  $\text{NO}$  键等同的观点。

为什么硝基会给出两个峰是容易理解的。如同  $\text{OH}$  和  $\text{NH}_2$  的关系一样，问题的关键在于，同一官能团中有多少完全一样的键存在。羰基和烯烃很明显都只有一根双键。第一眼看硝基，您会发现它有两根不同的键， $\text{N}^+–\text{O}^-$  和  $\text{N}=\text{O}$ ，但离域 (delocalization) 意味着，它们是完全相同的，我们也能看到对称和反对称伸缩振动的吸收。和  $\text{NH}_2$  一样，反对称型振动需要更多的能量，因而发生在更高频率处 ( $>1500 \text{ cm}^{-1}$ )。



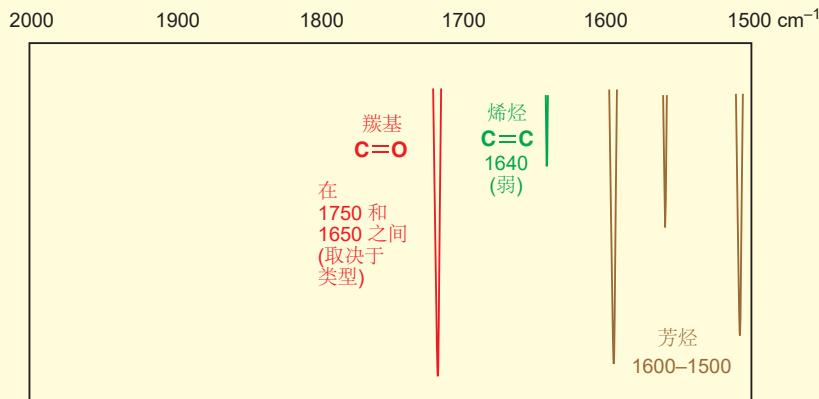
芳烃，处于环中，它的振动模式复杂得多，因而无法被简单地分析。然而，值得注意的是，芳烃  $\text{C=C}$  键振动的频率 ( $<1600 \text{ cm}^{-1}$ ) 比烯烃  $\text{C=C}$  键的 ( $>1600 \text{ cm}^{-1}$ ) 低。为什么？苯环中分离的  $\text{C}-\text{C}$  键当然不是完整的  $\text{C}=\text{C}$  双键——全部六根键都是相同的，平均每根键为三分之二根。这些键的吸收正好落在单键和双键区域的边界线上，这并不令人惊讶。

在本章中，您已认识过如下的三种羰基化合物的 IR 光谱。在它们的光谱中，很容易识别出  $\text{C=O}$  峰—— $\text{C=O}$  峰往往是强峰 (稍后您会认识到原因)，并且出现在  $1700 \text{ cm}^{-1}$  附近的某个位置。



对于为什么峰的位置会变化(注:如羰基),以及我们能从峰的位置的信息中获取什么,我们将在 Chapter 18 中讨论。

### ● 双键区域中重要的吸收



### IR 吸收的强度取决于偶极矩

如果您回头看 pp. 66–67 四个光谱中的 X–H 区域( $3000\text{--}4000\text{ cm}^{-1}$ ),您会发现一些乍一看有些奇怪的事情。虽然这些分子中的 C–H 键都比 O–H 或 N–H 键多, N–H 和 O–H 吸收仍位于 $3000\text{ cm}^{-1}$ 处的 C–H 吸收强。这个现象的原因在于,当键伸缩时,IR 吸收的强度随偶极矩(*dipole moment*,见下方文字框中的定义)的变化而变化。如果键完美地对称,那么偶极矩便不会有变化,因而也就没有 IR 吸收。很明显, C=C 键的极化比不上 C=O 或 N=O,因而前者的吸收在 IR 中也就没有后两者的强;事实上,若烯烃对称,则前者的吸收可能并不存在。相比之下羰基非常极化,其中氧从碳上吸引电子,它的伸缩会导致偶极矩较大的变化。C=O 伸缩通常是 IR 光谱中最强的峰。O–H 和 N–H 伸缩比 C–H 伸缩强,也是因为 C–H 仅仅弱极化。

■ 对比术语“强度”在用于描述吸收和描述键时的区别。强的吸收代表更高的峰。强的键(其他条件相同时)意味着吸收频率更高。

### 偶极矩

偶极矩取决于沿着键的电子分布的变化,也取决于键的长度,因而键的伸缩会导致偶极矩的变化。对于不同原子间的键,它们电负性上的差异越大,偶极矩就越大,在伸缩时改变得也就越多。对于完全相同的原子间的键(例如 C=C),偶极矩本身,和伸缩时偶极矩的改变能力都小得多。对称分子的伸缩频率可以通过一种被称为拉曼光谱法(Raman spectroscopy)的方法测量。这是一种使用散射光的基于 IR 的技术,依赖于键的极化能力(polarizability)。拉曼光谱不属于本书的讨论范围。

下表的总结,可帮您回忆目前为止我们对于 IR 光谱各种各样的推论。

### ● IR 谱图中的吸收

波段的位置 取决于:	原子的约化质量和 键强	轻原子和强键 给出高频率
波段的强度取决于:	偶极矩的改变	大偶极矩给出强吸收
波段的宽度取决于:	氢键	强 H 键给出宽峰

### 单键区域被用作分子指纹

低于  $1500\text{ cm}^{-1}$  的区域，是单键振动发生的位置。我们希望个别键可以独立于分子的其余部分振动，但我们的希望常常落空。 $\text{C}$ ,  $\text{N}$ , 和  $\text{O}$  原子的原子质量几乎相同， $\text{C}-\text{C}$ ,  $\text{C}-\text{N}$ , 和  $\text{C}-\text{O}$  单键的键强也几乎相同。

单键

原子对	约化质量	键强
$\text{C}-\text{C}$	6.0	$350\text{ kJ mol}^{-1}$
$\text{C}-\text{N}$	6.5	$305\text{ kJ mol}^{-1}$
$\text{C}-\text{O}$	6.9	$360\text{ kJ mol}^{-1}$

■ 匹配的指纹可用于将嫌犯与罪犯建立联系，但您不能通过诠释指纹，推知罪犯的身高、体重、眼睛颜色。指纹区也是一样：匹配的指纹可用于确认两个化合物相同，但弱没有“嫌犯”，您只能依赖于光谱的其他部分，即  $1500\text{ cm}^{-1}$  上方的部分来分析。

此外， $\text{C}-\text{C}$  键还经常与其他有基本完全相同的强度和约化质量的  $\text{C}-\text{C}$  键连接，并且基本没有偶极矩。这些单键中唯一具有任何价值的是  $\text{C}-\text{O}$ ，它足够极化，可在大约  $1100\text{ cm}^{-1}$  处表达出一个强吸收。其他的一些单键，例如  $\text{C}-\text{Cl}$  (弱，约化质量大，因此出现在低频率)，出现于  $700\text{ cm}^{-1}$  处，也很有用。这些情况之外，单键区域则常常挤满来源于各种各样的振动的成百上千的吸收，被用作分子的“指纹”特征，不会得到诠释。

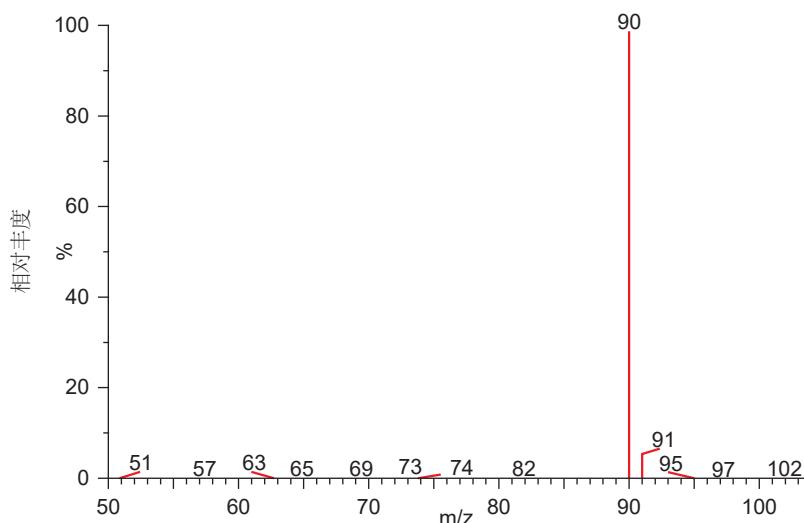
在指纹区成百上千的峰当中，有一些很不同的种类。伸缩并非导致 IR 吸收的键的唯一运动方式。键的弯曲，尤其是  $\text{C}-\text{H}$  和  $\text{N}-\text{H}$  键的弯曲，也会得到很强的峰。它们被称作位移 (*deformations*)。弯曲一根键比旋转它更容易 (试想弯曲和旋转一根铁棒哪个容易？)。因此，弯曲吸收相比于相同的键的伸缩吸收，需要的能量更少，吸收的频率更低。这些弯曲可能常常不会被用于分子的识别/鉴定上，但由于它们通常很强 (例如，通常比  $\text{C}=\text{C}$  伸缩强) 可能会被您注意到并令您疑惑。

形变频率

基团	频率, $\text{cm}^{-1}$
$\text{CH}_2$	1440–1470
$\text{CH}_3$	~1380
$\text{NH}_2$	1550–1650

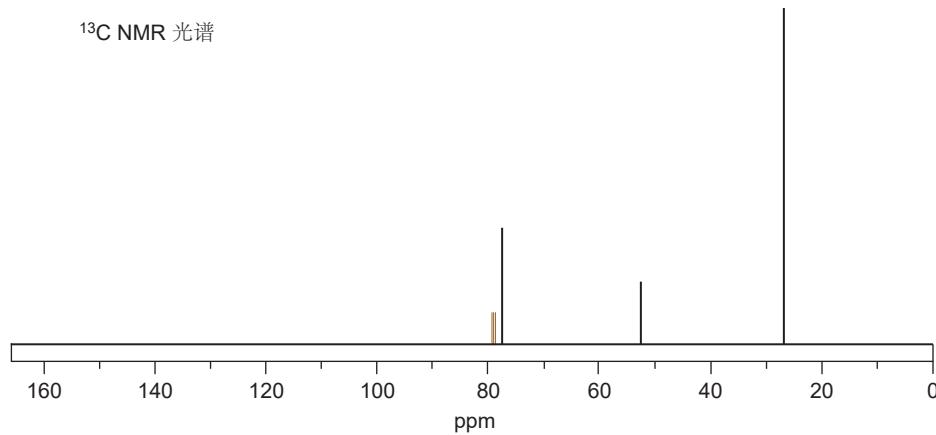
### 质谱法, NMR, 和 IR 的结合使快速识别成为可能

如我们所见，这些方法本身都很强了，那么如果将它们结合起来，会是多么有效啊！我们会以对一些简单未知化合物，运用这三种方法的识别/鉴定完成本章。第一种是一种用于将固体和液体混合为光滑的糊状的工业乳化剂。它的电喷雾质谱法显示， $\text{M} + \text{H}$  质量为 90，奇数分子量 (89) 表明分子中存在一个氮原子。高分辨率质谱法揭示，它的分子式为  $\text{C}_4\text{H}_{11}\text{NO}$ 。

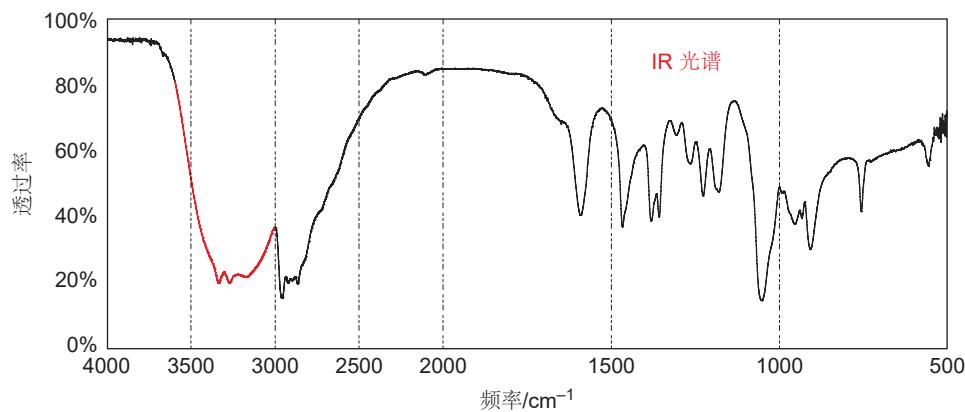


$^{13}\text{C}$  NMR 谱图仅有三个峰，因此其中有两个碳原子必然是相同的。有一个与氧相连的饱和碳原子的信号，和两个其他的饱和碳原子的信号，其中一个比另一个在更低场区。

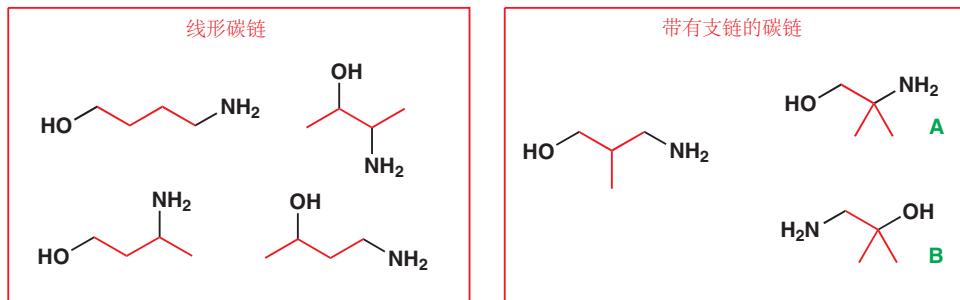
$^{13}\text{C}$  NMR 光谱



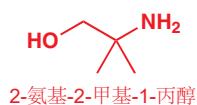
IR 光谱揭示了一个 OH 基的宽峰，和两个凸出的锐利的  $\text{NH}_2$  峰。如果我们将其放在一起，我们便知道分子中含有一个  $\text{C}-\text{OH}$  和一个  $\text{C}-\text{NH}_2$ 。这些碳原子都不能重复 (由于仅有一个 O 和一个 N)，因此另两个 C 原子一定是相同的。



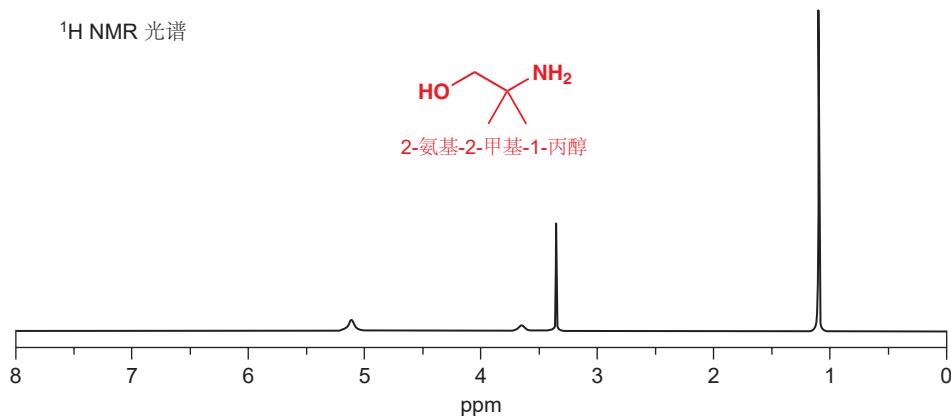
下一个阶段经常被忽略。虽然看起来，我们没有掌握太多的信息，但我们可以试着将两个片段放在一起，由于知道分子式，可能的选择是很少的。碳链（以红色显示）既可以是线形，也可以带有支链。



由于我们需要容纳 11 个氢原子，因而没有空间留给双键或者环。我们不能将 N 或 O 放进链中，因为我们由 IR 得知，分子中有 OH 和 NH<sub>2</sub> 基团，它们都只能再连接一个其他基团。七种可能性当中，只有最后的两个，A 和 B，含有两个相同的碳原子（均为甲基）因而是可能的，其他的所有结构都会在 NMR 中含有四个信号。

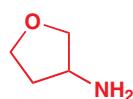
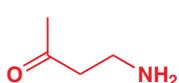
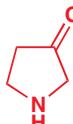


那么，我们怎么在其中选择呢？我们需要 <sup>1</sup>H NMR 光谱，如下所示。只有两个可见的峰：一个在 3.3，另一个在 1.1 ppm. 在 <sup>1</sup>H NMR 光谱中看不到连在 O 或 N 上的质子是很正常的（您会在 Chapter 13 知道为什么），因此我们可以排出有两种以上连在 C 上的 H 的种类的所有结构。同样剩下 A 和 B，这验证了之前的推断。但位于  $\delta$  3.3 处的信号的化学位移可以告诉我们更多：它被去屏蔽了，所以一定是与氧原子相邻的 H 原子。工业乳化剂因而是 A: 2-氨基-2-甲基-1-丙醇。



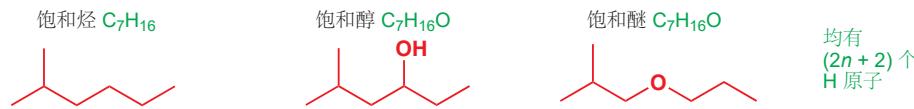
## 双键的等价物有助于结构搜索

对于一个未知化合物，一旦您知道它的分子式，就应立即算出它是否是饱和的，这对于结构推断通常是有帮助的。上一个例子 C<sub>4</sub>H<sub>11</sub>NO 是完全饱和的，不含双键，似乎很明显，C<sub>4</sub>H<sub>9</sub>NO（失去两个氢原子）含有一根双键，C<sub>4</sub>H<sub>7</sub>NO 含有两根，以此类推。不过事实并不如此简单。这些分子式还可能有以下可能的结构。

$C_4H_9NO$  的一些结构 $C_4H_7NO$  的一些结构

其中一些结构含有正确数目的双键 ( $C=C$  和  $C=O$ )，其中一种含有一根三键，其中三种用环作为一种替代方式弥补了“失去的”氢原子。每形成一个环，或一根双键，分子都需要失去两个氢原子。因此 (任何种类的) 双键和环被称为**双键等价物 (double bond equivalent, DBEs)**。

只画出一种符合分子式的可能结构，您便能知道该分子组成含有多少种 DBEs (相同的分子式的每种可能结构都有相同数目的 DBEs)。同样，如果您愿意，DBEs 可以通过计算得到。一个含有  $n$  个碳的饱和烃含有  $(2n + 2)$  个氢原子。氧原子的加入不会造成影响：饱和醚或醇与饱和烃的 Hs 的数目相同。



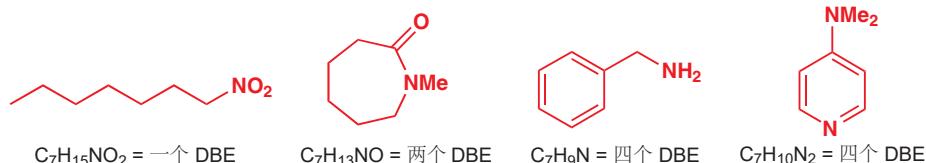
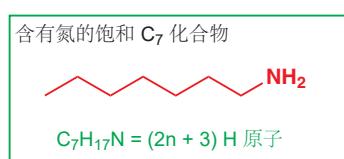
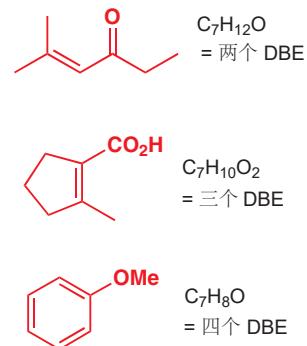
因此，对于一个仅含有 C, H, 和 O 的化合物，DBEs 的数目为实际氢的数目与  $(2n + 2)$  的差值除以二。让我们检验它是否有效，对于一个不饱和酮  $C_7H_{12}O$ ，计算如是：

1. 7Cs 的 H 原子的最大数目:  $2n + 2 = 16$
2. 减去实际 H 原子数 (12):  $16 - 12 = 4$
3. 除以 2 得到 DBEs:  $4/2 = 2$

另有两个说明该方法的例子。对于第二个，不饱和环状酸： $16 - 10 = 6$  除以 2 = 3 DBEs，它含有一个烯烃，一个  $C=O$ ，和一个环。正确。

芳香醚： $16 - 8 = 8$  除以 2 得到 4 DBEs，它的环中含有三根双键，还有环本身。还是正确的。苯环通常给出四个 DBEs: 双键的三个，和环本身的一个。

氮会造成影响：因为氮成三根键，因而每个氮都会添加一个额外的氢。这意味着公式会变为：实际氢与  $(2n + 2)$  的差值，加上氮原子数目，再除以二。我们同样可以尝试这个公式。下面有一些含有七个 C 原子，一个 N 和各种不饱和环的结构例子。



饱和化合物含有  $(2n + 3)$  个 Hs [而不是  $(2n + 2)$  个]。对于饱和硝基化合物： $(2n + 2) = 16$ ，减去 15 (Hs 实际数目) 再加上一 (氮原子数目) = 2. 将其除以 2 则可得到 1 DBE，这是  $N=O$  键。我们将第

第三和第四个例子留给您尝试，对于最后一个化合物 (DMAP 我们之后将见到它)：

■ 不要将这一计算与我们在考察质谱时做出的，关于含有一个氮原子的化合物的分子量必为奇数的观察混淆了。当然，那个观察与 DBEs 的数目是相关的，但它们是为了不同目的所做的不同计算。

1. 7Cs 的 H 原子的最大数目:  $2n + 2 = 16$

2. 减去实际 H 原子 ( $10$ ):  $16 - 10 = 6$

3. 数加上氮原子数:  $6 + 2 = 8$

4. 除以 2 得到 DBEs:  $8/2 = 4$

确实含有三根双键和一个环，总体为四。确保您能轻松做出这些计算。

如果还含有其他元素，那么您可以画出一个试验结构，然后找出 DBEs 的数目，这是很容易的。对于所有化合物，这可能都是您倾向于选择的方法，因为它可以在您真正开始前，先给出一个可能的结构。一个很好的提示是，如果您发现氢原子相对于碳原子的数目很少 (至少四个 DBEs)，那么化合物中很有可能包含一个芳环。

通过高分辨率质谱法测得的分子式，了解双键等价物的数目，是生成一些可信的结构的捷径。然后您可以通过将它们与 IR 和 NMR 数据对比，以排除。

### ● 计算未知化合物的 DBEs

1 计算饱和结构中期望的 Hs 数目

(a) 仅含 C, H, O 的  $C_n$ , 会是  $2n + 2H$

(b) 对于  $C_nN_m$ , 会是  $2n + 2 + m$  个 H 原子。

2 减去实际 Hs 数目并除以 2, 则得到 DBEs.

3 如果还有其他原子 (Cl, B, P, 等) 最好先画一个试验结构。

4 一个 DBE 表明一个环或一根双键 (一根三键为两个 DBEs).

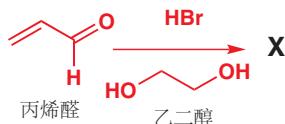
5 一个苯环含有四个 DBEs (双键的两个和环的一个)。

6 如果 Hs 很少，例如少于 Cs 的数目，则怀疑有苯环。

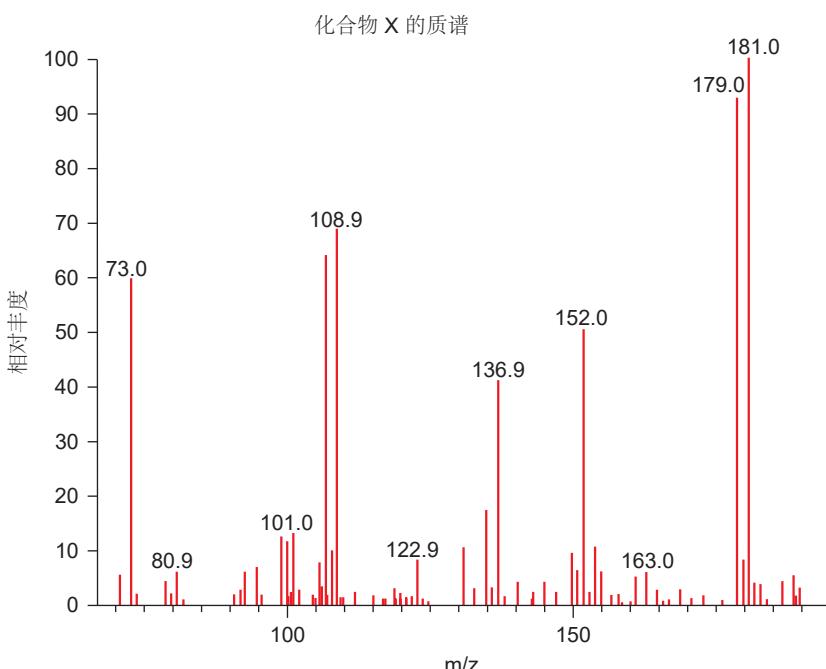
7 一个硝基只含有一个 DBE.

注：即  $DBE(s) = 1 + C(H-N)/2$ .

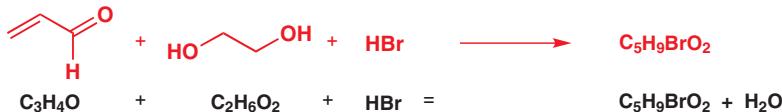
### 由一个化学反应得到的未知化合物



我们的最后一个例子讨论的是化学中非常常见的一个情境——得到一个反应的产物的结构。情境如下：您将丙烯醛 (propenal/acrolein) 用乙二醇溶剂中的 HBr, 在室温下处理了 1 小时。蒸馏反应混合物得到了一种无色的液体，混合物 X. 它是什么呢？

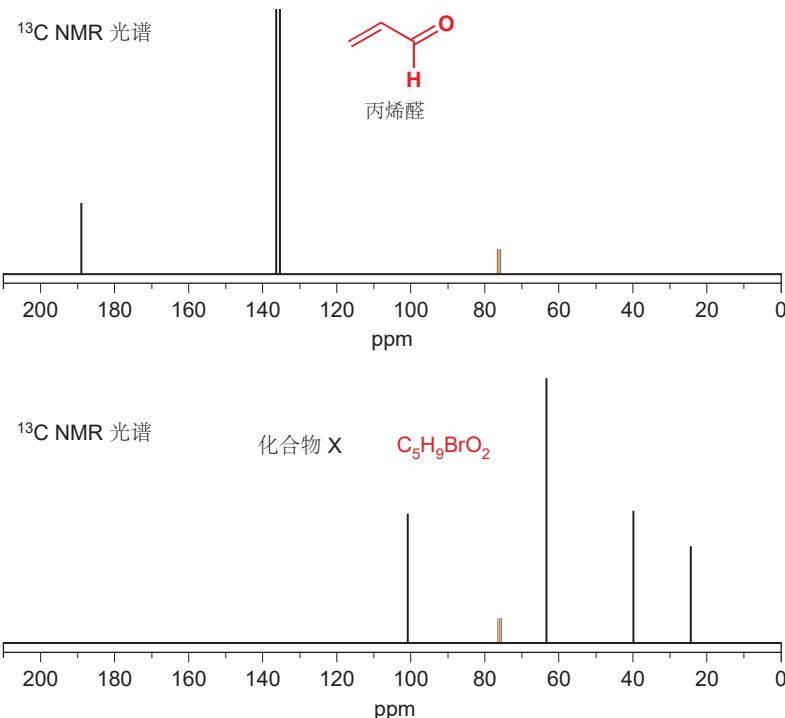


质谱显示了一个比起始原料,  $C_3H_4O = 56$  更重的分子离子 (181)。事实上它在 181 和 179 显示了两个分子离子, 这是典型的溴代物, 因此看上去像是 HBr 加成到了醛的某个位置。高分辨率质谱揭示了分子式为  $C_5H_9BrO_2$ , 含有的五个碳原子使之看上去像是也被乙二醇加成了。如果我们将它们放在一起, 则可以发现, 未知化合物是三个试剂加在一起并脱去一分子水的结果。



现在, 我们得到了多少个 DBEs? 对于像这样的分子式, 最安全的选择是画出一个符合分子式的试验结构——它不必是您所认为的产物。侧边栏展示了其中一种——我们仅仅添加原子, 然后再加入一根双键。 $C_5H_9BrO_2$  有一个 DBE。

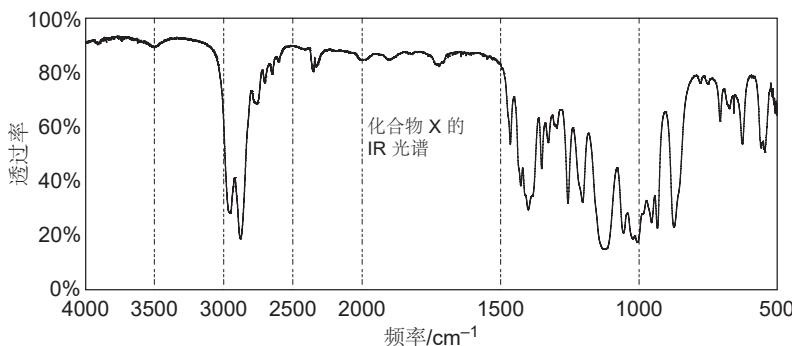
下一件事, 是通过 NMR 来看看丙烯醛的碳氢骨架还剩下什么。 $\text{CH}_2=\text{CH}-\text{CHO}$  的  $^{13}\text{C}$  NMR 光谱很清楚地显示, 有一个羰基和两个位于双键上的碳原子。它们在产物中都消失了, 对于五个碳原子, 存在四个信号: 两个普通饱和碳, 一个与氧相连的饱和碳, 一个在 102.6 ppm 处, 刚刚进入双键区域的信号。



当处理未知产物时, 从它的分子量中减去起始原料的分子量, 这可以帮您发现被加成上去(或被脱除下来)的事物。

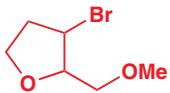


IR 光谱给予了我们另一个难题——似乎根本没有官能团出现! 没有 OH, 没有羟基, 没有烯烃——那我们还能有什么? 答案是一个醚, 或者说由于有两个原子, 就是两个醚。现在既然我们怀疑它是醚, 那么我们可以在 IR 光谱中寻找 C–O 单键的伸缩, 我们在  $1128 \text{ cm}^{-1}$  处找到了它。

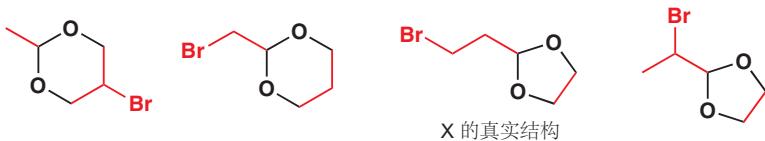


每个醚氧，都需要在它的两侧各有一个碳原子，但在  $^{13}\text{C}$  NMR 中，似乎只含有一个处在与 O 相连的饱和碳的区域 (50–100 ppm) 的饱和 C。当然，我们已经认识到，这些限制是武断的，事实上在 102 ppm 处的峰也是与 O 相连的饱和 C；形成一个烯烃需要两个碳，因此它不太可能是一个双键碳，那么，是什么让一个饱和 C 被如此地去屏蔽呢？答案是两个氧原子。如果我们假设一个占据五个碳原子中的三个的，对称的 C–O–C–O–C 片段，那么便可以解释  $^{13}\text{C}$  光谱了。

所以，双键等价物在哪里呢？我们知道我们并没有得到一根双键（没有烯烃也没有  $\text{C}=\text{O}$ ），因此 DBE 必然是一个环。您可能对环感到不适，但您必须习惯它们。五、六和七元环非常常见。事实上，大多数已知的有机化合物都含有环。我们可以画出很多符合这一分子式的环状结构，如侧边栏所示的一个。



但这不是真实的结构，因为它含有五个不同的碳原子。更有可能的情况是，有机试剂的基本骨架都被保存了下来，即，我们有一个两个碳的片段（来自乙二醇）和一个三个碳的片段（来自丙烯醛），它们通过氧原子相连。这会给出四种可能性，都含有我们之前推得的 C–O–C–O–C 片段（黑色显示）。



它们都很合理，由于很容易能看出第三种结构可以由试剂衍生得到，我们更倾向于第三种。产物事实上就是第三种可能性，然后，我们还需要用  $^1\text{H}$  NMR 光谱法确认，我们将在 Chapter 13 中回到这个过程。

## 展望 Chapters 13 和 18

我们刚刚开始探索通过光谱法，鉴定结构的错综复杂的世界。认识到结构被指派，不是因为一些理论性原因或者说因为反应“应该”给出某种特定产物而给出的，它们是通过光谱上的证据被指派的。您在本章中，见到了四种有力的方法——质谱法、 $^{13}\text{C}$  和  $^1\text{H}$  NMR，以及 IR 光谱法。在 Chapter 13 中，我们会更加深入地考察其中最重要的一种 ( $^1\text{H}$  NMR)，最后，在 Chapter 18 中，我们还会进一步地使用每一种方法，并展示较复杂的未知化合物的结构是如何真正被推断出来的。我们在本章所讨论的最后一个问题是，如果没有  $^1\text{H}$  NMR 是无法真正得到解决的，现实中，没有人会舍弃这种，所有技术中最强的一个，来应付任何结构问题。从现在起，光谱证据将会出现在几乎每一章。每一种新的化合物出现时，即使我们没有明说，它们的结构事实上也都是通过光谱法确定的。化学家制取新的化合物，并用一整套图表征它。若不将全部的光谱，及对其的完整描述一并提交，没有一本科学杂志会接受这样的新化合物。光谱法使有机化学的科学前进。

## 延伸阅读

如果您手边有一本关于光谱分析的短书，这会有好处的，因为它可以给您全面的数据表，问题和解释。我们推荐 *Spectroscopic Methods in Organic Chemistry*, 6th edn, by D. H. Williams and Ian Fleming,

McGraw-Hill, London, 2007, 和牛津初级读本 *Introduction to Organic Spectroscopy* by L. M. Harwood and T. D. W. Claridge, OUP, Oxford, 1996.

## Check your understanding

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To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 4

## 分子结构

### 联系

#### ► 基础

- 如何绘制有机结构 ch2
- 用于确定有机结构的证据 ch3

#### 目标

- 我们如何知道电子含有不同能量
- 电子如何填入原子轨道
- 原子轨道如何组合形成分子轨道
- 有机分子采取直线型、平面型或四面体型结构的原因
- 形状和电子结构间的联系
- 描绘简单分子的分子轨道的形状和能量
- 预测孤对电子和空轨道的位置

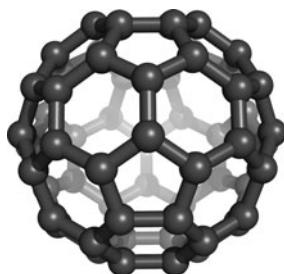
#### ► 展望

- 取决于原子轨道相互作用的反应 ch5 & ch6
- 源于分子轨道能量的反应性 ch5, ch10, & ch12
- 轨道重叠形成的共轭结果 ch7
- NMR 涉及分子轨道 ch13

### 概述

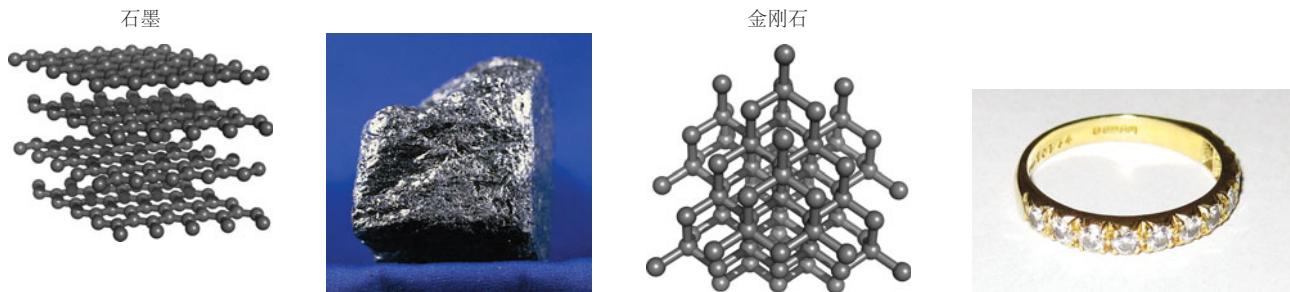


您也许会根据左侧的模型认出 DNA，携带地球上生命的遗传指令的分子。DNA 的螺旋结构在 1953 年被发现，而 DNA 中原子的具体排列方式则由它来自蚂蚁、羚羊、金鱼草还是炭疽来决定。



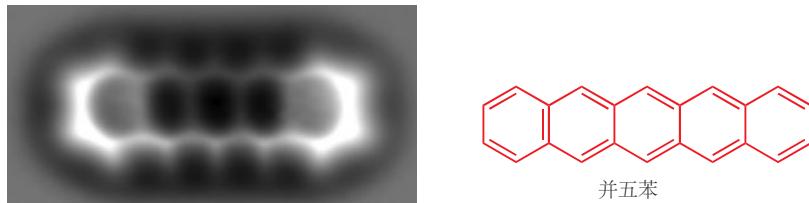
您也许也会认得这个分子，它是巴克明斯特富勒烯，一种足球形的碳的同素异形体。巴克明斯特富勒烯以网格球形穹顶（看上去非常像）的建筑设计师的名字命名，它的结构在 1985 被确定，确定他的科学家在 1996 年被颁发了诺贝尔化学奖。

现在，我们的问题来了：您是如何识别出这两种化合物的呢？您是根据形状。分子并不是原子杂乱无章的摆放形成的，而是原子以确定的三维结构聚集形成的。一个化合物的性质，不仅取决于原子组成，还取决于它的结构。石墨与金刚石——它们都是碳单质的同素异形体——都只有碳原子构成，然而它们的性质，既包括化学性质又包括物理性质，都是完完全全不一样的，这是因为碳原子的排列方式的不同造成的。石墨是碳原子构成的六边形堆积而成的层状结构，而金刚石是碳原子构成的四面体堆积形成的。



我们知道分子的形状是什么样的，因为我们可以看到它们——并非字面意思，而是指使用例如原子力显微镜 (AFM) 等方法。下图是利用 AFM 获得的并五苯的结构。利用这种方法，我们可以“看见”原子本身，这是我们离原子最近的观察方法。

Interactive structures of buckminsterfullerene, graphite, diamond, and pentacene



然而，大多数分析技术采用的是间接获得分子结构的方法。X-ray 衍射实验可以揭示原子在空间中的排列方式，而您在 Chapter 3 遇到的那些光谱分析方法，则可以揭示分子的组成 (质谱法) 和分子中原子的连接方式 (NMR 和 IR)。

利用这些方法，我们就可以了解分子的形状。这就是为什么在 Chapter 2 中，我们一直要求您将分子结构画得尽可能逼真——正是因为我们知道真实的分子长什么样，我们才被允许将结构绘制得逼真。本章中我们要解决的是另一方面的问题，为什么分子表现出它们表现出的那种形状。所含原子的哪些特征决定了那些形状？我们会找到一种不仅帮助我们解释和预测分子结构，而且能帮助我们解释和预测分子的反应性 (Chapter 5 中的重点主题) 的答案。

首先，我们需要思考为什么原子会结合形成分子。有些原子（例如氦原子）非常不情愿那样做，但周期表中的大多数原子都不如形成分子后稳定。例如下面的甲烷：四个氢原子围绕着碳原子并构成了四面体形状。



Interactive structures of methane, ammonia, and water

分子的形成是由于正电性的原子被负电性的原子吸引，因此电子显然起到了“粘合”原子的作用。甲烷中的 C 和 H 当然都是正电性的，但十个电子(六个来自 C, 四个来自 H) 将这些正电荷绑在了整个分子上。氨 ( $\text{NH}_3$ ) 和水 ( $\text{H}_2\text{O}$ ) 也有十个电子，它们的形状事实上也与甲烷类似，只是有一个或两个氢原子(氢原子核)被删去了。



这告诉了我们重要的一点：决定分子形状的是电子的数量，而不仅仅是原子(或原子核)的数量。但究竟是什么因素决定了电子如是排列呢？例如，为什么十个电子必然形成四面体结构呢？

在回答这个问题之前，我们需要先简化一下讨论的方式，将电子想象在孤立的原子中，而不是整个分子中。这样我们可以通过考虑原子如何结合，来近似地得到分子的电子结构；记住这一思想对理解本章十分重要。然而，分子很少直接通过原子之间相互连接来生产；我们只是对分子既定结构的分析，而不是对分子制备方式上的讨论(这是我们将在书的后部分专门讨论的问题)。我们将要涉及的很多内容都建立于 1900 年前后的工作中，它们都来自实验观察。量子理论则注重解释细节，您可以在物理化学的书上阅读到那些内容；本书介绍这些理论的目的，只是帮助您建立足够的理解，并且能够使用这些原则解释和预测有机分子的结构。

所以首先，是一些证据。



■ 您在 Chapter 3 中有关 NMR 的文段中曾遇到了这种说法：低能状态吸收能量移动到高能状态，随后再释放能量。在此处我们所提到的低能与高能之间能量差会更大，因此发射光的波长也会短得多。

有两种元素，铯和铷，就是 Robert Bunsen 在 1860 和 1861 年通过研究发射光谱而发现的。它们的命名也来自光谱中两条明亮的谱线——“铯 (caesium)”来自拉丁文 “caesius” 意为灰蓝色，“铷 (rubidium)”来自拉丁文 “rubidus” 意味红色。

■ 您可以在物理化学的教材中找到 Balmer 的公式的细节。

## 原子发射光谱

许多城镇和街道的夜晚都被钠蒸汽灯所点亮，它发出干净的橙黄色光芒。灯的内部是金属钠。当灯被打开时，钠会慢慢地蒸发。当电流通过钠蒸汽时，钠就会发射橙色的光——与您将少量含钠化合物置于本生灯上所观察到的颜色相同。供能充足(来自电流或火焰)时，钠总能发射出相同波长的光，这是由钠原子上电子的排列方式所导致的。钠获得能量，并从低能级跃迁到高能级，或激发态，然后电子再跃迁回基态，后者多余的能量会通过光的形式释放。这个过程有一点像举重运动员把重物举过头顶(激发态)，然后他很快就会让重物重新掉回地上，通过碰撞释放能量，如果没有造成脚趾骨折的话。钠是原子光谱 (atomic spectrum) 研究的起源，然而不仅对于钠，对于所有元素：电子得到能量跃迁到高能级，并在返回低能级时以光的形式释放能量。

如果使钠橙色的光芒通过棱镜，您会得到一系列非常清晰的谱线，在 600 nm 附近的橙色区域包含两条十分明亮的线。其他原子也产生相似的谱线——甚至是氢；由于氢原子是最简单的原子，我们会首先由其入手。

## 电子有量子化的能级

1885 年瑞士的一名校长，约翰·巴耳末 (Johann Balmer) 测量了氢的吸收光谱，并且注意到了它谱线的波长可以用数学公式预测。当前您不需要知道这个公式的细节，相反，让我们想一想氢原子的光谱具有分立的谱线和确切的波长这一观测结果的意义。这一结果意味着电子可以占据的能级

是由确切的数值决定的，换句话说就是围绕质子(氢原子核)运动的电子的能量是**量子化的(quantized)**。电子的能量只能有几种确切的取值，因此这些(产生光谱的)能级之间的间隔也同样是确切的数值：想象您在爬楼梯——如果您精力充沛，可以一次走一节、两节、五节或更多节，但您不能走半节或三分之二节；同样，在下楼时，您可以跨越一节直接跳到下一节——多种不同的组合都是可能的，但组合的总量应当是一个有限的数值，它取决于台阶的数量。

在上一段中我们特意提到了电子“围绕”氢原子核运动，因为这是我们思考原子结构的一个方式——作为一个微缩的( $10^{-23}$ 倍！)太阳系模型，其中原子核是太阳，电子则是行星。当我们详细研究原子时(您马上就会看到)，这个模型会被破坏；但此时，我们可以借助它思考电子必须处于量子化的能级的原因。

为此，我们需要从十九世纪的物理学中引入一个概念——实验观测的事实表明，像质子和电子这样的粒子，同时扮演**波**和**粒子**的角色。因此当思考为什么电子的能量是量子化时，我们通常从电子作为波的角度出发。

想象一个在两端固定了的紧绷的琴弦——例如钢琴弦或吉他弦。您可能知道这样的弦有一个基频(基本频率, fundamental frequency)：如果您通过按或拨的方式使其振动，它则会按照右侧第一幅图中的振动方式振动。它是对于琴弦描述的“模糊图像”：任何涉及到琴弦振动的地方都大致有如图的特点，通过慢速快门您可以拍到类似的照片。

但这不是琴弦振动的唯一方式。右侧的第二幅图也同样是一种可能性，其中不仅弦的两个终端是固定的，而且在中间还有一个点——被称作“波节(node)”是静止不动的。这根弦振动的波长是上一根弦的一半，因此频率是上一根的两倍。这种振动在音乐效果上听起来比第一种高八度，它被称为一次谐波(first harmonic)。后几幅图分别对应的是其他可能情况，为高次谐波。

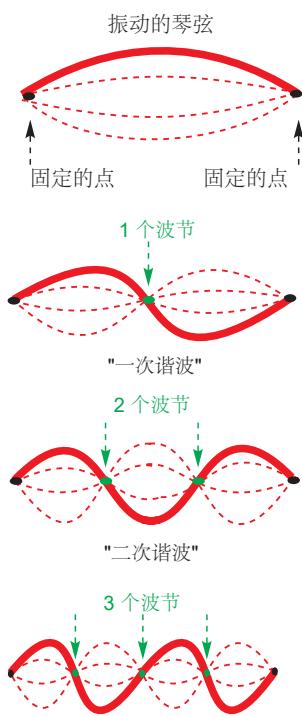
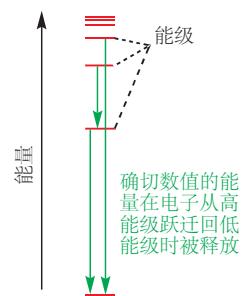
您从前在音乐和物理课上可能没有遇到过这个想法：琴弦除了这些量子化的频率值外别无选择——它的频率只能表现为某些确定的值，因为末端已经固定，琴弦长度必须是波长的整数倍。正如我们之前看到的，频率与能量相关：因此振动着的琴弦的能量是量子化的。

我们已经知道电子也是一种波，那么电子的能量必须处于几个特定值的结论，就变得很好理解了。电子绕原子核的环形运动可以想象成琴弦首尾相连，经历一个循环后回到自己本身，那么电子的波长就只能取确定的可能值。而频率与波长相关，能量与频率相关：我们对电子能量的量子化有了合理的解释。

## 电子占据原子轨道

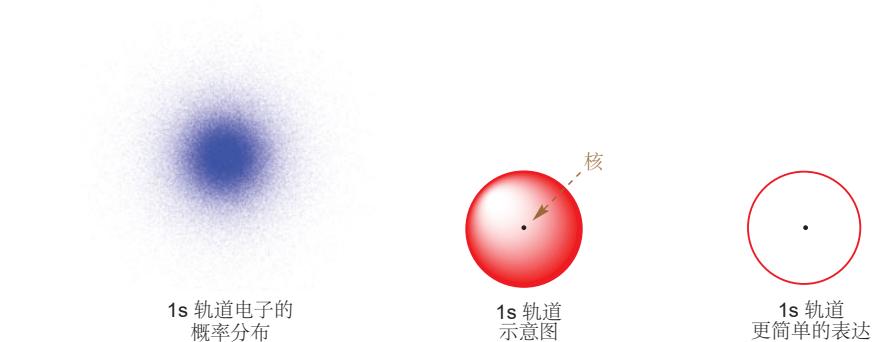
行星模型虽然十分流行，但它只在某些情况下发挥作用，我们现在要将它抛在脑后。存在于这种对原子结构的理解中的问题在于，电子永远不可能被精确地定位，相反我们只能将它们看作在有限空间上的分布。其原因源于**海森堡不确定性原理(Heisenberg's Uncertainty Principle)**，您可以在有关量子物理的任何书上读到。不确定性原理告诉我们，我们永远无法同时确切地知道任何粒子的位置和动量。如果我们知道一个电子的能量(和量子化的能级)，我们就知道它的动量，但这时我们就不能确切地知道它的位置了。

因此，我们对原子(和分子中)中电子位置的研究，就只限于在一个确定的时间中，在一个确定的位置出现的**概率**了，在不同位置概率的总和构成了电子的分布图，就像我们用慢速快门记录的琴弦

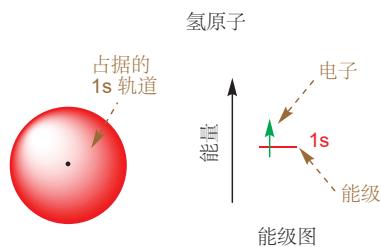


丹麦物理学家 Niels Bohr 第一次用振动的类比阐释了轨道只能有确定的能量值的原因。虽然我们接下来不会继续使用它，但它在量子物理中的作用十分广泛，同样可以用来形象化轨道的其他方面，例如波节和波函数的图像。

振动图。由于电子在三维空间上运动，因此它采取的“振动”也是三维的，也就是我们常说的轨道，或者（当我们考虑单个原子中的电子时）称为**原子轨道 (atomic orbitals)**。这些轨道的形状被数学公式所决定，也就是**波函数 (wavefunctions)**。左下图展示了氢原子中基态电子的概率分布图（即电子云），这是最简单的轨道分布图。可见，用点的密集程度表示在任何一个点找到电子的概率（概率密度）是不方便的，因此我们更常用的表达方式是用实线圈出（现实中是三维的）电子出现的时间超过 95% 的位置，即右下图所示的。这种最简单的轨道是球状的，被称为 **1s 轨道**。不同能量的轨道具有不同的形状，您马上就会看到。

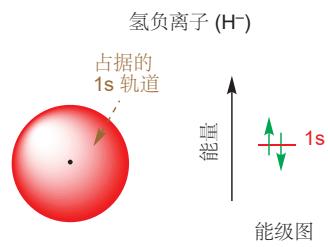


原子轨道表述的是电子能量的可能取值（能级）中的一种，当电子处于某一能级时，我们称其为“占据”某一轨道。在基态氢原子中，只有一个电子，占据最低能量的 1s 轨道。因此 1s 轨道的图片同样是 H 原子的图片。当我们把 1s 轨道想成一种能级时，可以将电子使用一个小箭头来表示。



即泡利不相容原理  
(Pauli exclusion principle).

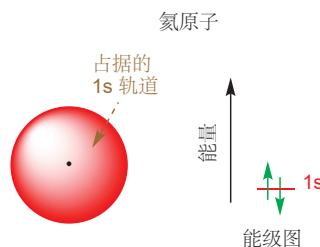
如果您把多个电子放入一个原子轨道中会发生什么？虽然我们不能在这里告诉您原因，但每个原子轨道至多容纳两个电子。如果您在 H 原子的基础上加入一个电子，您会获得氢负离子 (hydride anion),  $\text{H}^-$ ，即两个电子围绕 H 原子核（质子）运动。这两个电子都占据球形的 1s 轨道。



我们在 NMR 的内容中 (p. 53) 谈到了原子核的旋转。电子的自旋是与之不同的——例如，您不能通过 NMR 观察电子，但您可使用一种称为电子自旋振动或 ESR 的技术观察。

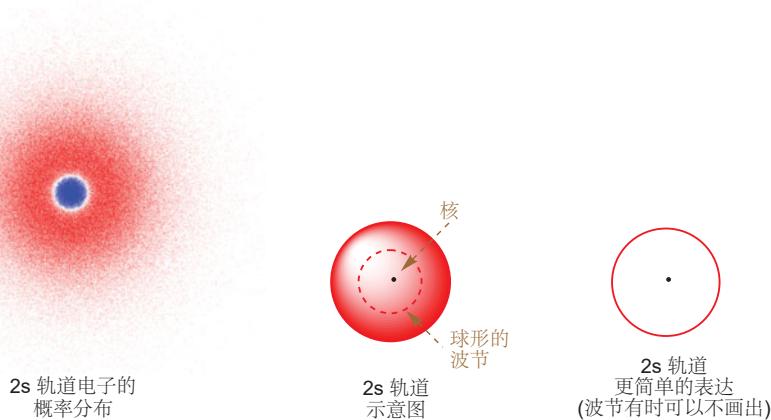
在这里我们同样可以将轨道占用情况表述成能级图：能级用水平线表示，电子用箭头表示。为什么我们要用箭头表示电子？这是由于电子有自旋 (spin) 的性质，两个相反的箭头代表电子处于相反的自旋方向。箭头正是作为一种表述方向的符号。

氦原子的情况与氢负离子相似：两个电子占据同一原子轨道。然而，该轨道（和其他可能的能级/轨道）的能量却与氢中的不同，因为氦原子核两个单位的正电荷对电子的吸引比氢原子核更强。我们可以将其表示成下图，轨道的能量较低于 H 中的。

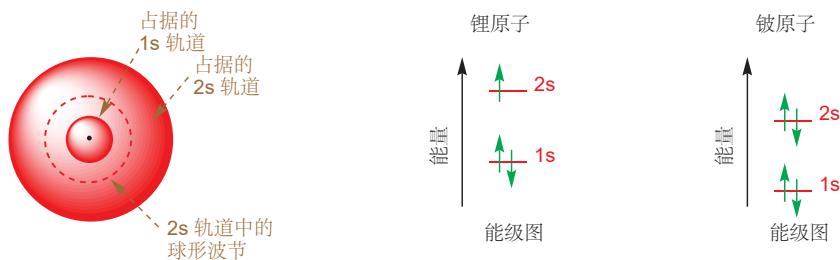


### s 轨道与 p 轨道有着不同的形状

前面的事情已经解释清楚了，现在我们要来关注锂。Li 核周围最低能的 1s 原子轨道只可以容纳两个电子，所以第三个电子必须前去占有更高能的轨道——原子吸收光谱分析 (atomic absorption spectroscopy) 可以表明它的存在。您可以将这个轨道想象成三维琴弦的一次谐波；正像是琴弦的振动一样，这个新的轨道有一个波节。在琴弦的振动上，波节意味着保持静止的点；而在原子轨道上，波节则表示永远无法找到电子的点——轨道分离成的两个部分之间的空隙。对于填有 Li 第 3 个电子的轨道，它的波节是球状的——它将整个轨道分成了两个彼此依偎的轨道，像是洋葱中的层或者桃子中的核。我们叫这个轨道 2s 轨道——因为“2”才会有波节的出现（像一次谐波），而因为“s”则表明它仍然是球形的。虽然“s”的由来并不是“球 (spherical)”的缩写，但所有“s”轨道都是球状的，您可以使用这种方法记住它。



在锂原子中，离核较近的 1s 轨道被两个电子所占据，而离核较远的 2s 轨道则被一个电子占据。对于铍原子，2s 轨道又被填充了第二个电子。与之前相同，轨道的能级随着核电荷数的增加而降低，因此 Li 和 Be 的能级图可以画成下列形式。

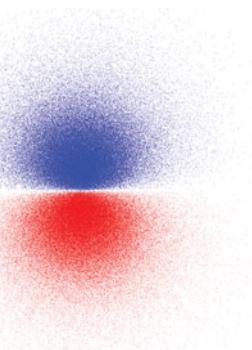


当我们说到硼时会出现一些不同。这时，原子轨道中的波节（就像 2s 轨道中的）不一定是球状

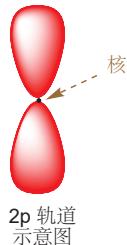
的，它同样可以是一个平面。随着这种平面的波节而产生的，是原子轨道的另一种类型，即  $2p$  轨道。 $2p$  轨道的电子云（电子概率分布）如左下图所示，我们通常将它画成如中图的螺旋桨型，右下图同样是简便画法。

■ 我们稍后将解释  $p$  轨道为什么被画成一半填满一半空心的样式。

 Three-dimensional representations of the shapes of atomic orbitals



2p 轨道中电子的概率分布

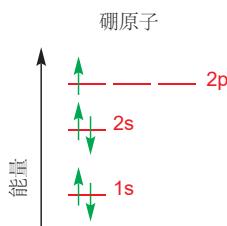
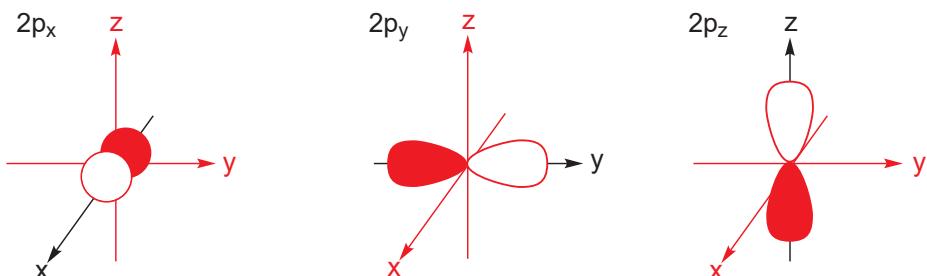


2p 轨道示意图



2p 轨道更简单的表达

与  $1s$  或  $2s$  轨道不同的是， $2p$  轨道是具有方向性的——它沿着一根轴生长。因此沿着三根坐标轴，会同时出现三个  $2p$  轨道（需要的时候，我们通常会使用  $2p_x$ ,  $2p_y$  和  $2p_z$  分开称呼）。

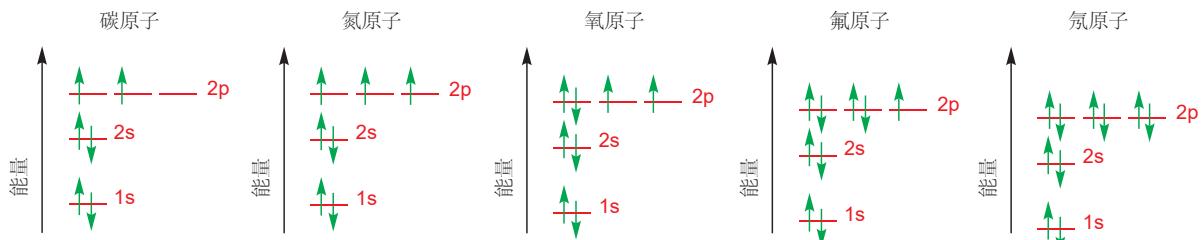


这条规则被称为洪特规则 (Hund's rule)，其内容为：原子中的电子倾向于成单排列在简并的轨道中。这个规则虽然是经验规则，但有些许理论依据，因此很少有反例出现。您接下来会看到，同样的规则也适用于分子中的电子分布。

三个  $2p$  轨道平面的波节让它们的能量，比包含球状波节的  $2s$  轨道略高。因此硼原子在  $1s$  轨道上填有一个电子， $2s$  轨道有两个，三条  $2p$  轨道上仅有一个。左侧的能级图显示了上述的电子填充情况。您可以想象每个轨道的形状，我们无需展示它们中的所有混合后的情形。

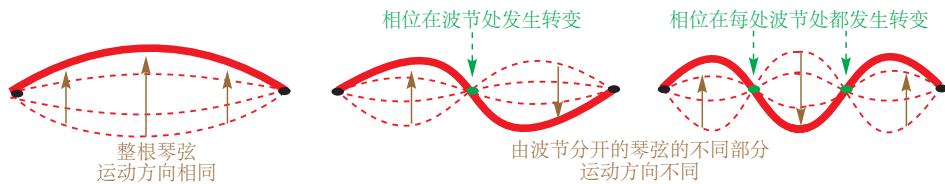
下一个元素，碳，又多含有一个电子（第六个），在这里我们有两种选择——第一种是在同一个  $2p$  轨道中与已经填好的第五个电子凑成一对；第二种是另辟一个新的  $2p$  轨道，第五、六个电子均成单。事实上它选择了后者：由于电子带负电，成对时会在彼此之间存在排斥力；因此如果有空着的、能级相同的轨道，电子更愿意选择分别成单。在这个例子中可选择的轨道完全相同；但要注意的是，电子成对的排斥力远远小于不同能级轨道间的能量差，因此如果只能在成对或占据更高能级的轨道中做选择，电子还是会不情愿地成对。

下面我们给出了前两个周期中剩余元素的轨道能级图，我们可以观察出如下规律。从始至终，由于原子核对电子吸引力的提高，这些轨道整体的能量都在降低。另一点，在填充  $2p$  轨道时，首先成单排列，直到无法成单时，再开始成对。到氖原子为止，所有含有一个波节的轨道都被填满了，我们因此称氖原子为一个“闭壳层 (closed shell)”。一个“壳层 (shell)”表示的是一类能量相近、波节数相等的轨道（“2”即指一个壳层，包含  $2s$  和  $2p$ ）。



## 轨道的相位

下面是与 p. 83 中展示的相同的图片：它们表示琴弦的前三种振动频率。现在让我们来想一想琴弦本身的运动：在第一种震动中，整根琴弦同时上下运动——虽然琴弦上的每个点速度不同，但方向都是相同的。这个特点不能体现在第二种“能级”的琴弦上——在这种振动中，当波节左侧的一部分向上运动时，右侧的一部分向下运动——两半琴弦的相位 (phase) 相反，并且在波节处发生转变。第三种能级的琴弦与之相同，只是在两个波节处相位都发生了转变。



轨道亦是如此。像  $2p$  轨道中那样的波节平面 (nodal plane, 简称节面)，同样会将轨道分为两个不同相位的部分；一侧的波函数为正，另一侧的波函数为负。我们通常使用阴影来表示相位的区别——即一侧涂满阴影，而另一侧留为空白，之前展示的  $2p$  轨道就采用了这种表示方法。值得说明的是，轨道的相位是任意规定的，将哪一侧涂阴影是无足轻重的。另外，相位指的是波函数的正负，与电荷也同样没有关系：充满的  $2p$  轨道每一侧都充满电子，因此它们都是带负电的。

那为什么相位还如此重要呢？稍后我们学习原子结合形成分子时，就会遇到它，分子轨道就是原子轨道的波函数相加的结果，它能告诉我们分子中电子的位置、能量的多少等等。

碰巧，电子在空间中每个点的概率密度，在数学上是通过波函数的平方计算的。相位表示的是波函数的正负，但不论波函数的正负，给出的概率密度总是正的。

### s, p, d, f

为什么使用  $2s$ ,  $2p$ , . . . ? 这些字母来自早期的光谱法研究，分别表示原子发射光谱中主要谱线的外观：“s”表示“锐利 (sharp)”, “p”表示“主要 (principal)”. 您接下来还会遇到  $d$  和  $f$  轨道，都有不同的波节排布方式，这两个字母分别来自“漫散 (diffuse)”和“基本 (fundamental)”. s, p, d, f 这些字母是您必须记住的，但您并不需要知道它们源自哪里。

## 对于轨道的简短澄清

我们将继续发展轨道路理论，以便研究分子中的电子。但在此之前，我愿先澄清一些有关轨道易混淆的要点：

1. 轨道中不一定含有电子——它们可以是空的（就像楼梯的存在也不随是否有人站在上面而改变）。氦的两个电子只占据  $1s$  轨道，但如果向体系输入能量——例如太阳的酷热——其中一个电子就会跃迁到从前空置的  $2s$ ,  $2p$ , 或  $3s$  等轨道中。事实上，这种现象曾被观察到，人们正是从此过程中吸收的能量入手发现了太阳中存在的氦气。
2. 电子可以在除波节外轨道的任意位置被找到。在含有一个电子的  $p$  轨道中，除去中间，任何一侧都可以找到这个电子；当轨道包含两个电子时，也并不是双方各居一侧，而是在任何位置都可以找到它们两个（除去波节处）。
3. 一个原子中的所有这些轨道都与其他轨道相互重叠。 $1s$  轨道并不处于  $2s$  轨道中间，它们二者彼此都是独立的。每一个轨道都最多容纳两个电子，而  $2s$  轨道中填充的电子同样有可能进入  $1s$  轨道的区域（即与  $2p$  轨道重叠的区域中）中。例如氦原子，共含有十个电子：两个在  $1s$  轨道中，两个在  $2s$  轨道中，六个在  $2p$  轨道中。

道中，两个在(更大的)2s轨道中，在每个2p轨道中都另含有三个。所有这些轨道都彼此重叠。

- 当我们沿着周期表继续探索时——到钠，由于1s, 2s, 和2p轨道都被填满了，因此我们必须转向3s和3p轨道，接着是4s, 3d, 和4p轨道。到d轨道(和从镧系元素开始的f轨道)就有很多波节的排列方式了。我们不会详细讨论这些轨道——您会在无机化学的教材中找到那些讨论——但贯穿始终的原则与我们熟悉的简单轨道相似。

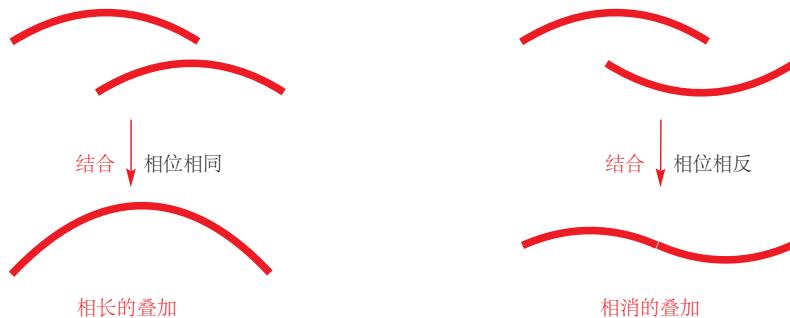
### Three-dimensional representations of d and f orbitals

■ 原子轨道组合形成分子的过程被称为**原子轨道的线性组合 (linear combination of atomic orbitals, 简写作 LCAO)**。

## 分子轨道—双原子分子

研究原子时，我们研究的是填充电子的原子轨道；而当我们开始研究分子时，同样我们要研究**分子轨道 (molecular orbitals)**。我们曾将分子想象成原子的组合(虽然分子通常并不由原子直接化合得到)，而当下我们也可以将分子轨道想象成原子轨道的组合。

原子轨道是波函数，因此原子轨道的组合是波函数组合的体现。您可能会想到，波的叠加有两种不同的方式，即**相长 constructively**(相位相同时)和**相消 destructively**(相位相反时)：



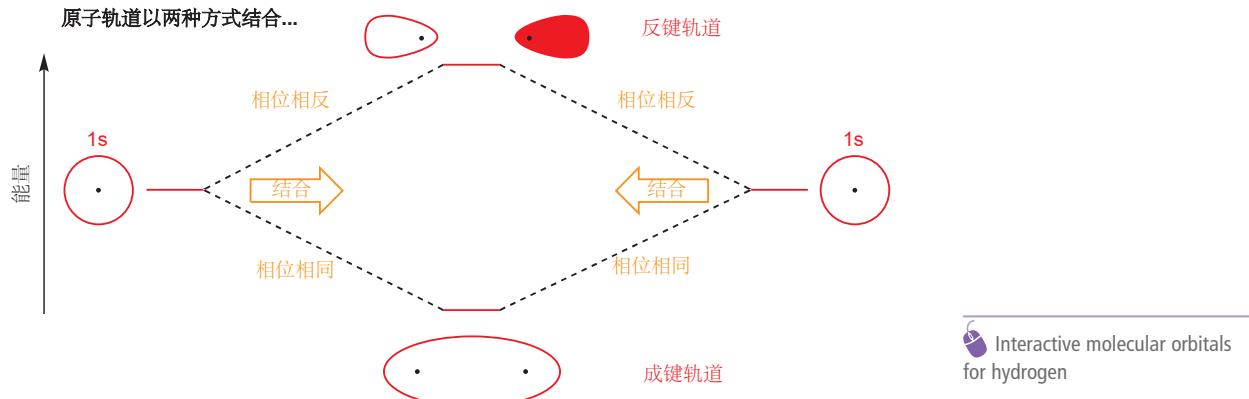
原子轨道同样以这两种方式结合——相位相同或相反。下图中用圆圈(代表球状)绘制了两个1s原子轨道，用点表示了原子核，用阴影表示了相位。我们可以让它们以相位相同的方式结合(即两个轨道相加)，这样得到的是一个在两个原子间蔓延的分子轨道；我们同样可以让它们以相位相反的方式结合(即两个轨道相减)，这样得到的分子轨道，是由中间的节面分开的两个相位相反的部分构成的。



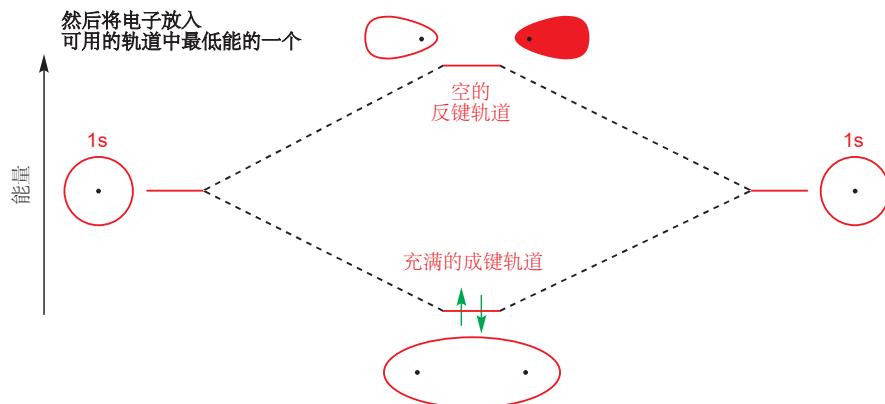
生成的分子轨道归两个原子所共有一——它们是分子轨道而不是原子轨道。在所形成的两个分子轨道中，参与成键的两个电子会填充在第一个轨道(成键轨道)中。这是由于电子带负电，原子核带正电，因此当电子处于两个原子核之间时，可以同时受到两个原子核的吸引，电子因此而稳定了。再次提醒，您可以在一个轨道中填充零个、一个，或两个电子，但绝不能更多。填充过后，我们得到了一根化学键！由于这个原因，我们称相位相同的叠加得到的分子轨道是**成键分子轨道 (bonding molecular orbital)**。

相位相反而生成的分子轨道没有上述可能性——事实上将电子放入这个轨道对成键起反作用。处于这个轨道中的电子可以在大多数地方被找到，但唯独不能在两个原子和之间，因为那里有一个波节。裸露的正电荷彼此排斥，这就是为什么它被称为**反键分子轨道** (**antibonding molecular orbital**)。

两个 **1s** 原子轨道相互叠加的过程同样可以被分子轨道能级图所描述。左右两侧分别是叠加前的两个原子轨道，而中间是相位相同、相反的两种方式结合得到的两个分子轨道。整张图表示的是成键前、后轨道情况的总和——相互作用前的轨道在左侧和右侧，相互作用后的在中间。您应当注意到成键轨道的能量低于先前的原子轨道，而反键轨道的能量高于先前的原子轨道。



现在我们依旧按照 p. 84 中讨论的方法将电子放置在轨道中。氢分子 (图中间显示的) 中的键由两个电子构成，每个氢原子均提供一个电子。电子的填充通常由低能到高能，填满后进入下一能级，因此两个电子理所当然放入成键轨道；而反键轨道则仍保持空置。因此电子更大概率地出现在两个原子核之间，这是我们对于  $\text{H}_2$  分子中的化学键的一个合理解释。



像这样的图表是我们在使用分子轨道理论 (molecular orbital theory, MO theory) 解释结构、反应性的核心，您会在将来经常用到。因此在我们继续之前，需要澄清以下几点：

- 两个原子轨道 (AOs) 叠加后生成两个分子轨道 (MOs)。其他数目的原子轨道叠加时往往得到的也是相等数目的分子轨道。
- 两个 AOs 的波函数相加 (相位相同的结合) 生成成键轨道，相减 (相位相反的结合) 生成反键轨道。

- 当参与成键的两个原子相同 (例如均为 H) 时 (虽然并不总是这样), 每个 AO 对于 MOs 的贡献是相同的。
- 成键 MO 轨道能量低于 AOs.
- 反键 MO 轨道能量高于 AOs.
- 每个氢原子最初含有一个电子, 它们的自旋方向并不重要。
- 两个电子最终处在能量最低的 MO 中——成键 MO.
- 就像 AOs 中, 每个 MO 都可以填充两个自旋相反的电子 (使用相反方向的箭头表示). 您不需要纠结电子对自旋的细节, 您只需要知道任何轨道都不能包含超过两对电子。
- 成键 MO 轨道中处于两个原子核之间的两个电子将整个分子构成一个整体——它们就是化学键。
- 由于这两个电子处在 MO 中, 比分别在 AOs 中有更低的能量, 因此形成的分子比独立的原子更加稳定, 即成键时释放能量。
- 如果您愿意, 您也可以通过向体系中输入能量来断键。

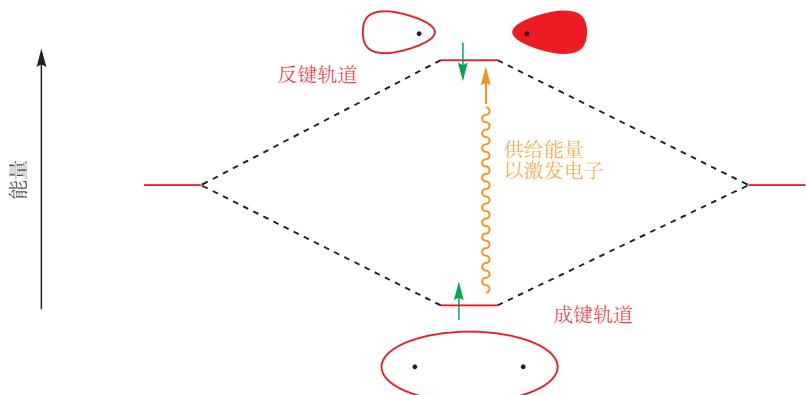
从现在开始, 我们将始终按照能量顺序表示分子轨道——最高能的 MO 处在最上面 (通常是一个反键 MO), 最低能的处在最下面 (通常是一个成键 MO, 所填充的电子最稳定).

当您离开这节之前, 让我们来回顾一下我们是如何绘制  $H_2$  的 MO 图的, 下面的步骤可以帮助您检查是否可以画出自己的 MO 图。

1. 在纸面的两侧分别画两个的 H 原子, 以及带有一个电子的 1s 轨道。
2. 画出波函数相加或相减得到的两个 1s 轨道, 即成键和反键 MOs. 这二者与 AOs 相比一高一低 (高能的反键轨道在顶端)。
3. 数清参与成键的电子总数, 并将它们按照能量从低到高, 即从图的底端到顶端的顺序放入 MOs 中, 记得每个轨道填充两个电子。

## 断键

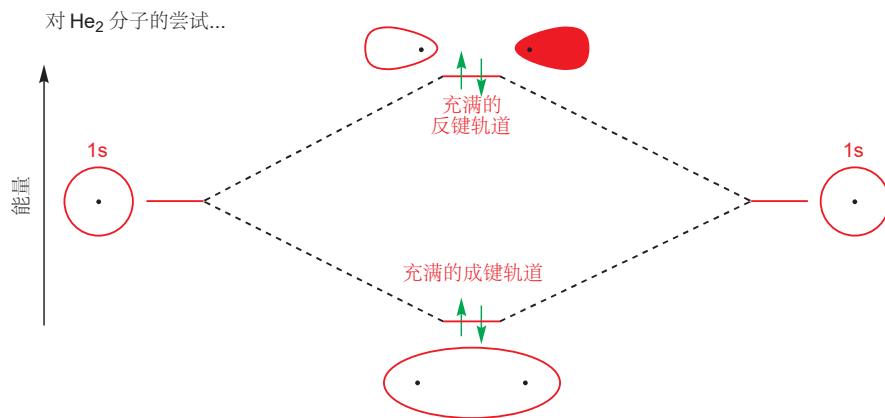
刚才的图表展示的是氢分子最稳定的形态, 电子的能量尽可能地低。那如果成键 MO (能量最低) 中的一个电子被激发到了反键 MO (能量最高) 上会发生什么? 轨道能级图会再一次帮助我们。



现在，反键轨道中的电子抵消了成键轨道中的电子，这时两个原子之间使得它们结合的键没有了，能量上也没有获得降低。它们当然可以与彼此分开，电子占据 1s AOs，从而回到两个独立原子的状态。换句话说，将一个电子由成键 MO 移动到反键 MO 会破坏化学键。这一操作对于氢分子是困难的，但对于溴分子是容易的。光照可以使  $\text{Br}_2$  分解为溴原子。

## 为什么氢是双原子分子而氦不是

就像 H 原子，He 原子同样有 1s 轨道和其中的电子，因此我们也可以照葫芦画瓢，给出  $\text{He}_2$  的轨道能级图。但它们最大的区别在于：每个氦原子含有两个电子，于是成键 MO 和反键 MO 都是满的！成键轨道中的任何电子都被反键轨道中对应得电子所抵消， $\text{He}_2$  于是分裂回原子。因此  $\text{He}_2$  是不存在的。



## 键级

成键 MOs 每比反键 MOs 多填入一对电子，两个原子之间就会多形成一根键。因此，我们将两个原子之间成键的根数定义为键级 bond order (两个电子形成一根化学键，因此除以二)。

$$\text{键级} = \frac{(\text{成键 MOs 轨道电子}) - (\text{反键 MOs 轨道电子})}{2}$$

因此  $\text{H}_2$  和  $\text{He}_2$  的键级为

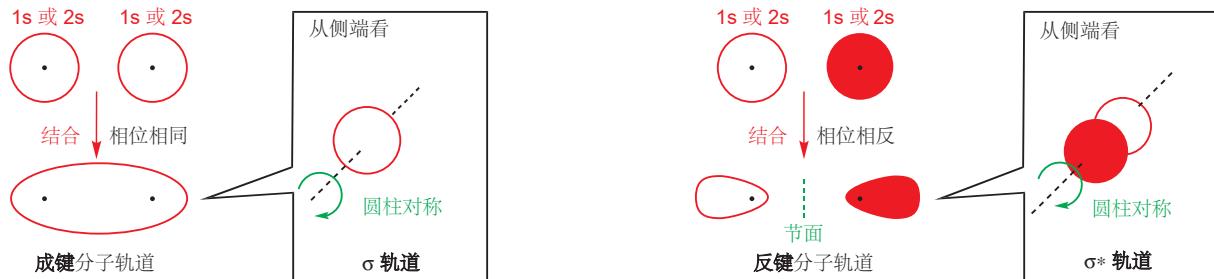
$$\begin{aligned}\text{键级}(\text{H}_2) &= \frac{2-0}{2} = 1, \quad \text{即一根单键} \\ \text{键级}(\text{He}_2) &= \frac{2-2}{2} = 0, \quad \text{即不成键}\end{aligned}$$

## 2s 和 2p 原子轨道参与成键形成的: $\sigma$ 和 $\pi$ 轨道

元素周期表中，自 Li 到 F 的原子都使用在 2s 和 2p 轨道上的电子成键，有机化学家常用的分子至少包含其中之一，因此我们必须学习 2s 和 2p 轨道相互作用的方式。另外我们还将向您介绍描述分子轨道对称性的术语。

我们将分析一种无处不在的双原子气体， $\text{N}_2$  的成键。 $\text{N}$  原子在 1s, 2s, 和 2p 轨道中含有电子，因此我们需要逐一考虑这些轨道之间的相互作用。

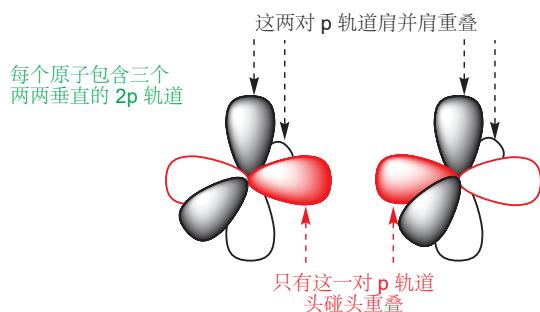
我们已经处理过 1s 轨道了，2s 轨道的叠加原理基本上是一样的。成键轨道与反键轨道的形状与 1s 形成的相似，但能量升高，这是由于 2s 轨道本身比 1s 轨道能量高。另外 2s 轨道比 1s 轨道体积更大。由于 2s 轨道“洋葱皮”的形状，它形成的 MOs 的确切性质要比 1s 形成的相对复杂，但您同样可以使用原先的方式表述：



1s-1s 和 2s-2s 的相互作用所形成的成键轨道有另一个常见特征：它们都是圆柱对称的。换句话说，当您从侧端看向这些轨道时，您可以将它们绕轴旋转任何角度，并得到与先前相同的形状。这是雪茄、胡萝卜、棒球棒的对称性。有球形对称性的这类成键轨道称为  $\sigma$  (sigma, 描述对称性的符号) 轨道，而将电子填入其中生成的键称为  $\sigma$  键。因此 H<sub>2</sub> 分子中的单键为  $\sigma$  键。

这些 AOs 结合生成的反键轨道同样有圆柱对称性，它们被称为  $\sigma^*$  轨道，其中 \* 为反键轨道的标志。

现在我们来讨论 2p 轨道。正如 p. 86 上的描述，每个原子都含有三个两两垂直的 2p 原子轨道。在例如 N<sub>2</sub> 的双原子分子中，这些 2p 轨道必须以两种不同的方式结合——每个原子中的一个 p 轨道（红色所示的）互相头碰头重叠 (end-on)，剩下的两对 p 轨道（黑色所示的）则以肩并肩重叠 (side-on)。



我们将首先处理头碰头重叠。当我们把两个 2p 轨道以相位相反的方式结合时：就像在 2s 轨道中的情形一样，我们会得到一个处于两原子间的波节，MO 中的任何电子都不会在任何时间处于两原子核之间，那个最稳定的位置——您应当猜出，这是反键轨道。



接着，如果我们以相位相同的方式使其结合，情形如下。

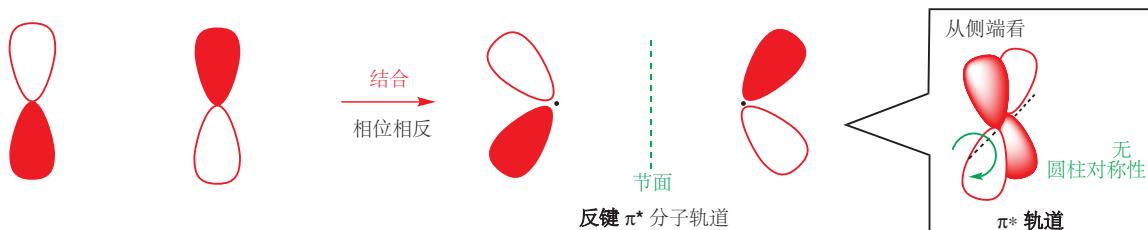


在两原子核之间的位置电子云密度较大，而在两侧则较小，因此在这个分子轨道填充电子会得到两原子核共同的吸引，以及一根化学键。

这两种 MOs 均为圆柱对称的，因此它们是  $\sigma$  和  $\sigma^*$  轨道；而来自相互作用的两个 2p 轨道上的电子填充在成键 MO 上，从而构成一根  $\sigma$  键。

- $\sigma$  键可以从 s 或 p 原子轨道得到，只要形成的轨道是圆柱对称即可。

每个原子剩余的两个 2p 轨道肩并肩重叠。其中两个 p 轨道以相位相反的方式肩并肩结合得到的反键 MO 如下图所示：



相位相同的方式肩并肩结合得到的成键 MO



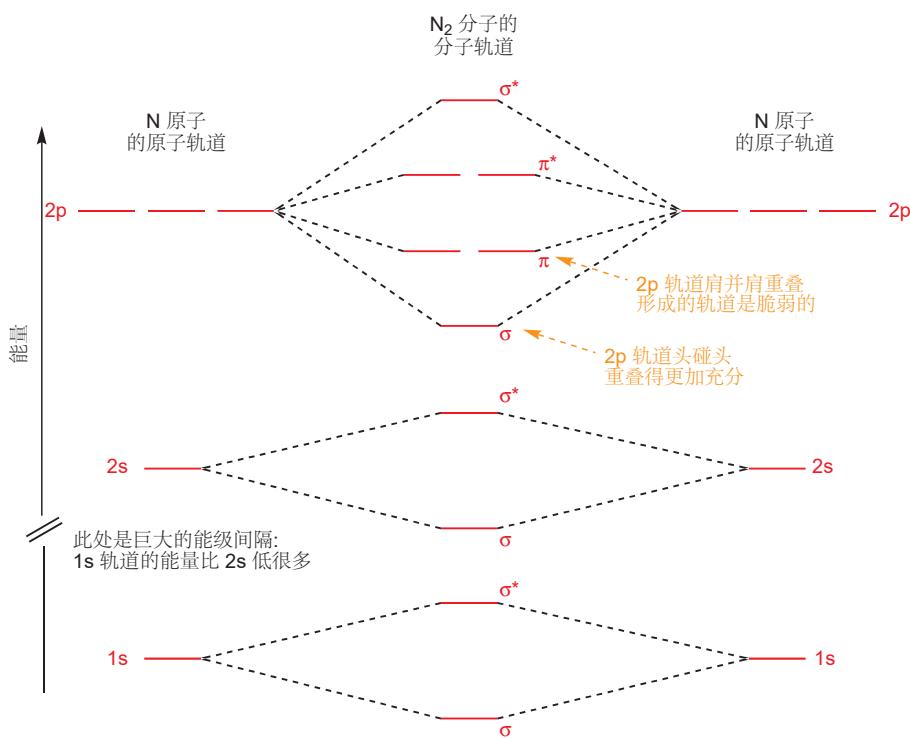
这两个 MOs 没有圆柱对称的——事实上您至少要绕穿过两个原子核的轴，旋转  $180^\circ$  才能得到与原先相似的性质，而且相位是相反的——作为结果，这种轨道的对称性用符号  $\pi$  表示：成键轨道是  $\pi$  轨道，而反键轨道是  $\pi^*$  轨道。由填充在  $\pi$  轨道上形成的键称为  $\pi$  键，您会注意到由于  $\pi$  对称性，这类键的电子云集中于过两原子核连线的两侧，而不是两原子核的中间。

由于原子中含有的三个 2p 轨道两两垂直，因此以肩并肩相互作用所生成的两个轨道也是相互垂直的；即形成的是一对简并的 (degenerate, 能量上相等) 相互垂直的  $\pi$  轨道，以及一对简并的相互垂直的  $\pi^*$  轨道。(第三对 p 轨道头碰头相互作用，形成的是  $\sigma$  轨道和  $\sigma^*$  轨道)。

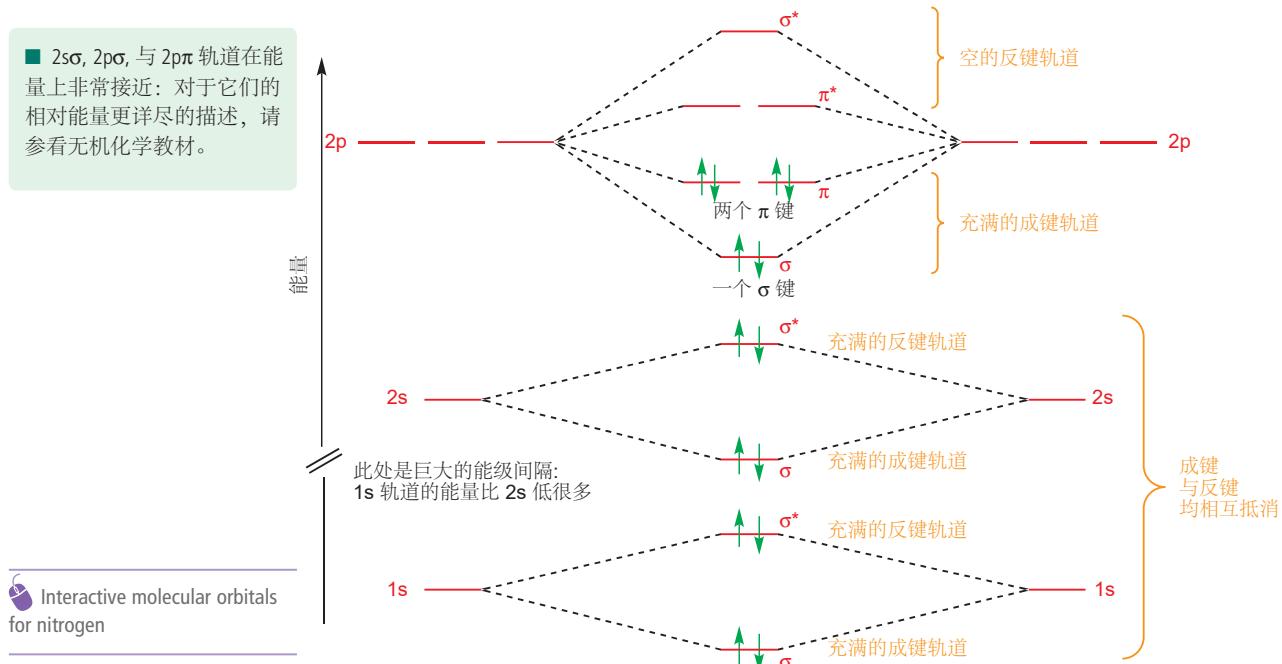
这两组 MOs 之间 (形成  $\sigma$  键与  $\pi$  键的) 不会发生简并，即能量会有所不同——显然，AOs 通过头碰头比肩并肩重叠地更好；因此，2p-2p  $\sigma$  轨道比 2p-2p  $\pi$  轨道具有更低的能量。

我们现在可以绘制一幅含盖 1s, 2s, 2p 的 AOs 形成 MOs 的能级总图，并根据需要使用  $\sigma$ ,  $\sigma^*$ ,  $\pi$ ,  $\pi^*$  标记每个能级。

■ 由于精确地表示 p 轨道的加碱是很难的，因此您会看到简单地用“结合前的” p 轨道 (像上图左侧) 表示  $\pi$  和  $\pi^*$  的图表——例如 p. 105 的例子。

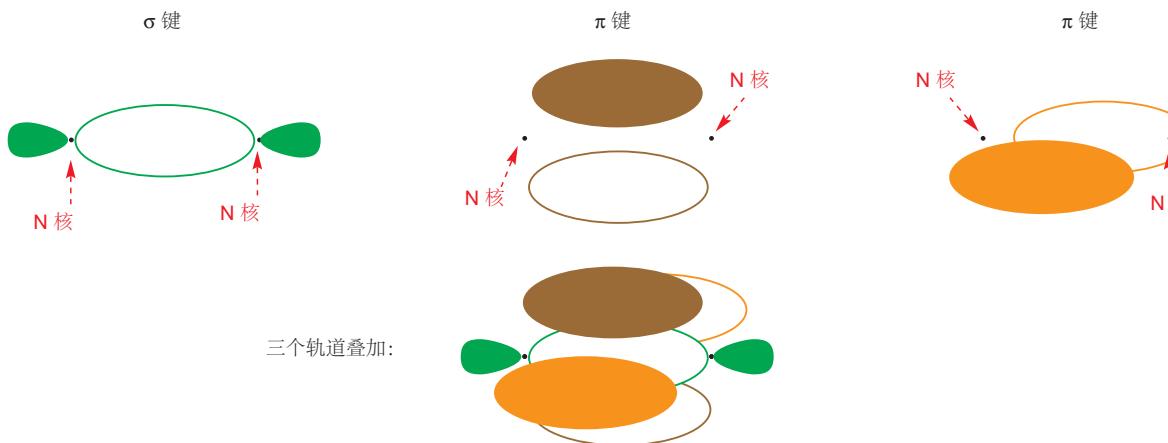


下面讨论电子。每个氮原子对于分子贡献了七个电子，因此我们将由下至上填充共 14 个电子，结果为：



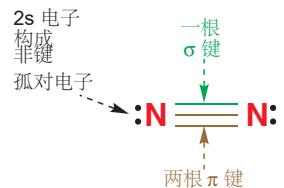
两个 1s 和两个 2s 轨道相互作用形成的 σ 和 σ\* MOs 都充满了电子：由于成键轨道与反键轨道相互抵消，总体上并没有成键效果。剩余的六个电子构成了该分子中的所有化学键：其中两个 p 轨道及其电子构成了一根 σ 键，另两对构成了两根 π 键。σ 键的电子排列在两原子核之间；π 键的电

子则排列在位于中心  $\sigma$  键侧面的两个彼此垂直的电子云中。



计算  $N_2$  的键级是很容易的——十个成键电子与四个反键电子，对于成键的贡献总计为六个，因此键级为三。 $N_2$  具有三重键结构。

然而，我们不能直接忽略未参与成键的电子：共计八个。这些非键 (non-bonding) 电子可以被当位于每个 N 原子上的孤对电子。四个 1s 电子位于低能的内部壳层中 (不属于价电子)，它们不包含在  $N_2$  的化学中；不过四个 2s 电子则作为未参与成键的孤对电子，附着在每个 N 原子上。在绘制结构时我们需要将它们画上；不过若不需要特殊强调 (在反应图示中涉及)，孤对电子通常不画出。



## 不同原子之间的键

时至当下，我们仍只考虑了两个相同元素成键的情况；由于相同元素的两个原子，相同轨道的能量相同，因此这实际上将问题简单化了。但当两个原子不同的时候事情会发生改变。第一点十分明显——每个原子贡献的电子数 (价电子数) 是不同的；这一点较容易考虑，因为它只是影响了我们最后在 MO 图的能级中放入电子的个数。即所以如果您想画出 NO，一氧化氮 (一种在人体中具有显著生理作用的生物信使) 的 MO 图，您只需要将  $N_2$  图中的 14 个电子换成 15 个即可；因为 O 贡献八个电子，而 N 贡献七个。

### 一氧化氮, NO

人们对于一氧化氮的认识长期局限于石油，或其他化石燃料燃烧时产生的空气污染的罪魁祸首。然而，在过去的 20 年中，科学家们证实了它的更多作用——例如作为生物信使，通过控制平滑肌收缩来调节血流量，发现一氧化氮这一令人意想不到的角色的科学家获得了 1998 年的诺贝尔生理学奖。

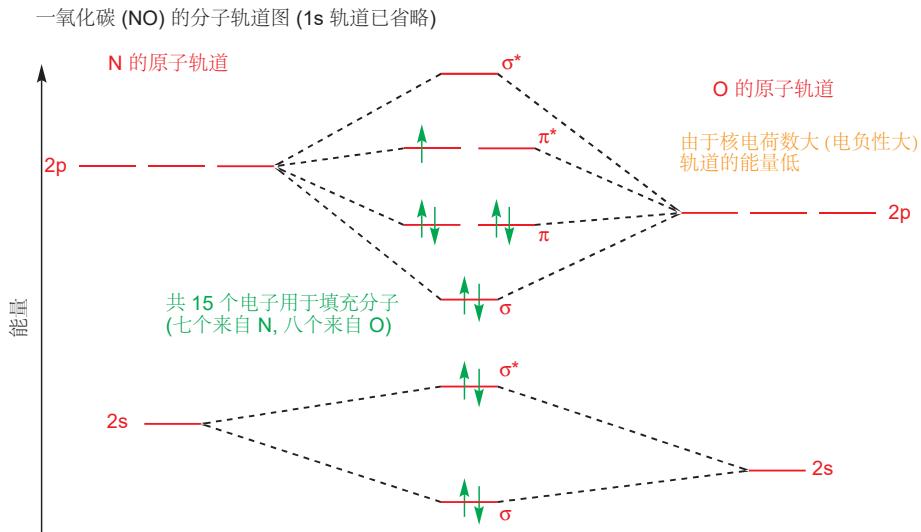
第二点改变则聚焦于两个原子成键结合时 AOs 的相对能量。也许可以很自然地假设任何地方找到的 2p 轨道都具有相同的能量，但由于 2p (或其他) 轨道受不同核电荷数的吸引并不相同，因此能量显然是不同的。原子核中的质子数越多，电子受到的吸引也就越大，由此它们结合得也就越紧密、越稳定，电子的能量也就越低。

这就是电负性 (electronegativity) 的起源。电负性越强的原子，其原子核对电子的吸引也就越强，它 AOs 的能量也就越低，所填充的任何原子结合得也就越紧密。因此，当您沿着横向浏览元周期表

电负性由左至右升高，由上至下则降低(虽然核电荷数增加)。这是因为当电子开始填充一个新的壳层时，上一层的电子会屏蔽掉原子核吸引的一部分。有关屏蔽效应的细节您可以在无机化学教材上找到。

时，电负性会随着原子轨道能量的下降而增加；由 Li (电负性 0.98) 到 C (2.55)，再到 N (3.04)，O (3.44)，和 F (3.98)，元素的电负性逐渐下降，AOs 的能量也随之下降。

因此 NO 的分子轨道图应该如下。



■ 这只是对于极性键 (polarized bonds) 的结构、反应性讨论的开始。在 Chapter 6 中我们会再次利用这一观点，审视羰基 C=O 的键向 O 极化的特点，不过反键  $\pi^*$  轨道的不对称性导致 C=O 的亲核位点为 C 原子。

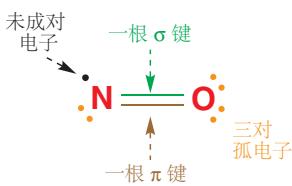
在本图中，我们只画了 2s 和 2p 轨道形成分子轨道的情况，这是由于 1s 轨道与它们的能量差距太大了；而且即使我们像 p. 94 中绘制  $N_2$  时一样将它们纳入考虑，它们也会由于成键和反键的抵消而并没有意义。

O 的轨道比 N 的轨道能量低，但它们之间仍然可以很好地相互作用。这还导致了一个有趣的结果：每个成键轨道的能量都与 O 原先的轨道更近，而与 N 稍远；每个反键轨道都与 N 更近，而与 O 更远。即 MOs 是不对称的：氧原子的 AOs 对每个成键轨道的贡献更大，而氮原子的 AOs 对每个反键轨道的贡献更大。现在我们纵观全图：成键轨道中含有八个电子，反键轨道中含有三个电子；因此两个原子共用的电子对更偏向 (极化 polarize) O，您还可以直接通过比较 N 和 O 的电负性来得到这一结论。

八个成键电子和三个反键电子同样意味着 NO 的键级为  $2\frac{1}{2}$ 。它包含一个未成对电子——因此它是自由基。我们无法简单地用价键理论的方法表示半根键，因此我们通常先在 NO 中用双键表示四个成键电子。然后再画出三个孤电子对和一个未成对电子。MO 图告诉我们，未成对电子的能量更接近 N 而非 O，因此我们将未成对电子放在 N 上。

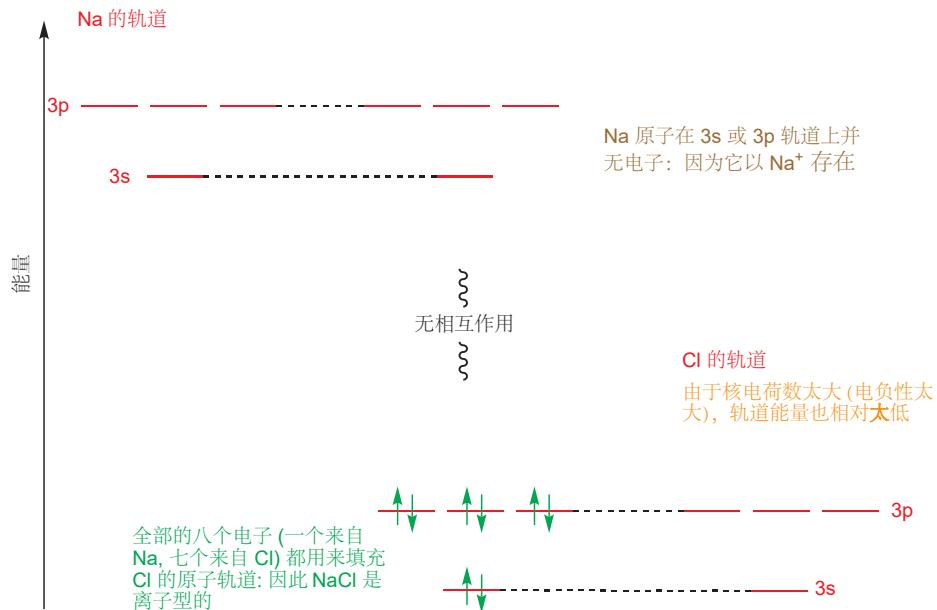
N 和 O 在电负性上的差距事实上是较小的 (分别为 N 3.04; O 3.44)：因此它们的轨道在能量上接近，成键也十分稳定。但我们仍然要考虑两个电负性相差十分大的原子的成键情况，以钠 (电负性 0.93) 和氯 (电负性 3.16) 的成键作为例子。我们都知道这两种元素化合 (不要在家中尝试) 的产物是离子固体  $Na^+Cl^-$ ，而 MO 能级图会告诉我们原因。

$Na$  原子中需要考虑的 AOs 是 3s 和 3p 轨道 (低能的 1s, 2s, 和 2p 轨道都充满了，因此我们可以像在  $N_2$  和 NO 时一样忽略它)， $Cl$  原子中则是 3s 和 3p 轨道 (同样，1s, 2s, 和 2p 轨道都充满了)。如下图所示， $Na$  上的轨道上的能量显著高于  $Cl$  上的轨道。



■ 我们还未讨论过周期表第三周期的事情。但毫无疑问，由 Na 到 Cl 的电子结构都由 3s 和 3p 轨道的填充而产生。若想知道这些轨道的形状，您可以查阅无机化学教材。

尝试构造 NaCl 的分子轨道图



Three-dimensional structure of sodium chloride

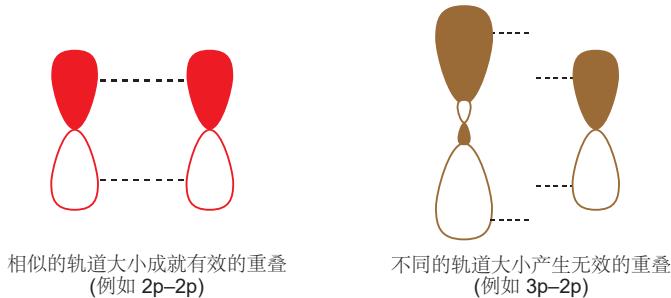
AOs 在能量上相差太远时，就无法有效地重叠形成新的 MOs，因而也不能形成共价键 (covalent bond)。因此电子填充的仅仅是 Cl 原子上的 3s 和 3p 轨道。填充轨道的电子，有七个来自 Cl, 有一个来自 Na: 最终结果为  $\text{Na}^+$  和  $\text{Cl}^-$ .  $\text{NaCl}$  中的离子键 (ionic bond) 仅仅来源于两个异种电荷的相互吸引——而不含任何轨道重叠。

这三种不同的情形包含了能量相差极大的轨道，能量相差较小的轨道，和能量相同的轨道，下面是总结。

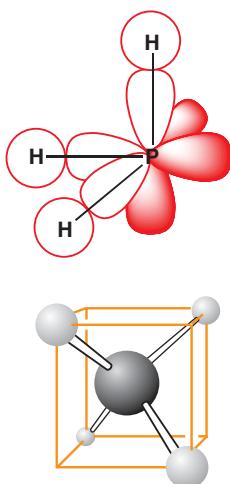
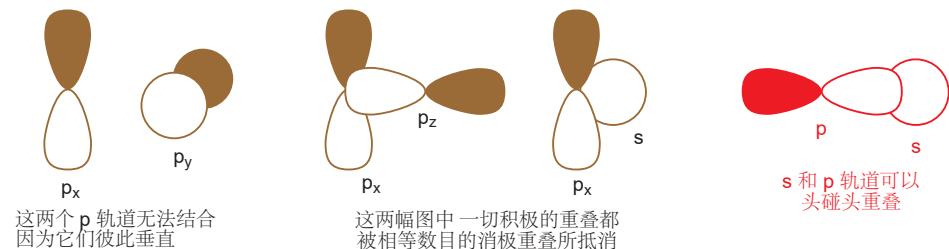
AOs 能量完全相同	B 原子上的 AO 能量稍低于 A 原子上的 AO	B 原子上的 AO 与 A 原子上的 AO 相差很大
AOs 间相互作用得十分充分	AOs 间相互作用相对较少	AOs 在能量上离得太远而不能相互作用
成键 MO 能量比 AOs 低很多	成键 MO 的能量相对于 B 的 AO 仅下降一点	充满轨道的能量与 B 原子的 AO 相同
反键 MO 能量比 AOs 高很多	反键 MO 的能量相对于 A 的 AO 仅上升一点	阳离子上空轨道的能量与 A 原子的 AO 相同
两个 AOs 对 MOs 的贡献相当	B 上的 AO 对成键 MO 的贡献大 A 上的 AO 对反键 MO 的贡献大	只有一个 AO 对 MO 有贡献
两个电子平等地占有成键 MO 中的电子	成键 MO 中的电子被两个原子共享，但更偏向 B	充满轨道的电子被 B 独有
A 与 B 之间的键是经典的共价键	A 与 B 之间的键是共价的，但稍有离子键成分	A 与 B 之间的键是经典的离子键
容易将键均裂 (homolytic fission) 为两个自由基	容易将键异裂为两个离子 $\text{A}^+$ 和 $\text{B}^-$ , 均裂得到自由基也是可能的	化合物以 $\text{A}^+$ 和 $\text{B}^-$ 的形式存在
键的异裂 (heterolytic fission) 生成 $\text{A}^+$ 和 $\text{B}^-$ 或者 $\text{A}^-$ 和 $\text{B}^+$ (这一点会在 Chapters 24 和 37 中被充分讨论)		

### 影响轨道相互作用程度的其他因素

决定两个 AOs 有效相互作用的因素不止能量接近，轨道重叠的方式也对此产生影响：我们曾经了解过 p 轨道头碰头的重叠（形成  $\sigma$  键）比肩并肩重叠（形成  $\pi$  键）更加充分。第二个影响因素是 AOs 的大小。为了更好地重叠，轨道应当处于相同大小——一个 2p 轨道与其他 2p 轨道重叠得比与一个 3p 或 4p 轨道好。



第三个影响因素是轨道的对称性——结合时，两个 AOs 必须有合适的对称性。因此一个  $2p_x$  轨道不能与其他  $2p_y$  或  $2p_z$  轨道结合，因为它们彼此垂直（它们是正交的）。尝试不同的对齐方式，我们发现：要么根本没有重叠，要么任何积极的重叠都被相等数目的消极重叠所抵消。同样地，一个 s 轨道仅能与 p 轨道头碰头重叠，尝试进行肩并肩重叠则会导致成键、反键相互作用数目相等，最终在能量上没有任何降低。



立方体中的甲烷分子

### 多原子分子的分子轨道

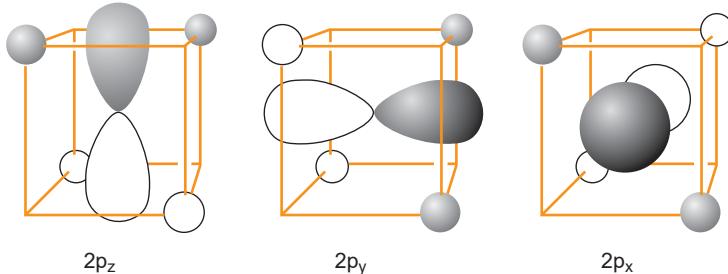
我们现在需要了解多原子分子，即含有两个以上原子的分子，中原子的结合方式。对于一些分子，例如  $H_2S$  和  $PH_3$ ，它们中的任何键角均为  $90^\circ$ ，思考它们的成键方式是十分简单直率的——中心原子的 3p 轨道（两两夹角  $90^\circ$ ）与氢原子的 1s 轨道重叠。

您可能会果断地认为氨， $NH_3$ ，的情形与之相同，因为在元素周期表中，N 就在 P 的上方。但问题是，实验测得氨、氨的水和甲烷溶液中的键角，分别是  $104^\circ$ ,  $107^\circ$ , 和  $109^\circ$  而非  $90^\circ$ 。每个由 Li 到 Ne 这一周期形成的共价化合物都遭遇了这一难题。我们如何能从  $90^\circ$  夹角的轨道中得到  $109^\circ$  的键角呢？

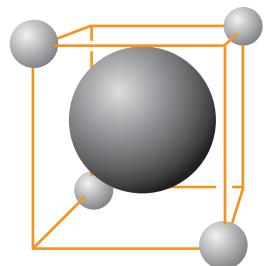
为了了解发生了什么，我们会从甲烷入手，并将其放入一个立方体中观察——这样做是符合事实的，因为立方体的四个体对角正好构成了完美的四面体。放入其中的甲烷，其碳原子在立方体中间，氢原子在四个体对角（即四面体的四个顶点）。

现在让我们用先前的理论，轮流考察碳的每个 2s 和 2p AOs。首先，碳的 2s 轨道可以与四个氢全部的 1s 轨道使用相位相同的方式同时重叠。

其次，每个  $2p$  轨道都指向立方体的一组对面；在这里，所有四个氢的  $1s$  轨道都可以与每个  $p$  轨道结合，结合时两侧的氢的 AOs 应当处于相反的相位。



氢的  $1s$  轨道可以与三个  $2p$  轨道重叠



碳的  $2s$  AO 可以与四个氢的  $1s$  AOs 同时重叠

第二种结合所生成的三个 MOs 是简并的。算上第一种结合，整个过程共生成了四个成键轨道。再加上四个反键轨道，我们共得到了八个 MOs，这与原先的八个 AOs (C 提供  $2s$  与  $3 \times 2p$ , 4 × H 提供  $4 \times 1s$ ) 在数量上是吻合的。

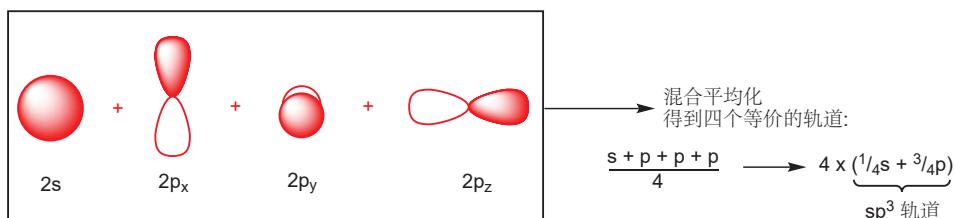
使用这种方法，绘制一幅甲烷的 MO 图当然是可能的——比甲烷复杂得多的分子也同样可以。但我们知道，在实验观察中，甲烷为正四面体型。而现在的问题在于：我们分析出的甲烷，中的四个充满的成键轨道并不等价 (其一来自 C 的  $2s$  轨道，剩下三个来自 C 的  $2p$  轨道)；如果甲烷是正四面体型，那么四个 C-H 必然是等价的。

一定有什么错了，但目前还不能解释。MO 理论告诉了我们：甲烷中的一种 MO 有一个，而另一种有三个，它们中的电子在五个原子中共享；没有任何一个氢原子比其他氢原子的电子多或少，它们是等价的。观察告诉了我们甲烷分子的结构，但无法告诉我们键具体在哪里；它只告诉了我们原子在空间中的位置——而键则是我们人为添加的；原子形成一个规则的四面体，当然并不代表电子也是如此。那么，难道我们应当放弃甲烷成四根 C—H 键的结论吗？如果我们放弃了这个结论，就相当于否决了前边认可的理论，对于再简单的分子或者反应，就都需要计算机计算出一整套 MOs 及其所有的相互作用来解决了。

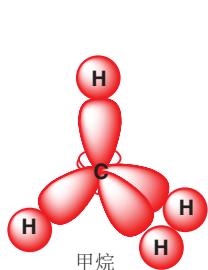
使用物理来处理化学问题，虽然无比准确的，但它扼杀了化学家特有的创造性。因此我们需要有一套替代方案：分子由彼此独立的键构筑，每根键包含一对电子——这一观点将被保留，但我们需要使其更加适应 MO 理论。因此，我们需要一个新概念的引入，它被称为杂化。

## 原子轨道的杂化

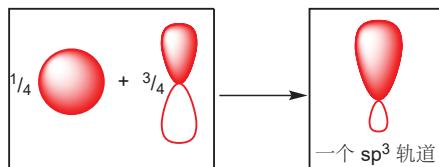
为了得到甲烷分子上用于成键的四对等价的电子，我们的 C 必须含有四个等价的 AOs，这是我们目前没有得到的。不过如果我们能让  $2s$  和  $2p$  轨道首先混合，形成四个新的轨道，它们就会是等价的了；平均下来，新的轨道由四分之一的  $2s$  轨道和四分之三的  $p$  轨道构成。为了展示这一组成比例，它被叫做  $sp^3$  (读作  $s-p-三3$ ，而不是  $s-p-的立方$ ) 杂化轨道 (hybrid orbital)。这个混合平均化的过程被称为杂化 (*hybridization*)。杂化轨道在数学上等同于之前的  $2s$  和  $2p$  轨道，它的优点仅在于形成 MOs 时与成键电子对数相吻合。



这四个杂化轨道长什么样？每个  $sp^3$  轨道都含有四分之三的 p 轨道成分和四分之一的 s 轨道成分。和 p 轨道一样，它有一个贯穿原子核的平面波节，但由于含有  $2s$  轨道成分，其中一个波瓣要比另一个大：考虑  $2s$  轨道的对称性，当将它与  $2p$  轨道叠加时，会同时使一个波瓣的波函数值增加，另一个波瓣的减少。

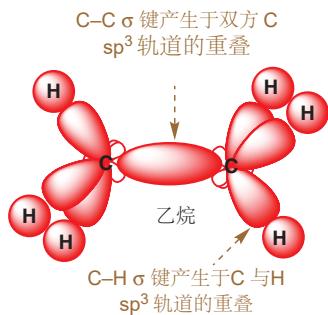
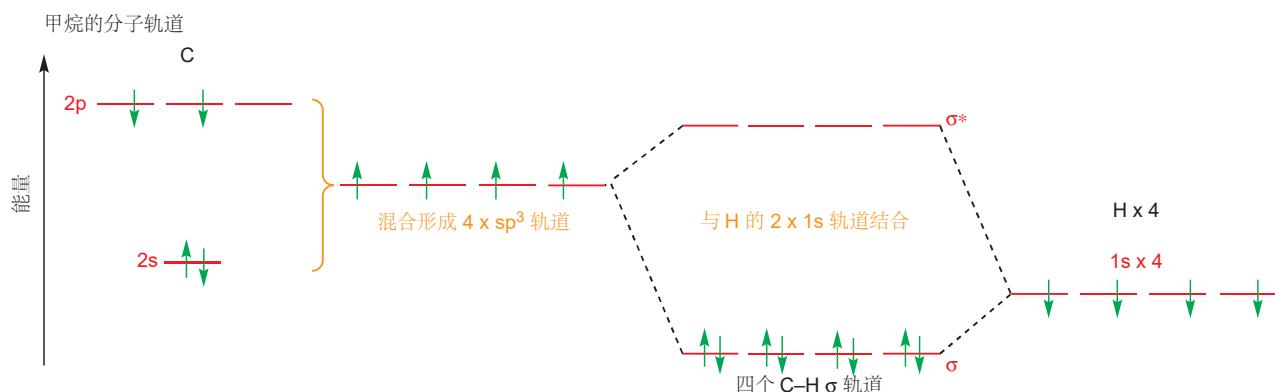


Interactive bonding orbitals in methane



C 原子上的四个  $sp^3$  轨道指向四面体的四个顶点

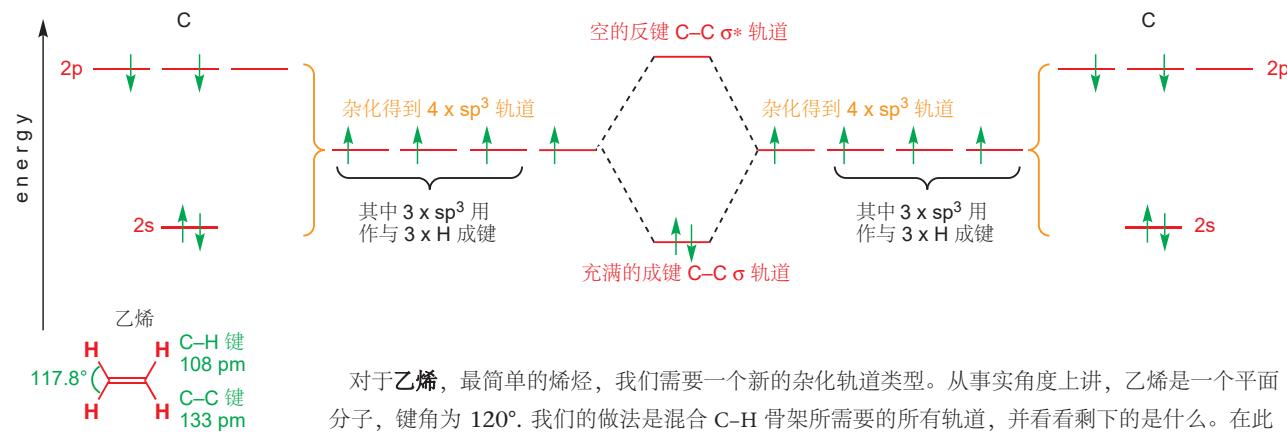
四个  $sp^3$  轨道指向四面体的四个顶点，因此我们可以使用每个  $sp^3$  轨道中的大波瓣与每个氢原子的  $1s$  轨道重叠组成分子。每次重叠都形成一个 MO ( $2sp^3 + 1s$ )，我们可以在其中填入两个电子以形成 C–H  $\sigma$  键。每种情况下，还会同时产生一个反键 MO,  $\sigma^*$  ( $2sp^3 - 1s$ )，它们是空置的。这时理论分析的电子空间分布就与事实相吻合了，因此我们可以认定它们确实处在四根键中了。



这个方法最大的优势是分析的高效性，您可以很快地分析一个较大的结构，并不需要将其中每个原子都纳入考虑。拿乙烷作为例子，每个碳原子都将其中三个  $sp^3$  AOs 指向氢原子，而留下一个  $sp^3$  轨道与另一个碳原子形成 C–C 键。

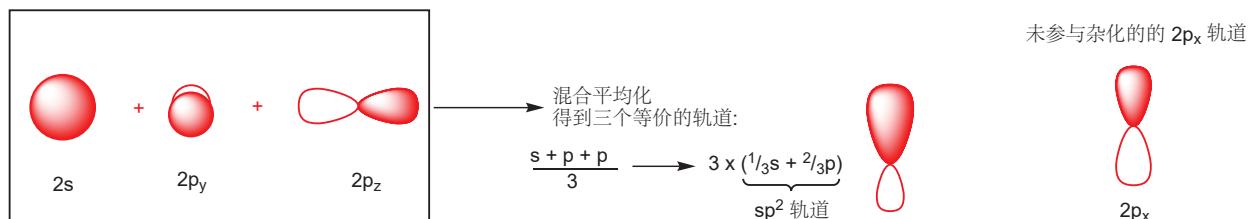
在 MO 能级图中，应既包含六组 C–H 成键  $\sigma$  和反键  $\sigma^*$  轨道（产生于 C 的  $sp^3$  轨道与 H 的  $1s$  轨道），又包含一组 C–C 成键  $\sigma$  和反键  $\sigma^*$  轨道（产生于两个 C 分别的  $sp^3$  轨道）。下图仅表示了后者，C–C 键的轨道。

乙烷的分子轨道（仅展示了 C–C 键的部分）

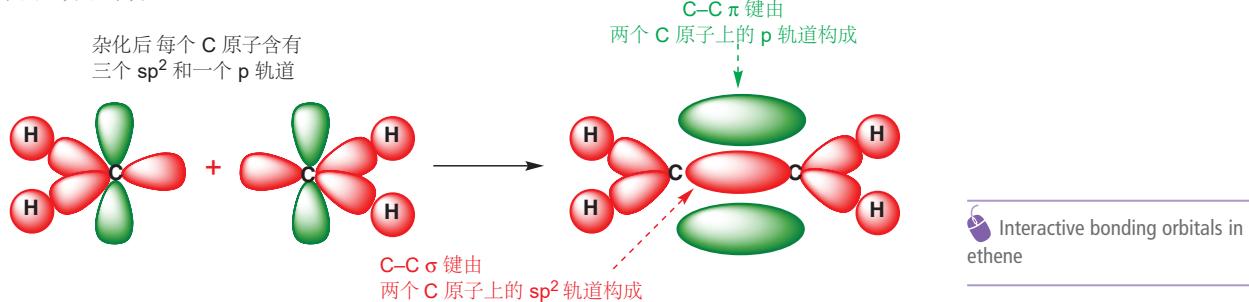


对于乙烯，最简单的烯烃，我们需要一个新的杂化轨道类型。从事实角度上讲，乙烯是一个平面分子，键角为  $120^\circ$ 。我们的做法是混合 C–H 骨架所需要的所有轨道，并看看剩下的是什么。在此

时，每个碳原子都连有三根等价的键（一根为 C–C 键，两根为 C–H 键），因此我们需要将每个碳原子上的一个 2s 轨道与两个 p 轨道混合（这样可以产生三根键）。我们可以将 2s, 2p<sub>y</sub> 和 2p<sub>z</sub> 轨道进行杂化（任取位于同一个平面上的所有 AOs），生成三个 sp<sup>2</sup> 轨道，并留下依旧如故的 2p<sub>x</sub> 轨道。生成的 sp<sup>2</sup> 杂化轨道含有三分之一的 s 轨道成分和三分之二的 p 轨道成分。

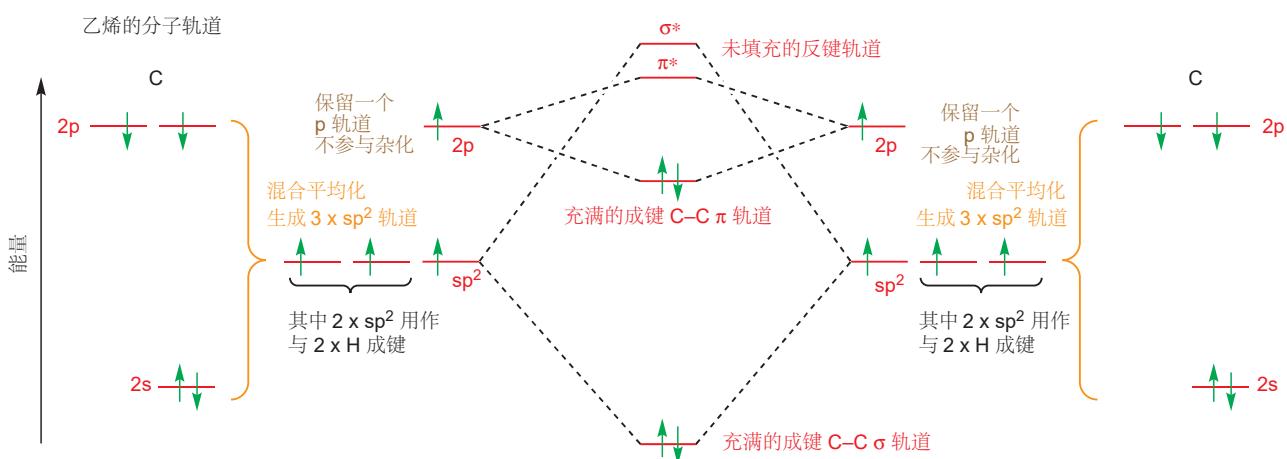


每个碳原子上的三个 sp<sup>2</sup> 杂化 AOs 可以与其他原子上的三个轨道（两个氢原子上的 1s AOs 和另一个碳原子上的 sp<sup>2</sup> AO）重叠形成三个  $\sigma$  MOs。杂化的过程在每个碳原子上都留下了一个 2p<sub>x</sub> 轨道，它们与它们各自含有的一电子构成了  $\pi$  MO。分子的大体骨架由五根  $\sigma$  键架构（一根 C–C 和四根 C–H），它们在同一平面内；而  $\pi$  键则由两个碳原子未参与杂化的 2p<sub>x</sub> 轨道构成，电子云位于平面上方和下方。

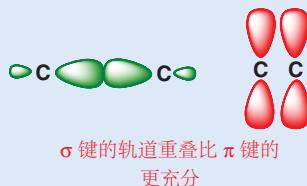


这是我们第一次构建含 C=C 双键分子的 MO 图，您需要花时间想一想轨道的能量顺序。我们仍然会忽略使用掉 C 原子两个 sp<sup>2</sup> 轨道的 C–H 键。请记住，对于每个 C 原子，只有三个 2p 轨道中的两个与 2s 轨道参与杂化，产生  $3 \times \text{sp}^2$  轨道，并留下未参与杂化的 2p 轨道。

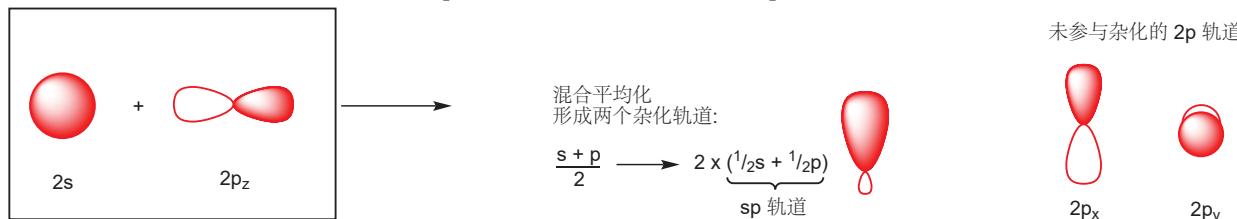
再次梳理思路：首先双方碳原子各给出一个 sp<sup>2</sup> 轨道，它们相互作用形成  $\sigma$  和  $\sigma^*$  轨道；然后双方 C 再各给出一个 p 轨道，肩并肩相互作用形成  $\pi$  和  $\pi^*$  轨道。未参与杂化的 p 轨道能量略高于 sp<sup>2</sup> 杂化轨道，但它们之间的相互作用却不是很好（肩并肩重叠的不充分性，p. 93），因此  $\pi$  轨道与  $\pi^*$  轨道的能量在  $\sigma$  和  $\sigma^*$  轨道之间。填充上每个 C 原子提供的两个电子（价电子中还有两个与 H 成键），总图如下所示。两个 AOs 生成两个 MOs.



$\sigma$  轨道肩并肩形成  $\pi$  键没有头碰头形成  $\sigma$  键更充分，这一分析在实验事实上的证据是：打破一根 C—C  $\pi$  键需要的能量比 C—C  $\sigma$  键少（分别为  $260 \text{ kJ mol}^{-1}$  和  $350 \text{ kJ mol}^{-1}$ ）。

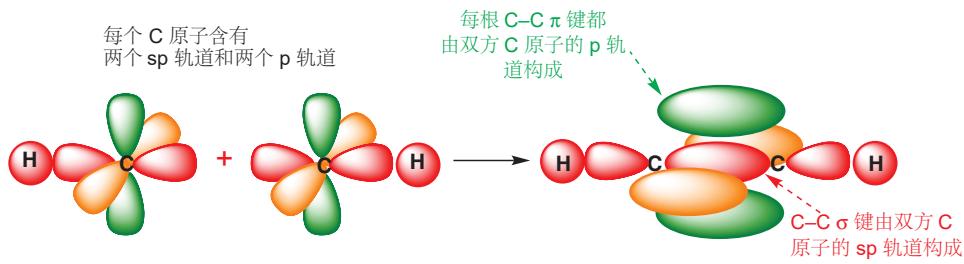


乙炔中含有一根  $\text{C}\equiv\text{C}$  三重键。每个碳原子只和两个其他原子结合形成直线形 CH 骨架。因此，首先参与杂化的是两个轨道；其次，参与杂化的两个轨道一定是能形成这种对称性的  $2s$  和  $2p_z$  轨道。杂化后的轨道称为  $sp$  杂化轨道。而双方碳原子余下的  $2p_y$  和  $2p_z$  轨道分别构成两根  $\pi$  MOs。本分子中的  $sp$  杂化轨道包含 50% 的 s 成分和 p 成分，并形成直线形碳骨架。

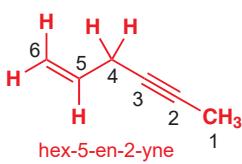


接下来我们可以如下构建 MOs. 碳原子的两个  $sp$  AO 分别与一个氢原子  $1s$  AO 和另一个碳原子的  $sp$  轨道重叠成键。剩余的两对  $p$  轨道结合形成相互垂直的  $\pi$  MOs.

Interactive bonding orbitals in ethyne



以上三种分子种类对应的也是三种杂化类型的碳，它们的空间构型亦相互对应。对于杂化类型、空间构型、键的种类，我们是可以知一推二的。当您想分析一个碳原子的空间构型时，唯一需要做的就是数清它连有几个原子：如果连有两个，那么碳原子是  $sp$  杂化的直线型；如果连有三个，则为  $sp^2$  杂化的平面三角型；如果连有四个，则为  $sp^3$  杂化的四面体型。由于未参与杂化的  $p$  轨道通常用作形成双键或三重键中的  $\pi$  轨道，您同样可以通过数碳原子上连有的  $\pi$  键个数判断：如果不连有  $\pi$  键，则为四面体型 ( $sp^3$  杂化)；连有一根，则为平面三角型 ( $sp^2$  杂化)；连有两根，则为直线型 ( $sp$  杂化)。



左侧展示的是一个有代表性的离子。这个烃类 (hex-5-en-2-yn) 含有两个直线型  $sp$  碳原子 (C2 和 C3)，两个平面三角型  $sp^2$  碳原子 (C5 和 C6)，一个位于分子中间的四面体型  $sp^3$   $\text{CH}_2$  (亚甲基，C4)，和另一个在分子最右端的四面体型  $sp^3$  甲基 (C1)。推理它的构型时，我们不需要分析每一个 AOs —— 我们只需要数清键数就够了。

### 任何原子都可以发生杂化

我们可以在任何一种原子上应用这一策略。下一页展示了三种四面体型的分子，它们同样也是由四根等价的  $\sigma$  键与  $sp^3$  杂化的四面体型中心原子构筑的，所包含的总电子数也相同；其中心原子分

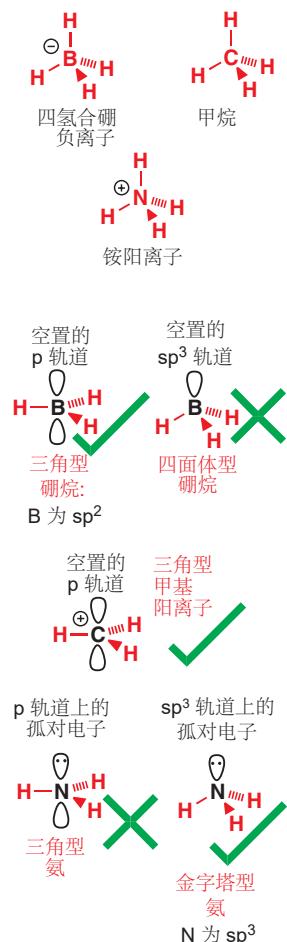
别为 B, C, 和 N——结构、电子数均相同的几种分子或离子互为等电子体(isoelectronic)。不同元素贡献的电子数(价电子数)是不同的,为了形成八隅体,我们需要给硼添加一个电子以形成  $\text{BH}_4^-$ ,并减少氮一个电子以形成  $\text{NH}_4^+$ ——这是它们电荷的来源。在每个例子中,中心原子都是  $\text{sp}^3$  杂化的,它们均使用  $\text{sp}^3$  轨道与四个 H 原子成键,并得到四个由两个电子构成的  $\sigma$  键。

这三种元素同样都可以形成连有三根键的化合物。硼烷,  $\text{BH}_3$  的分子中含有三对成键电子(三个来自 B, 三个来自 H)。由于中心硼原子仅和三个原子相连,我们不难想象它的杂化类型为  $\text{sp}^2$ ,空间构型为平面三角型。硼的三个  $\text{sp}^2$  轨道与三个氢的 1s 轨道重叠形成新轨道, B-H 键由填入其中的电子构成;硼上还有一个未参与杂化的、空置的 p 轨道。您可能会问为什么不能以  $\text{sp}^3$  杂化,并空置其中一个  $\text{sp}^3$  轨道形成四面体构型呢。这是因为我们必须使填充电子的轨道具有更低的能量,由于  $\text{sp}^2$  轨道的 s 成分比  $\text{sp}^3$  大,因此前者的能量低于后者;从另一个角度讲,当分子中必须含有一个空轨道时,往往要尽可能使它的能量最高;由于这个轨道没有电子,它并不会影响分子的稳定性,然而余下的、用来填充电子的轨道能量就很低了。

硼烷是甲基阳离子,  $\text{CH}_3^+$  或  $\text{Me}^+$  的等电子体。因此我们刚才对于硼烷的讨论也同样适用于  $\text{Me}^+$ ,因此它的杂化类型为  $\text{sp}^2$ ,并同样含有一个空置的 p 轨道。这一特征当我们在 Chapters 15 和 36 中讨论碳阳离子的反应时十分重要。

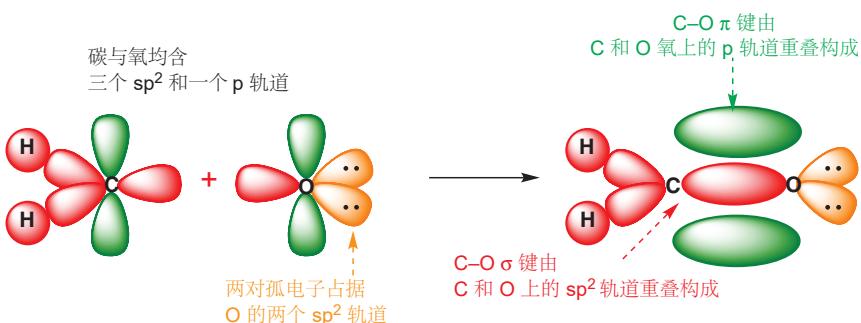
那么氨,  $\text{NH}_3$  中的情况是怎么样的呢?氨并不是硼烷和  $\text{Me}^+$  的等电子体!氨分子共含有八个电子——五个来自 N, 三个来自  $3 \times \text{H}$ 。除去三根 N-H 键用掉的六个电子,中心氮原子还含有一对孤对电子。我们再次面临两种选择:氮原子  $\text{sp}^2$  杂化并将孤对电子填入 p 轨道,或者氮原子  $\text{sp}^3$  杂化并将孤对电子填入其中一个  $\text{sp}^3$  轨道。

氨分子选择了硼烷和  $\text{Me}^+$  的相反结果。和空置相比,余下的孤对电子确实对氨分子的整体能量有贡献,因此它也需要填入低能轨道,即  $\text{sp}^3$  而不是 p。实证明 H-N-H 的键角均为  $107.3^\circ$ ,更接近  $109.5^\circ$  的  $\text{sp}^3$  角,而不是  $120^\circ$  的  $\text{sp}^2$  角。但由于键角并不完全是  $109.5^\circ$ ,因此氨也不能完全以  $\text{sp}^3$  杂化概况。对于这个问题的一种看法是,孤对电子对键的排斥力比键与键之间的排斥力大;或者您可以解释为由于孤对电子的电荷更集中,需要比 N-H 成键电子占据更低能的轨道,因此前者轨道的 s 成分稍稍多于后者,后者轨道的 p 成分稍稍多于前者。



## 羰基

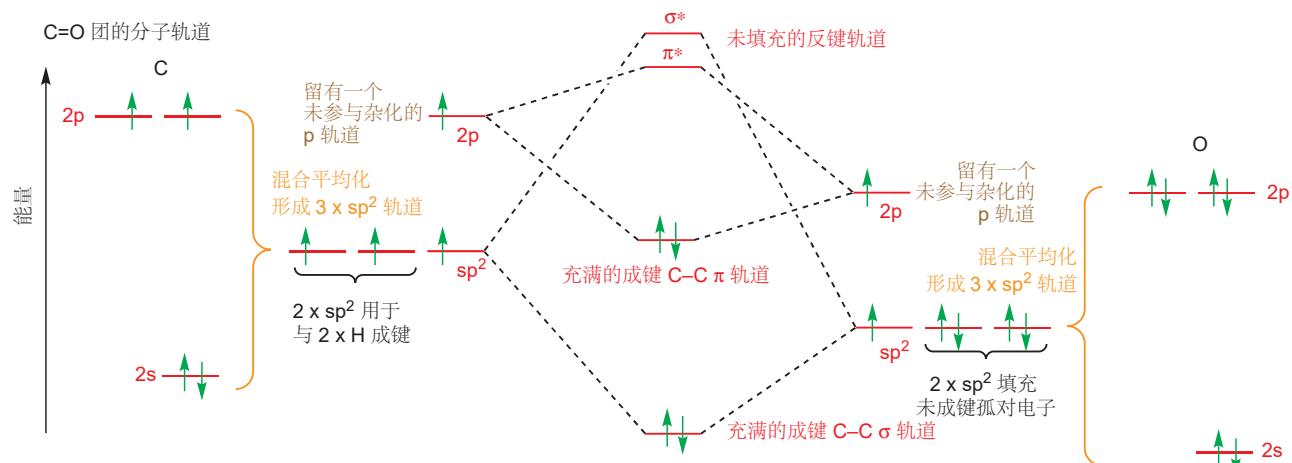
$\text{C=O}$  双键是有机化学中最重要的官能团,它在醛、酮、羧酸、酯、酰胺等等物种中出现。本书中的很多章都在讨论它的化学,因此在学习那些知识前请务必理清它的电子结构。我们会首先从最简单的羰基化合物,甲醛入手。像烯烃中的一样,碳原子需要三个  $\text{sp}^2$  轨道与两个 H 原子、一个 O 原子形成  $\sigma$  键。对于氧原子呢?它既需要与 C 原子形成一根  $\sigma$  键,又需要两个杂化轨道以盛放孤对电子:因此羰基上的氧原子是  $\text{sp}^2$  杂化的。最后,碳原子和氧原子分别提供一个 p 轨道一个电子形成  $\pi$  键。示意图如下。



我们如何知道 O 原子在  $\text{sp}^2$  轨道上的孤对电子呢?答案是,在一些羰基化合物中,这些孤对电子会通过形成氢键影响分子的朝向。

Interactive bonding orbitals in formaldehyde

对于 MO 能级图，我们会以 C 和 O 之间的键为中心。首先，我们需要这两个原子都分别进行杂化，并生成  $3 \times \text{sp}^2$  轨道和  $1 \times \text{p}$  轨道。注意到我们将 O 的 AOs 画在 C 的 AOs 的下方，这是由于 O 的电负性更大，轨道能量更低。首先 O 的两对非键电子，和两根 C-H 键占据了双方的各两个  $\text{sp}^2$  轨道，然后双方剩下的各一个  $\text{sp}^2$  轨道相互作用形成  $\sigma$  和  $\sigma^*$  轨道，双方剩下的各一个 p 轨道相互作用形成  $\pi$  和  $\pi^*$  轨道。

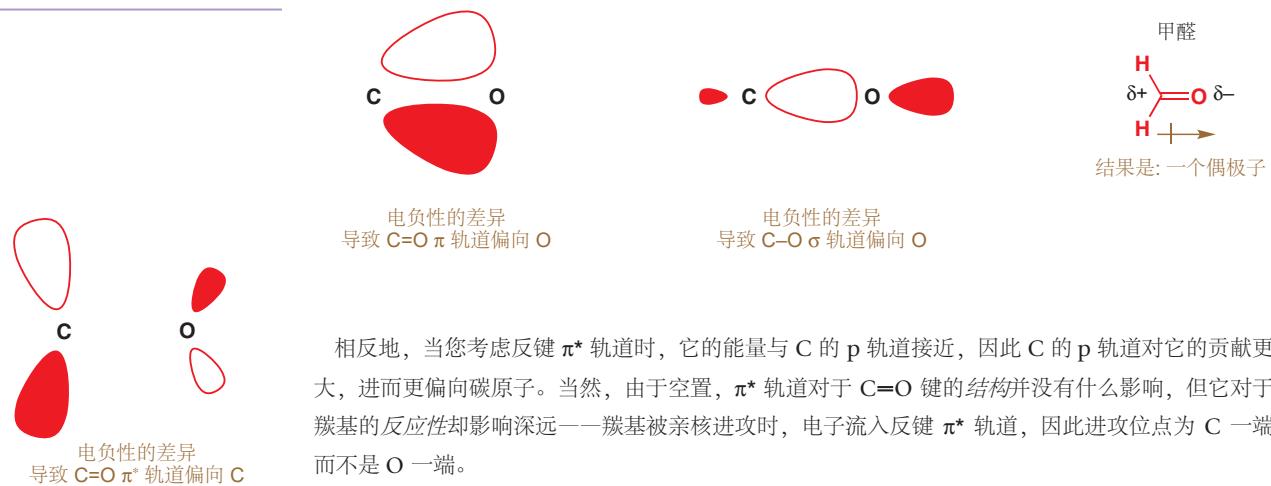


■ 烯烃的  $\pi$  键具有亲核性，然而羰基化合物的  $\pi$  键具有亲电性。如果您还不熟悉这一术语，您会在 Chapter 5 中学到它们。

氧的电负性比碳大的特点，反映在图中有两个事实。第一点是 C=O 键占据的轨道的能量比相应的 C=C 键低。这一点导致了烯烃和羰基化合物反应性的差异，我们将在下一章讨论。

第二点是极化。我们在讨论 NO 时向您介绍过极化的概念，现在来看 MO 能级图中充满的  $\pi$  轨道——它的能量距离 O 的 p 轨道比距离 C 的 p 轨道更近。因此我们可以理解为 O 的 p 轨道比 C 的 p 轨道对  $\pi$  分子轨道的贡献更大。因此这个变形的轨道在 O 上的占比比 C 上的大 (轨道“系数 coefficient”更大)，电子在 O 附近出现的概率也随之更大，这一分析同样适用于分子中的  $\sigma$  键。C=O 基总体表现为一个偶极子，可以用一或两个符号表示——带有竖线的箭头或者在原子上标明  $\delta+$  和  $\delta-$  记号 (此之谓“部分电荷 partial charge” )。

► We will develop this idea in Chapter 6.



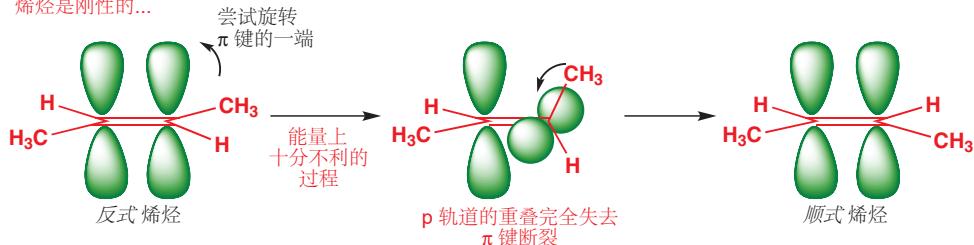
相反地，当您考虑反键  $\pi^*$  轨道时，它的能量与 C 的 p 轨道接近，因此 C 的 p 轨道对它的贡献更大，进而更偏向碳原子。当然，由于空置， $\pi^*$  轨道对于 C=O 键的结构并没有什么影响，但它对于羰基的反应性却影响深远——羰基被亲核进攻时，电子流入反键  $\pi^*$  轨道，因此进攻位点为 C 一端而不是 O 一端。

## 旋转和键的刚、柔性

在结束这一章的时候，我们要处理另一个可以用 MOs 回答的问题：分子的灵活性是怎么样的？当然，答案取决于分子，但更具体、本质的是取决于键的类型。您从前可能知道，很多构造相同的烯烃都有两种构型，*顺式* (*cis*) 和 *反式* (*trans*)，也可以是 *Z* 和 *E* 型（见 Chapter 17）。这两种构型都能稳定地存在，并在一般条件下不相互转化——即 C=C 双键是刚性的，不能发生旋转。

我们可以从 2-丁烯的成键中找到原因。它的  $\pi$  键来源于两个平行的 p 轨道；如果发生旋转，构成  $\pi$  键的两个轨道必须先停止相互作用，然后经历一个相互垂直的状态，最终再次平行。这个过程中经历的相互垂直的状态（半扭曲型过渡态），在能量上是非常不利的，因为形成  $\pi$  键获得的任何能量都将丧失。因此烯烃的旋转必须吸收充足的能量才可以进行，我们说它是刚性的。

**烯烃是刚性的...**



若想让烯烃在*顺式*和*反式*间转化，则需要相当大的能量——大约  $260 \text{ kJ mol}^{-1}$ 。其中一种破坏  $\pi$  键的方法是讲  $\pi$  轨道上的一个电子挪到  $\pi^*$  轨道。这时，成键  $\pi$  轨道和反键  $\pi^*$  轨道都分别有一个电子，它们相互抵消从而没有成键效果。完成这一操作需要的能量与紫外光 (UV) 的能量相符。因此使用 UV 光照射可以使烯烃的  $\pi$  键断裂（不会破坏  $\sigma$  键），进而导致分子绕双键旋转。

## 烯烃的异构体

马来酸和富马酸具有相同的构造，相同的官能团，但它们的性质是不同的——在十九世纪，对于这一现象的原因一直是个谜。直到 1874 年，范霍夫 (van't Hoff) 提出了双键限制自由旋转的观点，表明当双键的两侧都各自有两个不同基团时（两侧之间比较则不一定不同），异构体就会出现。他使用术语*顺式*（“*cis*”在拉丁语中译为“在同一侧”）和*反式*（“*trans*”在拉丁语中译为“对面或在另一侧”）分别命名了这两种异构体。而马来酸和富马酸哪个是顺式，哪个是反式？实验证据表明，在加热时，马来酸会脱水缩合成马来酸酐，而富马酸不能，因此马来酸中的羧基一定处于不能旋转的双键的同一侧。



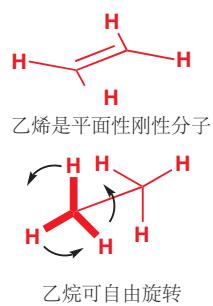
对于丁烷。由于  $\sigma$  键是圆柱形对称的，绕键旋转并不会破坏任何键。只由  $\sigma$  键连接的原子因此被认为是允许自由旋转的，即柔性的。

事实上，并非所有的  $\sigma$  键取向都同样有利。我们会在 Chapter 16 中重新提到它，即构象 (conformation)。

**烷烃是柔性的...**



对于乙烯和乙烷也有同样的比较：在乙烯中，由于 p 轨道重叠的需要，所有原子排列作一个平面；在乙烷中，分子两端可以自由地旋转。刚、柔性能在有机化学上有很重要的影响，我们会在 Chapter 16 中谈到。



## 小结

本章中，我们仅是触及了林林总总的分子中的沧海一粟，但我们更向您介绍了分析分子的思想。这些简单思想的组合甚至可以被用于处理已知最复杂的分子。我们可以用 AOs 结合生成 MOs 的方法处理小分子，或者大分子中的小部分。而配合 Chapter 7 中的共轭思想，您就可以掌握任何有机化合物的结构了。从现在起，我们将不加说明地使用例如 AO, MO, 2p 轨道,  $sp^2$  杂化,  $\sigma$  键, 能级, 填充轨道等等术语，如果您还不能准确地说出它们的概念，一定要重新回顾本章。

## 展望

我们由原子轨道，原子轨道构成的分子轨道展开了这一章的讨论。但这是局限于一个分子中的，当两个分子发生反应时会发生什么呢？在下一章中，我们将对化学反应过程做出解释。

## 延伸阅读

一本介绍有关轨道、成键的书: *Molecular Orbitals and Organic Chemical Reactions: Student Edition* by Ian Fleming, Wiley, Chichester, 2009.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 有机反应

## 联系

### ► 基础

- 真实地绘制分子 ch2
- 用光谱法侧端分子结构 ch3
- 什么决定了分子形状和结构 ch4

### 目标

- 为什么分子通常不与其他分子反应
- 为什么有些分子会与其他分子反应
- 分子形状和结构是如何决定反应性的
- 电子在化学反应中由充满轨道流入空轨道
- 识别亲核试剂和亲电试剂
- 用弯曲箭头表示电子在反应中的移动

### ► 展望

- 羰基的反应 ch6
- 本书其余章节

## 化学反应

绝大部分物质可以稳定存在。硫酸，氢氧化钠，水，丙酮可以被安全地长期存放在实验室，而其化学组成并不发生改变。然而，一旦这些物质被混合，化学反应——也许会很激烈——就会发生。

本章节主要介绍有机物分子的行为：为什么一些分子会相互发生作用，而另一些不会，以及如何通过电荷、轨道、电子移动来诠释反应。我们引入弯曲的箭头作为工具，来描述电子的运动，这就是反应机理。

为了熟练掌握有机反应，您需要熟练掌握两种化学语言。第一种是有关结构的语言：包括原子、键、轨道的结构。这一种语言我们已经在上面三章详细讨论过了：在 Chapter 2 我们学习了如何正确书写结构；在 Chapter 3 我们学习了如何通过技术手段证明结构；在 Chapter 4 我们学习了如何利用电子在原子间的排列来解释结构存在的合理性。

现在我们需要学习第二种语言：**反应性 (reactivity)**。化学是一门有关于分子动态特性的最重要的学科，例如，如何利用已有的分子，构造新的分子。为了理解这种特性，我们需要新的术语和工具来解释，预测以及讨论**反应 (reaction)**。

分子间发生反应是因为它们在运动。然而原子的运动被局限于分子之内，也就是说，原子只能够在分子之内进行伸缩，弯转运动，这种运动可以被红外光谱检测到；同时，烷烃之中的  $\sigma$  键可以自由旋转（但是烯烃中的  $\pi$  键不能）。在气体或液体中，分子连续地以整体形式发生着运动。他们互相碰撞，与容器内壁碰撞，和溶剂相互作用。这些不间断的运动驱动着反应的进行；首先，我们需要研究当分子碰撞的时候发生了什么。

贝特洛 (Marcellin Berthelot, 1827–1907) 在 1860 年指出：“化学的创造力就像艺术，使这门学科不再仅仅是一门自然科学或是历史科学。(Chemistry's creative capability, resembling that of art itself, distinguishes it from the natural and historical sciences.)”

## 并非所有分子之间的碰撞都会导致化学反应

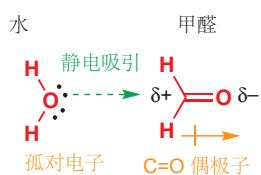
► 我们会在 Chapter 12 中继续讨论。

分子被电子包裹着，包括成键电子和未成键电子。因此，分子的表面显富电性，它们会相互排斥。只有当一对分子拥有足以克服这个排斥力的能量时，化学反应才会发生。如果它们不具有，它们只会单纯地碰在一起再反弹开，就像斯诺克台球相互碰撞一样，交换能量，以新的速度离开，但是化学上并未改变。容许反应发生的最低能量需求是一道阻止他们反应的顽强壁垒，这个最低能量被称为**活化能(activation energy)**。在任何样本或化学物质中，分子都会拥有不同的能量，但是如果它们想反应，就必须拥有高于活化能的能量。

## 静电吸引

如果您将氯化钠溶液和硝酸银溶液混合，银离子和氯离子间的静电作用足够将它们转化为稳定的离子型晶体，沉淀而离开溶液。两种离子当然是被电子包裹着的，但是缺电子的银离子对于富电子的氯离子的吸引力足够克服他们之间的排斥力，从而导致氯化银沉淀的生成。

带有负电荷的碳原子不稳定；通常稳定的有机阴离子上的负电荷带在氧或其他电负性较大的原子上，例如醋酸根离子， $\text{CH}_3\text{CO}_2^-$ 。



在有机反应中，阴离子和阳离子直接作用十分少见，因为稳定存在的有机阴离子相对稀少，而有机阳离子更是屈指可数。有机反应更加常见的则是一个离子与另一个拥有**偶极(dipole)**的有机分子间的相互作用。在本章中将讨论的一个典型的例子是，羧基化合物，例如甲醛，和少见的稳定有机阴离子氰根离子 ( $-\text{CN}$ ，来源于  $\text{NaCN}$ ) 的反应。由于氧原子的电负性比碳大许多，因此羧基是具有极性的。氰根阴离子会被羧基上带有正电性的碳原子所吸引。

实际上，不需要任何试剂都具有电荷。电中性的水也与甲醛发生反应，这是水上的**孤对电子(lone pair)**——水分子中氧上的非键电子形成的电子对——被醛羧基偶极中具正电性的一段(碳)吸引导致的。

## 轨道吸引

电荷和偶极可以帮助分子靠近并发生反应，帮助他们克服电子排斥并降低活化能。但是没有电荷和偶极的分子仍然可以发生反应。一种古老的测定不饱和键的方法是用溴水，如果红棕色褪去，则表示分子是不饱和的(含有双键)。光谱法的发展让我们很少需要用到这种试验，但对于反应本身还是十分重要的。即使烯烃和溴分子中都不含有电荷或者偶极，它们仍然可以发生反应。这二者之间的吸引力并不是静电吸引，而是轨道吸引，溴分子上有一个空轨道—— $\sigma^*$   $\text{Br}-\text{Br}$  键的反键轨道——可以接受烯烃的电子。一个充满的轨道与一个空轨道的作用同样可以引起轨道相互作用和化学反应的产生。

事实上，本页涉及的另两个反应同样涉及轨道相互作用，但在当时的情境下，轨道相互作用是随着静电吸引而发生的。



● 总结上述情况:

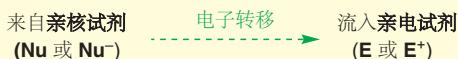
- 总地来说，分子之间会相互排斥。因此，如果想发生反应，则必须克服一个能量障碍，这个能量障碍称为活化能。
- 大多数有机反应涉及到充满的轨道与空轨道的相互作用。
- 许多，但不是全部的有机反应，还涉及静电吸引，这有助于克服电子排斥。
- 一些离子反应只涉及静电吸引。

我们不需要分析静电或轨道的相互作用，哪一个是使分子聚集在一起最重要的因素。但是您确实需要意识到，两者可能在不同程度上同时作用。

## 电子在分子之间流动时发生反应

当一对分子彼此靠近，只要电子从一个分子移动到另一个分子，就会发生反应。这就是我们所说的反应机理 (reaction mechanism)，即对电子转移路径的详细描述。在大多数有机反应中，电子从一个分子开始，然后向另一个分子移动。我们将接受电子的分子称为亲电试剂 (electrophile)，将贡献电子的分子称为亲核试剂 (nucleophile)。(注：也可称亲核体、亲电体，但本书中不采用。)

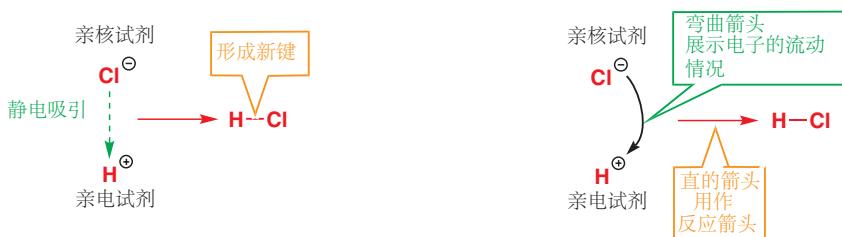
● 电子由亲核试剂转移至亲电试剂 并形成新的共价键:



亲核试剂贡献电子。

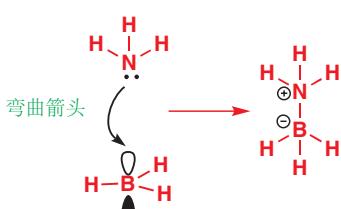
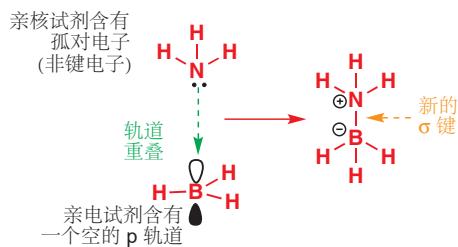
亲电试剂接受电子。

举一个非常简单的例子，亲核试剂是阴离子 ( $\text{Cl}^-$ )，亲电试剂是阳离子 ( $\text{H}^+$ )。两者通过电荷吸引结合在一起，新的键由亲核试剂提供的电子形成。我们很自然地用箭头表示电子的转移，也就是新键的形成过程。为了区分，显示反应本身的路径的箭头使用直的，而用于表示电子转移的箭头使用弯曲的：我们称它们为“弯曲箭头 (curly arrows)”。



在下一个例子中，亲核试剂 (氨， $\text{NH}_3$ ) 和亲电试剂 (甲硼烷， $\text{BH}_3$ ) 都不带电荷，但 N 原子上非键孤对电子与 B 原子上空的 p 轨道之间的相互作用可以使它们结合。电子由亲核试剂 ( $\text{NH}_3$ ) 流入亲电试剂 ( $\text{BH}_3$ ) 并形成新的化学键。

► 有关  $\text{BH}_3$  和  $\text{NH}_3$  中化学键的讨论在 p. 103.

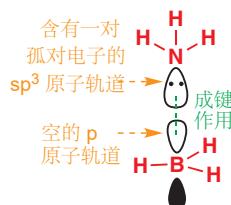


“配位键”(dative covalent bond)也是一种 $\sigma$ 键，只是构成它的一对电子都来自于同一原子；而大多数键是由一个原子向另一个原子贡献电子形成的。在电子的来源上作区分是没有意义的，对于共价键类型，您唯一需要区分的是 $\sigma$ 键和 $\pi$ 键。

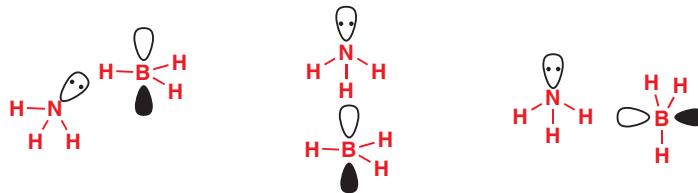
生成物分子中，B和N上的形式电荷，顾名思义是形式上的，仅是为了正确解释电子的来源和归属所人为添加的。通常，我们认为共价键中的两个电子分别来自两端的原子；但是在这里，氮同时提供了两个电子（这种键过去被称为配位键），所以我们不得不考虑这样一个事实，硼最终会额外增加一个电子，而氮会减少一个电子。但最终形成的键仍然是正常的 $\sigma$ 键。

### 轨道重叠是反应成功的重要因素

在氨与硼烷的反应中，不仅分子必须以足够的能量碰撞才能发生反应，而且分子还必须以正确排列正确的轨道发生碰撞才能相互作用。正如您在 Chapter 3 中看到的那样，氮原子的孤对电子位于一个完整的，未参与成键的 $sp^3$ 轨道中。该轨道必须与 B 上的空 p 轨道重叠以形成键。所以像这样的碰撞：



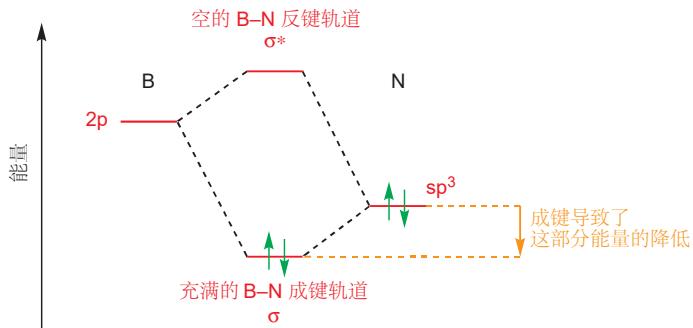
可以成功地形成化学键，但是如下这些碰撞：



则无法完成反应。

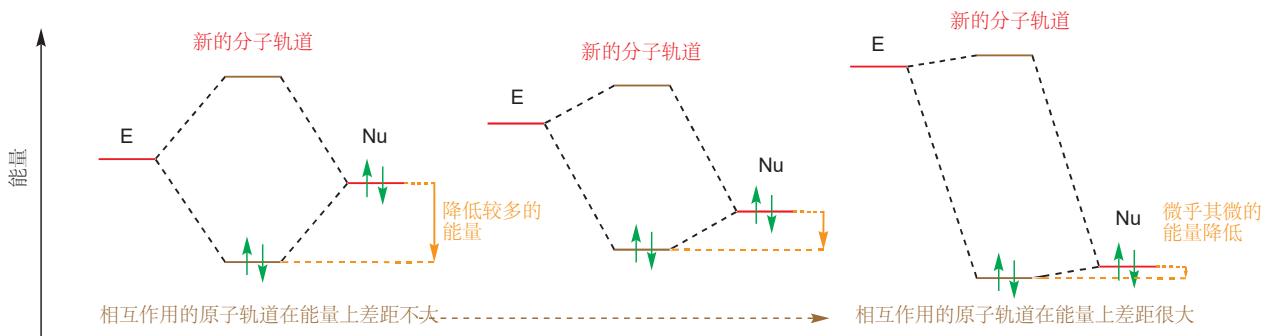
当然，我们还可以绘制分子轨道能级图，展示它们头碰头成键的过程：回顾 Chapter 4，您会重新理解是如何发生的。在这里，我们需要 N 上的完整 $sp^3$  原子轨道与 B 上的空 p 原子轨道相互作用，以给出一个新的 $\sigma$  成键轨道和一个空的 $\sigma^*$  反键轨道（分子轨道）。最后，放入 N 提供的一对电子形成 B-N 键。

■ 我们忽略了 N-H 和 B-H 键，因为它们不参与反应。N 上的 $sp^3$  原子轨道的能量低于 B 上的 p 轨道的能量，这有两个原因：首先，它的 s 成分更多；其次，N 的电负性比 B 大。



能级图清楚地说明了成键有利的原因：原本在 $sp^3$  轨道上的孤对电子，转移到新形成的势能更低的 $\sigma$  轨道，得到了能量降低。我们不需要考虑未填充轨道的能量发生了什么变化，因为它们是空的，并且对整个分子的能量没有贡献。

我们可以概括一下：决定亲核试剂与亲电试剂好坏的因素是什么？我们将使用一个抽象的亲核试剂 Nu，它在某个非键轨道（该轨道无关紧要）上具有一对电子，并可以贡献给亲电试剂 E 的空轨道。分子轨道能级图的三个不同情况：



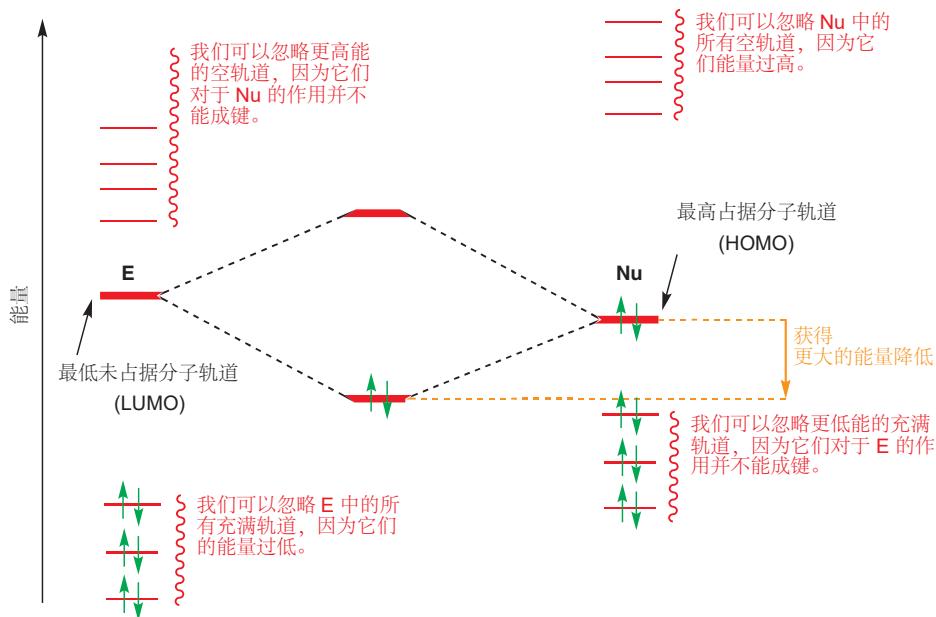
在左侧，填满的 Nu 轨道和空的 E 轨道的能量几乎相同，当它们之间形成新的键时，能量将显降低。但在右侧，填满的 Nu 轨道的能量与空 E 轨道的能量之间存在很大差异，这导致最终的能量降低是微乎其微的。因此：最好的反应需要亲核试剂、亲电试剂的轨道能量接近。

### ● 为了让反应发生，分子必须满足：

- 通过电荷吸引和/或轨道重叠来克服其电子排斥；
- 能量接近的轨道——亲核试剂上充满的轨道和亲电试剂上的空轨道——可以相互作用；
- 彼此靠近，以便这些轨道可以发生重叠。

## 亲核性与亲电性

轨道对亲核试剂和亲电试剂意味着什么？通常来说，充满的轨道的能量往往很低，这就是为什么它们是充满轨道的原因（电子首先占据能量最低的轨道）！相反，空轨道往往能量很高。因此，最佳的相互作用（能使新分子获得最大能量降低的）可能介于所有充满的轨道中能量最高的——我们可以称其为“最高占据分子轨道”（highest occupied molecular orbital），简称 HOMO；和所有空轨道中的能量最低的——“最低未占据分子轨道”（lowest unoccupied molecular orbital），简称 LUMO。下图可能有助于阐明这一想法。



请记住，我们可以忽略成对的充满轨道（成键轨道和反键轨道抵消，请参见第94页）和成对的非填充轨道（它们不包含电子，因此对分子的稳定性无贡献）之间的所有相互作用。在剩下的相互作用中，能量上最有利的相互作用是亲电试剂的 LUMO 和亲核试剂的 HOMO 之间发生的。为了使这些轨道的能量尽可能接近，我们希望亲核试剂具有高能量的 HOMO，亲电试剂具有低能量的 LUMO。

- 最好的亲核试剂具有高能量的最高占据分子轨道 (HOMOs)。
- 最好的亲电试剂具有低能量的最低未占据分子轨道 (LUMOs)。

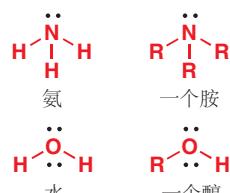
了解任何反应的首要任务是确定哪个是亲核试剂，哪个是亲电试剂。无论如何过分的强调正确识别亲电试剂和亲核试剂是多么重要都不为过。因此我们在下面的几个小标题中都设置了识别训练。我们将向您展示一些性质最佳的亲核试剂和性质最佳的亲电试剂，并在继续观察它们发挥作用之前，讨论他们为何具有极高的亲电或亲核性。

### 识别亲核试剂

亲核试剂是在最高占据分子轨道 (HOMO) 中带有一对电子的，负电性或电中性的物种。最常见的这一类亲核试剂具有非键的孤对电子。非键电子通常具有很高的能量，因为它们不受益于成键使电子对分散的作用，进而产生额外稳定性的贡献。具有孤对电子的典型中性亲核试剂是氨、胺、水和醇，这些物种都具有占据  $sp^3$  轨道的孤对电子 (N 上带有一对孤对电子，O 上有两对)。

元素周期表较高周期的其他带有孤对的原子，例如磷，硫醇和硫化物，也能形成良好的亲核试剂，特别是因为它们的孤对电子具有由 3s 和 3p 原子轨道组成的更高能量的最高占据分子轨道 (HOMO)。

含有一对孤对电子的亲核试剂



$\text{HOMO} =$   
非键的  $sp^3$  轨道



带有负电荷的亲核试剂



氢氧根离子

通常写作:



溴离子



$\text{H}-\text{O}$

$\text{HOMO} =$   
非键的  $sp^3$  轨道



氢氧根离子



通常写作:

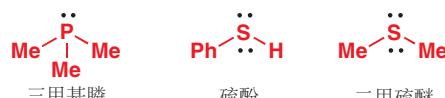


$\text{HOMO} =$   
在 C 上的  
 $sp$  孤对电子

sp 孤对电子

带孤对电子的离子通常也是很好的亲核试剂，一部分原因是它们与亲电试剂间存在静电吸引。离子的中心原子通常是 O, S, 或者卤素，它们都有多对孤电子，例如氢氧根有三对孤对电子。氢氧根中负电荷不能特别地分给其中的一个；而把电子对都画出来不如画一个负电荷容易，因此我们画的负电荷实际上通常表示的是一对电子——获得的“额外”电子和原本的一个电子形成的电子对——所以我们绘制机理时通常从负电荷引出箭头。

碳亲核试剂中最重要的一类是氰离子。虽然线性的氰离子 ( $\text{N}_2$  的等电子体) 中，碳和氮上都分别有一对孤对电子，但亲核原子通常是更偏负的碳而不是中性的氮，因为相比于负电性的氮，以  $sp$  杂化轨道成键的碳原子具有很高的能量，因此构成 HOMO 轨道。

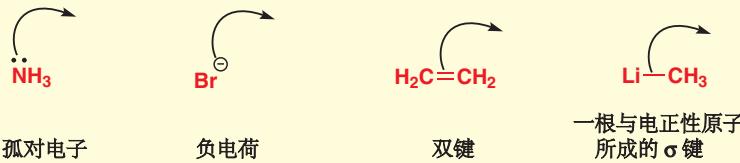


即使是没有非键孤对电子的分子，有时也可以作为亲核试剂。下一个常见的例子是成键的  $\pi$  轨道，尤其是 C=C 双键，这是因为它们的能量比  $\sigma$  轨道都要高（见 p. 93）。简单的烯烃有弱的亲核性，因此需要强的亲电试剂，例如溴才能与之反应。记住，虽然含  $\pi$  键的分子有亲核性，它们也可以有亲电性，当这根  $\pi$  键包含高电负性原子时体现的尤为明显。常见的  $\pi$  亲核试剂只有烯烃和芳香环。

最后，与高电正性原子结合形成的  $\sigma$  键，可以是 B, S 或金属，也容易给出电子而作为亲核试剂。您在 p. 97 看到过这些原子对于电子的吸引力是多么弱，也就是说它们的原子轨道（和因此它们贡献的分子轨道）有很高的能量。您曾经在 Chapter 4 中见过四氢合硼阴离子  $\text{BH}_4^-$ ：硼氢化合物是一类很好的亲核试剂——它可以进攻亲电性的羰基化合物，您会马上看到这个反应。它从它的 HOMO，即 B-H  $\sigma$  成键轨道贡献电子。注意这个时候负电荷并不表示一对电子：您不能从负电荷出发绘制弯曲箭头。

在接下来的章节中您会看到金属有机物 (organometallic)——一类包含 碳-金属键 的化合物，例如甲基锂——作为亲核试剂。它们可以反应的原因，在于正电性的 C 与更加正电性的 Li 所形成的  $\sigma$  轨道是十分高能的。

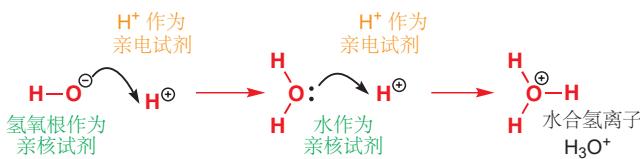
### ● 亲核试剂从可用的高能轨道贡献电子，下面是一些代表：



上面方框中的弯曲箭头表示出了电子从亲核试剂中流出。但电子必须流入某个位置：它们被贡献给亲电试剂。

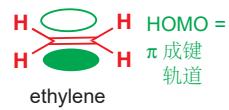
## 识别亲电试剂

亲电试剂是包含一个可以很容易地接纳电子的轨道的中性或带正电的物种，轨道可以是空的原子轨道的（例如硼烷中空的 p 轨道），也可以是低能的反键轨道。最简单的亲电试剂是氰离子  $\text{H}^+$ ，我们通常也叫它质子。 $\text{H}^+$  的轨道是一个没有任何电子的，空置的，非常低能的 1s 轨道。它极具活泼性，可以和几乎任何亲核试剂反应，甚至很难被察觉。例如酸溶液包含的  $\text{H}^+$  会被亲核的氢氧根中和；甚至强酸下水也会被质子化，水作为亲核试剂，质子作为亲电试剂，产物为水合氢离子/水合质子  $\text{H}_3\text{O}^+$ ，所有强酸水溶液中真正的酸性物种。下面是氢氧根和  $\text{H}^+$  结合反应的机理，包含使用弯曲箭头表明的电子流向。箭头由氢氧根离子的负电荷出发，这负电荷代表的是氧原子上的其中一对电子：

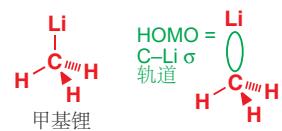
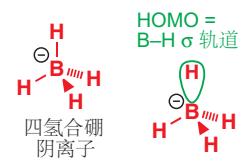


另一些包含空的原子轨道的亲电试剂还有硼烷，三氟化硼，三氯化铝等；对于硼烷，您会在 p. 103 遇到它。下一页的图展示的是  $\text{BF}_3$  与乙醚反应，并生成稳定的加合物。这次箭头开始于孤对电子。

一种包含 C=C 双键的亲核试剂

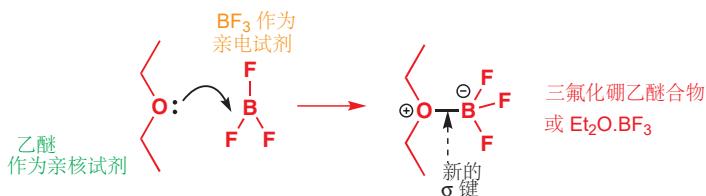


包含位于两个电正性分子间的  $\sigma$  键的亲核试剂



包含空原子轨道的亲电试剂

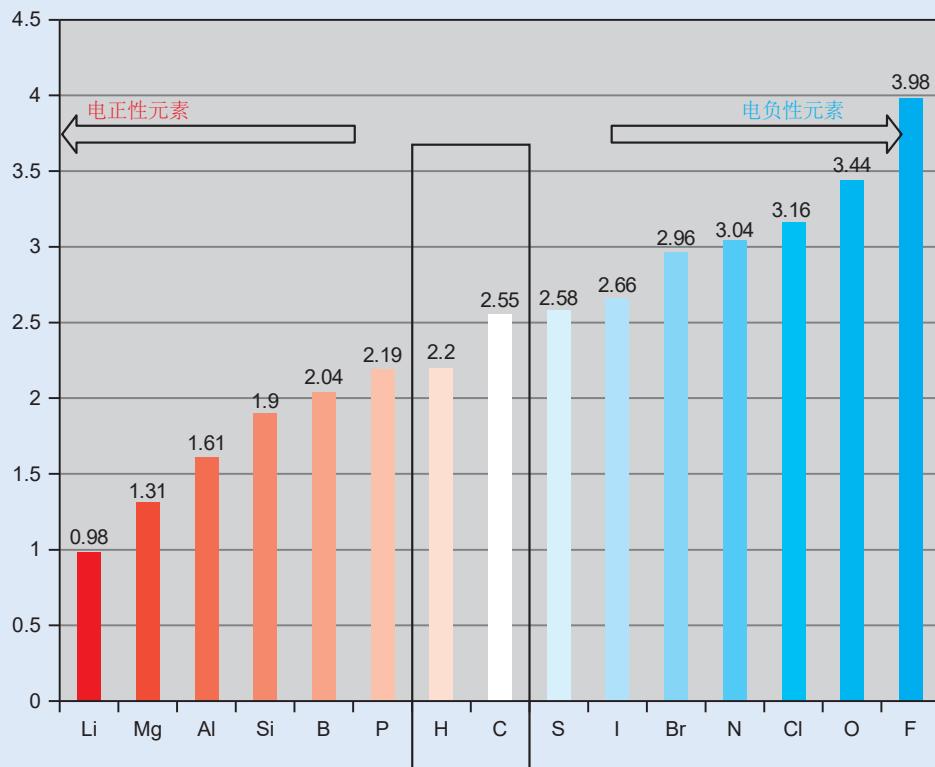




有机化合物很少包含上文那样的空的原子轨道；大多数亲电试剂，则由于高电负性原子的存在，包含低能的反键轨道（LUMO）。这些反键轨道可以是  $\pi^*$  轨道，也可以是  $\sigma^*$  轨道——换种说法，能作为良好的亲电试剂的分子，也许会包含一个与高电负性原子，如 O, N, Cl, 或 Br 成的双键或单键。一个高电负性原子参与成键并降低轨道的能量，对于接受电子是十分重要的（见 p. 96）。

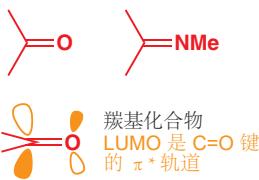
### 碳在电负性表中的位置

下面是对有机反应中常见原子的电负性的梳理



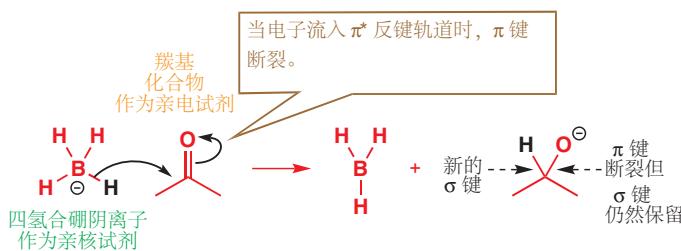
这张条形图清晰地展示了为什么碳是如此的特别：它可以和几乎任何原子，尤其是它自己形成很牢固的共价键。在表两端的原子和与之电负性相近的元素形成的键很弱（金属-金属键很弱，卤素-卤素键，O-O 键也很弱），但中间的元素可以与无论在两端还是中间的元素形成很强的键。处于电负性表的中间同时给予 C 带来了多彩的反应性：在一个更具电正性的原子成键时碳是亲电的，与一个更具电负性的原子成键时碳是亲核的。

与高电负性原子成双键  
形成的亲电试剂



包含与高电负性原子成双键的一类重要分子是羰基化合物 (carbonyl compound)。事实上羰基也是有机化学中最重要的官能团。我们在 p. 103 看到过它的轨道，并且我们会在下一章 Chapter 6 中专门研究它的轨道和反应性。低能的  $\pi^*$  轨道可以接受电子，它的亲电性随着碳原子部分正电性的增强而增加，而碳原子上的部分正电荷是由  $C=O$  偶极子产生的。下面是羰基化合物的一个例子，丙酮与一个阴离子亲核试剂发生反应——我们选择四氢合硼阴离子。记得当负电荷不代表一对

电子时，箭头不能由负电荷出发。

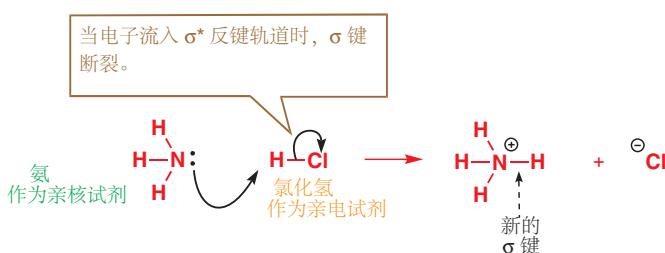


这次箭头涉及的电子移动稍微多一点，但它的解释同样是很直接的。左数第一个箭头显示了电子由亲核试剂的 HOMO (B-H  $\sigma$  轨道) 流入亲电试剂的 LUMO ( $\text{C}=\text{O}$   $\pi^*$  轨道)。而这个机理相比从前多出的，是由双键指向氧原子的第二个箭头。它的解释是这样的：当电子流入一根键的反键轨道（即  $\pi^*$ ）时，该键就会断裂。在这个示例中断掉的键是  $\text{C}=\text{O}$  的  $\pi$  键（双键中的另一根  $\sigma$  键完好无损）。但成键轨道中的电子必须找到合适的去处，即作为氧原子上额外的一对的孤对电子（使用负电荷代表）。在产物中的表象则是由一根 C-H  $\sigma$  键替代在了  $\text{C}=\text{O}$   $\pi$  键原有的位置上。

我们将 在 Chapter 6 回顾这个非常重要的反应。

包含单键与负电性原子相连的分子可以作为良好的亲电试剂，亲电位点是与负电性原子相连的那个原子。像  $\text{HCl}$  或  $\text{CH}_3\text{Br}$  中的  $\sigma^*$  轨道有非常低的能量，这是因为 Cl 或 Br 的负电性（见 p. 95）与偶极作用力，将亲核试剂的电子吸引到了 H 或 C 原子上。

下面是一个相关例子，其中氯化氢作为亲电试剂，氨作为亲核试剂。与羧基的理论相似，当电子流入任何一根键的反键轨道时，这根键就必须断裂。而此时，反键轨道换成了 H-Cl 的  $\sigma^*$  轨道，因此该断裂的是 H-Cl  $\sigma$  键。



含有与负电性原子连接的单键的亲电试剂

$\text{H}-\text{Cl}$  氯化氢     $\text{H}_3\text{C}-\text{Br}$  溴甲烷

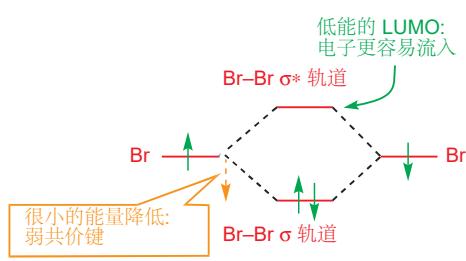
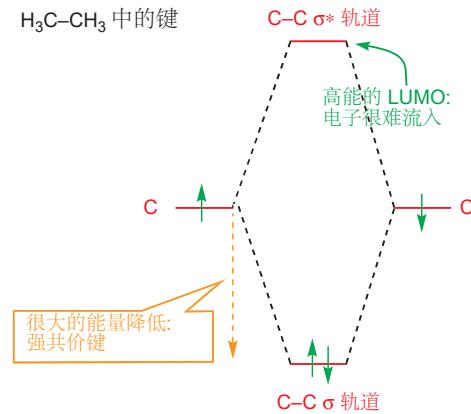
$\text{Br}-\text{Br}$   
溴单质

$\text{H}-\text{Cl}$   
LUMO 是  $\sigma^*$  轨道

您也许能认出这个反应，和 p. 113 的另一反应一样，都是酸和碱的中和反应。任何酸碱反应 (acid-base reactions) 都是一个亲核试剂 (碱) 和一个亲电试剂 (酸) 之间的反应。当亲电试剂中含有 X-H 键 (X 为任意原子)，并会在反应中失去  $\text{H}^+$  时，我们称之为酸；当亲核试剂贡献了电子以形成 X-H 键时，我们称之为碱。这是对于酸、碱的新的定义，我们将在 Chapter 8 中详细讨论，在那里您会遇到“路易斯酸 (Lewis acid)”一词。

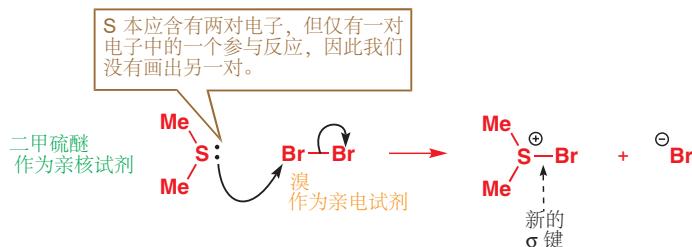
有些非极性  $\sigma$  键同样是具有亲电性的。卤素单质  $\text{I}_2$ ,  $\text{Br}_2$ , 和  $\text{Cl}_2$  中的键就属于这一类型。例如溴单质有很强的亲电性，这是因为它含有很弱的  $\text{Br}-\text{Br}$  键，和很低能的  $\sigma^*$  轨道。为什么  $\sigma^*$  能量低？因为溴的负电性微弱，但它的体积较大：溴单质使用的是 4s 和 4p 原子轨道成键，这些轨道很大、很分散，这意味着它们的重叠将会很差，因此成键时反键  $\sigma^*$  轨道的能量并不会上升很多，即能量较低，因此它很容易接受电子。用这种思路看 C-C 键则恰恰相反：因此 C-C 键从来没有亲电性。

## Br-Br 中的键

H<sub>3</sub>C-CH<sub>3</sub> 中的键

C-C 键的不活泼性正是我们将碳氢骨架与官能团在思考有机结构时分开的原因：碳氢骨架由较强的 C-C 键构成，包含低能的充满轨道和高能的空轨道，既不容易流出电子又不容易流入电子；官能团中通常包含电负性或电正性较强的原子，它们的反应性体现在较低能的 LUMOs 或较高能的 HOMOs 中。

溴单质与很多亲核试剂都能发生反应，例如在下面的硫醚与之的反应中。电子由硫上的孤对中流向 Br-Br σ\* 轨道。这一过程断裂了旧的 Br-Br 键，并在 S 与 Br 之间形成了共价键。



## ● 亲电试剂的较低能空轨道接受电子，表示方法如下：



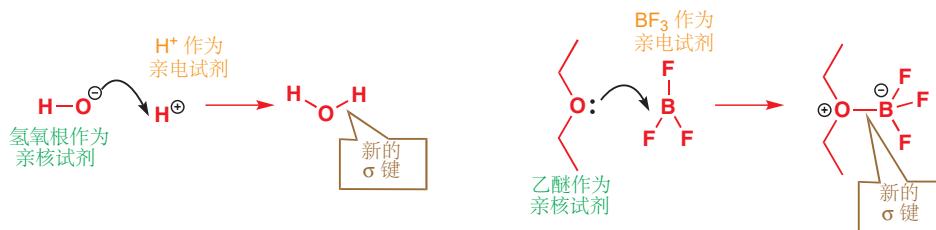
## 用弯曲的箭头表示反应机理

前两节中，您已经遇到了不少用弯曲箭头表示反应中电子流向的离子了，因此是时候讨论它们的细节了。毫不夸张地说，这一简单的工具是有机化学家清楚而准确地解释反应最有力的工具；所解释的内容，即反应发生的方式就是反应机理。我们在 Chapter 2 中介绍了绘制分子的准则，从那以后您可以通过十分简单的结构图表示十分复杂的分子；而且不但能清晰地表示分子所有重要的特征，而且还能抛弃不必要的细节。使用弯曲箭头绘制机理也是如此：我们知道化学反应涉及分子轨道的重叠和组合，并生成新的分子轨道，还涉及轨道中电子的移动，但很多部分是不需要表示出的。因此我们将要讨论的机理绘制准则同样需要保留重要的特征，并抛弃不必要的细节。

## 弯曲箭头表示电子的移动

一个弯曲箭头代表一对电子由一个充满的轨道流入一个空轨道。您可以将一个弯曲箭头想象成将

一对电子扔出去，或是爬山者的抓钩，由它原本在的地方到它想去的地方。下面是最简单的例子，亲核试剂上的孤对电子经过移动（移动到一个空轨道），变为连接亲核试剂和亲电试剂的一根共价键。



弯曲箭头的尾端总是处在代表一对充满轨道上的电子的位置——在上图的两种情况下分别是孤电子对和负电荷（实际上也表示的是一对孤电子）。弯曲箭头的前端则指向这一对电子的最终归宿——氧与氢或氧与硼间一根新的键。当我们形成一根新建时，箭头的头部应该指向两个成键原子之间连线上的某个位置。

为什么要让一个弯曲箭头代表两个电子？正如您在 Chapter 4 中所见，形成一根键需要两个电子，而孤电子也总成对出现，因此电子对的移动要比单电子的移动更加常见。我们会用另一种箭头来表示单个电子的移动，您会在 Chapters 24 和 37 中遇到。

当亲核试剂进攻反键轨道，例如我们讨论过的脆弱的 Br-Br 键时，我们需要同时画两个箭头，一个表示新键的形成，另一个则表示旧键的断裂。



用于形成新键的箭头和之前一样——由亲核试剂的孤电子对引出，然后终止于亲电试剂旁。但用于断裂旧键的箭头就有所区别，它展示了原本溴单质中成键的一对电子转移到了其中一端（右侧的溴原子）并且将其转化成了负离子。同样，这一个箭头始于一对处在充满轨道——Br-Br σ 键上的电子。在绘制时，箭头由键的中央引出，箭头的前端应指向接受电子的一端（本例中为 Br 原子）。

另一个例子是碱对酸，即氨对 HBr 的进攻。



所绘制箭头的曲率并不重要——只要它足够和反应机理的箭头区分，您可以根据自己的喜好决定曲率。只要箭头的出发点和目的地明确，那么朝左或右，朝上或下也是您自己决定的。下面的机理书写就是正确的：



有些化学家喜欢将箭头的末尾指向待生成的新键（成键两原子连线）的中间位置，这也是可以的。本书中我们选用了直接指向亲电原子的方式：这二者在面临简单问题时区别并不明显；但当我们面临较复杂的问题时，后者显得更加清晰和有意义，同时也是为了避免歧义。

注意到箭头的末尾总是指向一个负电性原子，电子的转移过程满足了它对高电子密度的渴望。这也是为什么连有负电性原子的双键或单键总是好的亲电试剂。

● 弯曲箭头总是从表示一对电子的某个东西出发：

- 负电荷
- 孤电子对
- 一根键

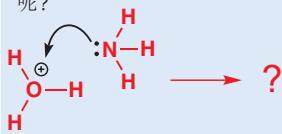
并结束于这些电子的最终去向。

### 电荷在反应中是守恒的

电荷不能凭空产生，也不能凭空消失。如果起始原料不带电，那么产物也应如此。在上一个例子中，为什么溴原子带上了负电荷是很明显的——它带走了原本他只占有半的共价键的全部电子。由于两个产物的总和必须仍保持中性，因此氮需要带正电荷——理解上，由于新形成的 N-H 键所需的两个电子都来自 N，因此 N 在交易中亏损了一个电子，故带正电。

如果起始原料带电荷，那么产物整体的电荷必须与之相同。下图是  $\text{H}_3\text{O}^+$  质子化氨的过程——原料和产物都带  $1+$  电荷。

$\text{H}_3\text{O}^+$  (水合氢离子, the hydronium ion) 在此处当然是亲电试剂： $\text{H}-\text{O}$  的  $\sigma^*$  轨道接受了电子。然而为什么反应不按下列方式发生呢？



这是由于氧原子已经达到了八电子结构(轨道已经占满了)——六个来自与 H 成的三根键，两个来自孤对电子。因此除非断掉已有的键，氧已经不能接受电子了。此处的正电荷并不像  $\text{H}^+$  中的代表一个空轨道。因此  $\text{H}_3\text{O}^+$  的亲电位点在 H 而不在 O 上。



在亲电的羰基团被亲核试剂进攻时，最寻常的莫过于断裂双键中  $\pi$  键的过程——这时仅有  $\pi$  键断裂，而  $\sigma$  键则完好无损。机理的绘制和  $\sigma$  键的断裂画法一致，箭头由  $\pi$  键的中心指向这根键两端的原子中电负性更强的一个，在这个情境下是氧原子(而不是碳原子)。



这个例子中，起始原料共含有一个单位的负电荷，它同样在阴离子产物中被表现了出来。氢氧根的负电荷消失了，这是由于它将一对电子与羰基碳分享，使得自己只占有其中的一个。而羰基氧则产生了负电荷，这是由于它完全地占有了原先只占有半的  $\pi$  键。

### $\pi$ 键作为亲核试剂

如您在上文所见，烯烃可以作为亲核试剂。烯烃与  $\text{HBr}$  的反应可以作为一个简单的例子。 $\text{C}-\text{C}$   $\pi$  键是亲核试剂的 HOMO 轨道。因此，最左侧的来自  $\pi$  键中央的箭头指向了其中一个碳原子和  $\text{HBr}$  的氢原子(待成之键)的中间。第二个箭头则将  $\text{H}-\text{Br}$   $\sigma$  键的电子全部转移给了溴原子，并生成一个溴负离子。由于电荷守恒，我们必须再生成一个碳阳离子(carbocation)。碳阳离子含有一个正电荷和一个空的 p 轨道(您可以自行清算下电子数)。

我们在 p. 103 讨论过最简单的碳阳离子,  $\text{CH}_3^+$ .

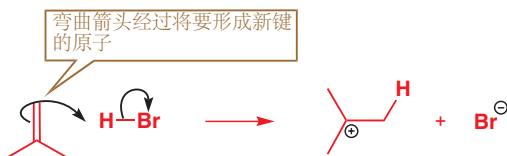
我们在产物中特意画出了反应所新形成的 C-H 键，这是为了使机理更加清晰。在该碳上，还有另两个 C-H，但我们通常不会画出。



请注意尤其在绘制刚刚的机理时，将两个反应物的方向排列正确是很重要的，因为箭头同时需要指明烯烃双键的哪一端与 HBr 发生反应。如果我们不按照刚刚的标准绘制，那么就有可能遇到麻烦，下面就是一个不令人满意的表述，并不能清楚地表示哪一端与 H 成键。



如果您在绘制机理时发现自己的表述含糊不清、模棱两可，那么重新检查如何画得更清晰是十分值得的。当亲核试剂是一根  $\pi$  (或  $\sigma$ ) 键而不是一对孤电子的时候，键的哪一端真正参与反应始终是一个问题。您可以使用“具体原子箭头 (atom-specific arrow)”表示：将机理箭头由键的中间出发，经过参与反应的原子并达到亲电位点上，如下：



■ 在 Chapter 19 中我们会解释这根新的 C-H 键成在一边而非另一边的原因。

反应不会就此结束，上一步得到的一对阴阳离子会马上结合并形成最终产物。溴负离子做亲核试剂，包含空 p 轨道的碳阳离子做亲电试剂。



### $\sigma$ 键作为亲核试剂

当  $\sigma$  键扮演亲核试剂的时候，也需要确认其两端的原子，哪一个与亲电试剂形成新键。我们可以回到一个从前提到过的例子，硼氢化钠 ( $\text{NaBH}_4$ ) 与羧基化合物的反应，并补充它的机理。在这个例子中，硼氢键一端的原子 (氢原子) 离开  $\text{BH}_4^-$  负离子剩下的部分，并于羧基化合物形成新键。亲电试剂的 LUMO 显然是  $\text{C}=\text{O}$  的  $\pi^*$  轨道。



完美的箭头应当由亲核试剂中即将断裂的键中间出发，并且更应当表达出键哪一端的电子转移到亲电试剂上。如果您想明确亲核试剂中  $\sigma$  键的电子经过氢原子，而不是经过硼原子；那么您也可以使用具体原子箭头：

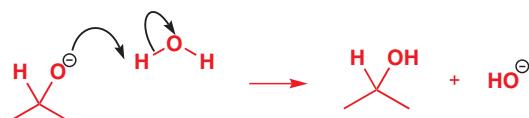


■ 本反应和上面的与  $\text{H}_3\text{O}^+$  的反应有明显的差异：与  $\text{H}_3\text{O}^+$  中的 O 原子不同，碳阳离子上的 C 原子只含六个电子，因此可以继续接受电子对。

■ 记得 (p. 115) 我们曾说过：不能从  $\text{BH}_4^-$  的负电荷上引出弯曲箭头，因为它并不代表一对孤电子：B 原子周围的全部八对电子都以 B-H 键的形式存在。这个负电荷概念上类似于  $\text{H}_3\text{O}^+$  中的正电荷，也不代表一个空轨道。

请将它们与  $\text{HO}^-$  中的负电荷 (代表一对  $\text{sp}^3$  孤电子) 和  $\text{H}^+$  中的正电荷 (代指一个  $1s$  空轨道) 比较

此反应产生的氧负离子是中间体，并不是最终产物。这个反应常在水体系中进行，因而随后氧负离子就会夺取水分子中的质子，而转变为醇分子的形式。水分子在这里是亲电试剂：LUMO 为  $\text{O}-\text{H}$  的  $\sigma^*$ 。



■ 和其他一些分子一样，水分子既可以做亲核试剂也可以做亲电试剂。因此对于这类分子，您需要综合考虑与之反应的另一试剂来判断它表现的性质。在左侧的例子中，由于负离子只能做亲核试剂，水故做亲电试剂。

● 总结：弯曲箭头的健康检查

- 一个弯曲箭头表示一对电子的移动。
- 箭头的尾部显示了电子对的来源，应当是一个充满轨道（而且是 HOMO）。这个轨道（这对电子）可以用如下几种方式表示：
  - 孤对电子记号
  - 或负电荷
  - 或一根  $\pi$  键
  - 或一根  $\sigma$  键。
- 箭头的头部显示了电子对的最终归宿，会是如下几种：
  - 一个将要形成新键的空轨道
  - 或  $\pi^*$ ,  $\sigma^*$  反键轨道，伴随着旧键的断裂和新键的形成
  - 或一个可以（用孤对电子）支持负电荷的、电负性强的原子。
- 电荷总数在反应中守恒。

## 绘制您自己的机理

遇到一个新反应时，您应当首先考虑以下两件事：

1. 识别哪根键断裂，哪根键形成；
2. 决定哪个分子是亲核试剂，哪个分子是亲电试剂。

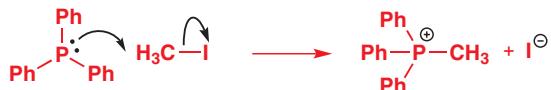
当您完成这一考虑后，您就可以很容易地用弯曲箭头绘制机理了。我们将以三苯基膦与碘甲烷的反应作为例子实施上述思路。



首先我们要观察发生了什么：磷原子和甲基形成了一根新键，碳-碘 旧键断裂。我们首先要更加合理地表示两个试剂的结构，以让我们能够更方便地绘制机理。最重要的一点是要将反应实际要用到的键都表示出来（在这时，细节多一点总比少一点好）：



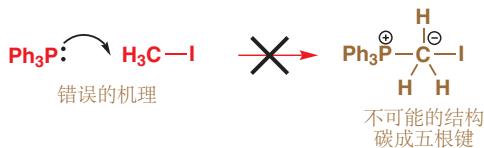
现在我们面临了最重要的问题：**哪个是亲核试剂，哪个是亲电试剂？**对于亲核试剂，我们需要寻找高能的电子对，例如三苯基膦中磷原子含有的孤对电子。同样的，碘甲烷也符合亲电试剂的条件，即 C 和负电性元素 (I) 之间的键。那么目前剩下的任务是绘制箭头。第一个箭头由电子对的来源，即磷的孤对电子出发，指向 C 原子来形成新的 P-C 键。然后 C-I 键随之断裂，电子对全部转移给 I 原子，这是第二个箭头。



诚然，这个反应实在是太简单了。但如果您能够第一次就自己写出来，您仍应给予自己鼓励。

## 警惕五价碳

我们现在要明确地阐明一件我们一直以来假设如此的事。稳定有机分子中用到的大多数元素都有一个对于周围电子数的限额（氢原子为二，碳、氮、氧原子为八），因此如果您要和这些原子形成新键，那么必须也断掉它原有的一根键。在上个例子中，假设您只是将  $\text{Ph}_3\text{P}$  “添加”到了  $\text{MeI}$  上，而没有断开 C-I 键：会发生什么？

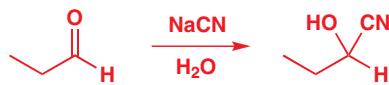


所生成的结构是错误的，因为碳原子不可能形成五根键——如果成五根键，那么意味着一个 2s 和三个 2p 轨道要装下十个电子。但四个轨道最多能装八个电子。

- B, C, N, 和 O 不可能形成四根以上的键。如果您想要与不带电的 H, C, N, 或 O 原子成新键；那么与此同时，您必须断开一条原有的键。

## 分步机理

在本章的开始，我们提到了羰基化合物与氰化物的反应。下面是这个反应，我们现在要推断它的机理：

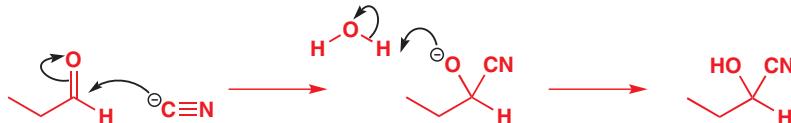


我们首先要理清发生了什么。 $\text{NaCN}$  是一个离子化合物，因此真正的试剂应当是氰离子，有关氰离子的结构我们在 p. 112 页介绍过。由于氰离子（负离子）必然做亲核试剂，因此羰基是亲电试剂。那么机理就不难书写了，第一个箭头由亲核试剂的负电荷出发，进攻  $\text{C=O}$  团；第二个箭头用于断裂原有  $\text{C=O}$  键：

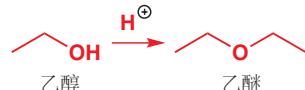


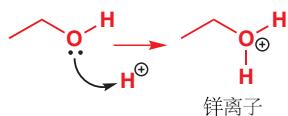
您将越来越熟悉这种绘制反应过程的方式：首先画出有机的反应原料，然后绘制箭头，并书写试剂和溶剂。我们称其为反应流程图 (*reaction scheme*)。使用这种图示时两侧可以不配平，我们使用直箭头  $\longrightarrow$  而不是等号。

为了得到最终产物，我们还需要将氧负离子转化为羟基，于是它必须从某个地方获得一个质子。这个情境下，唯一能提供质子就是溶剂，水，因此我们可以按次序完整地写出下列分布机理：



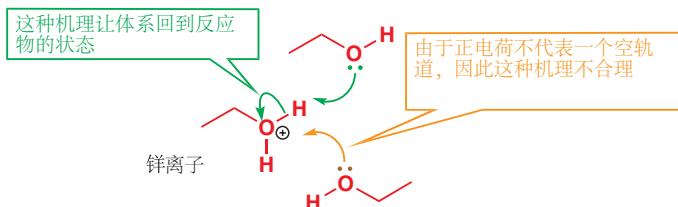
请尝试下面一个稍微复杂的例子：一级醇在酸性溶液中转化为对称醚。这是一个酸催化下，一个官能团转换为另一官能团的机理。



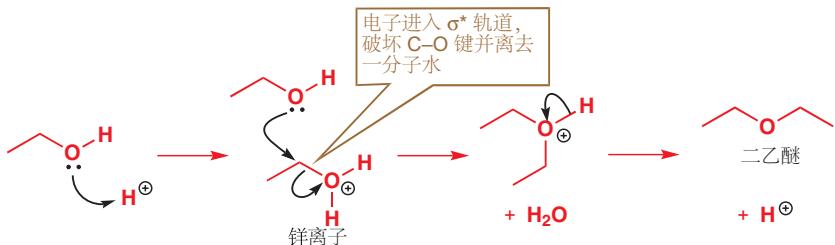


极性反应的第一步通常是由酸碱性控制的质子化或去质子的过程，在本反应中，第一步是醇与  $\text{H}^+$  的反应，其中  $\text{H}^+$  做亲电试剂，醇以其 HOMO，即 O 原子的其中一对孤电子做亲核试剂。这步分反应得到的中间体我们称为锌(氧鎓)离子 (oxonium ion).

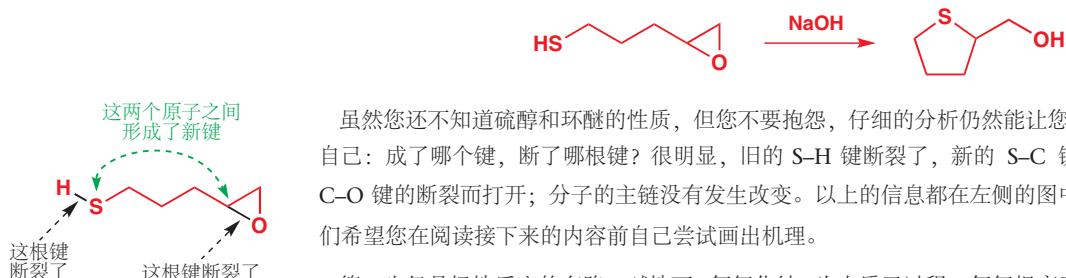
带正电的锌离子固然是第二步反应的亲电试剂，而唯一可能的亲核试剂也就是另一分子的乙醇了。但它们如何反应？静电吸引或许会让乙醇氧原子上的孤对电子进攻锌离子中的正电氧，但这会生成一个十电子氧，这种思路的错误和从前讲过的水合氢离子是一样的，记得  $\text{H}_3\text{O}^+$  中的正电荷并不代表一个空轨道。或许可以选择进攻  $\text{H}-\text{O}$  键，这虽然是合理的，但它又让体系回到了反应物的状态，整个过程没有意义。



观察生成物，我们需要的其实是一根新  $\text{C}-\text{O}$  键，因此孤对电子应当进攻碳原子；将电子对放入  $\text{C}-\text{O}$  的  $\sigma^*$  轨道，使其断裂并离去一分子水。下图是全部的反应机理，最后一步是通过去质子形成醚分子。



下面让我们尝试完成一个新的机理。



虽然您还不知道硫醇和环醚的性质，但您不要抱怨，仔细的分析仍然能让您写出机理。首先要问自己：成了哪个键，断了哪根键？很明显，旧的  $\text{S}-\text{H}$  键断裂了，新的  $\text{S}-\text{C}$  键形成了；三元环随着  $\text{C}-\text{O}$  键的断裂而打开；分子的主链没有发生改变。以上的信息都在左侧的图中标识出来了，因此我们希望您在阅读接下来的内容前自己尝试画出机理。

第一步仍是极性反应的套路，碱性下 (氢氧化钠) 为去质子过程。氢氧根离子做亲核试剂，夺取亲电试剂巯基的质子，并断裂  $\text{S}-\text{H}$  键，生成硫负离子：



随之形成的负离子必然为亲核试剂。通过分析成键和断键的情况，我们合理地推断三元环中的  $\text{C}-\text{O}$  键为亲电试剂。因此我们可以画出机理：



上一步反应得到的还不是产物：我们仍需要负离子从某个地方获得一个质子。质子可以来源于哪里呢？第一步反应中氢氧根离子夺取一个质子转变为了水分子，因此氧负离子重新从一分子水中夺取一个质子，使之重新回到氢氧根的状态，这样的思路是合理的。



即使您的机理可能没有如上给出的一样整齐，但如果您大致正确的话，您应感到自豪。因为经过这一节的学习，您掌握了画出陌生的三步机理的能力。

## 弯曲箭头在有机化学的学习上至关重要

弯曲箭头被用于解释反应物和产物结构之间的转化过程，被用于解释绝大部分有机反应中化合物的反应性，不论它们复杂与否。如果您能熟练掌握机理中的原理，您甚至可以预测未知反应的可能结果，并由此设计合成路线。它们是理解和发展有机化学的有力工具，在有机化学的学习中，您也会越来越深刻和熟练地掌握它们。它们是描绘有机反应机理的动态语言，因此您会在今后书中的任何一章找到它们。

我们即将开始学习各种各样的反应，但看起来数量庞大的“不同反应”其实并不是很多，大多数有机反应都涉及亲核试剂与亲电试剂中电子对的流动，而这些反应中所用到的常见亲核、亲电试剂也相对较少。因此掌握弯曲箭头另一同等重要的原因是，如果您能画出这些反应的机理，那么这些看起来不同的反应之中的相关性就会立刻显现出来。学习绘制机理的作用就是让您同时理解一组反应（原理上的），而不是逐个学习（经验上的）。

绘制弯曲箭头的机理就好像骑自行车。在您还没有掌握这项技能的时候，您经常摔跤；一旦您掌握了这项技能，您就会发现绘制机理是多么的简单直接，还会回想没有它的时候自己做了什么。到那时，您会穿过熙熙攘攘的街道和路口，您仍然需要小心才能通过。

■ 本书中的机理，通常用红色绘制主体部分，并用黑色绘制箭头、电荷、孤电子对等需要凸显的部分。我们也建议您在笔记本中绘制机理箭头和绘制结构时使用可区分的颜色。

► Chapters 34, 35, 37, 和 38 中将讨论不涉及亲核试剂、亲电试剂的那一少部分反应

► 您会在 Chapter 10 中体会到这一道理：羧酸、酰胺、酯、醛均有不同的官能团，但它们反应的机理相同。

## 绘制机理的步骤

如果仍然感觉上面的教学让您摇摆不定，我们罗列了对绘制机理一般步骤的指南，但您很快会发现您时常不需要严格完成它们。

- 按 Chapter 2 中的准则清晰地绘制反应物结构，并理解作为反应环境的试剂和溶剂。例如，如果反应在碱性条件下进行，您需要观察是否有某个化合物将以负离子形式存在。
- 审视反应原料和产物，并理清反应中发生的变化。哪根新键形成？哪根旧键断裂？有无新添加到分子上的事物？有无键在分子中移动了位置？
- 找到反应物中的亲核试剂和亲电试剂，并识别亲核试剂上的亲核位点，亲电试剂上的亲电位点。
- 如果这两个位点的结合正好能得到产物，那么您需要以合适的位置、合适的角度绘制这两个分子，使得成键的两个位点之间距离得当，使得进攻角度大致与轨道的方向一致。
- 由亲电位点指向亲核位点绘制箭头。起始点必须能代表一对电子——一个充满的轨道或者一个负电荷（箭头的尾端接触键、孤对电子或负电荷）——中止点为电子的最终去向（箭头的头端指向该位置）。

6. 思考有没有什么原子连有过多的键。如果有的话，那么为了避免荒谬的结构，该原子必须断裂原有的一根键。您需要选择一根将要断开的键，由该键的中央(即代表该键电子填充的轨道)引出一个新的箭头，指向某一合适的位置，例如一个负电性原子。
7. 根据弯曲箭头所示的电子转移过程画出所得到的生成物。断开的键是箭头的来源，箭头的目标为一根新的键。您还需要考虑单个电子电荷的转变，并保证整个体系电荷守恒。当您在前几步中将机理绘制出来后，得到的生成物的结构就已经确定了。如果照此画出的生成物有问题，那么机理就是错的，您没有进一步决定的空间。
8. 根据需要，重复 5–7 步并得到最终的稳定产物。

您现在已经了解了机理的语言，我们是时候讨论一些官能团反应性的细节了。下一章中，我们将从最重要的官能团，羧基出发。

## 延伸阅读

S. Warren, *Chemistry of the Carbonyl Group: A Programmed Approach to Organic Reaction Mechanisms*, Wiley, Chichester, 1974. 上一章我们建议的, *Molecular Orbitals and Organic Chemical Reactions: Student Edition* by Ian Fleming, Wiley, Chichester, 2009, 也对在化学反应的研究中运用轨道，和机理的绘制有指导作用。

关于反应性问题在理论/物理上的讨论，见 J. Keeler and P. Wothers, *Why Chemical Reactions Happen*, OUP, Oxford, 2003.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 对羰基的亲核加成

## 联系

### 基础

- 官能团，尤其是 C=O 基 ch2
- 用光谱法识别分子中的官能团 ch3
- 分子轨道如何解释分子形状和官能团 ch4
- 分子如何，为什么在一起反应；如何，为什么用弯曲箭头描述反应 ch5

### 目标

- C=O 如何，为什么与亲核试剂反应
- 用分子轨道和弯曲箭头阐释 C=O 基的反应性
- 什么样的分子可以通过 C=O 基的反应制取
- 酸或碱催化剂如何提高 C=O 基的反应性

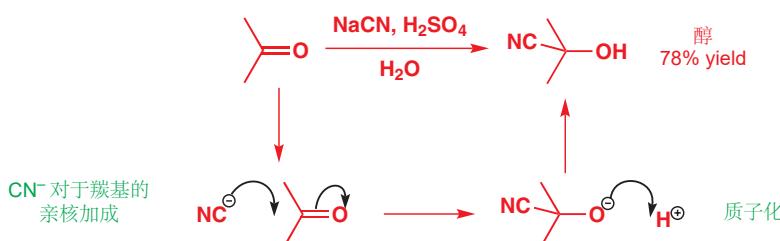
### 展望

- 有机金属试剂的加成 ch9
- C=O 基的氧原子的取代反应 ch11
- 羧酸衍生物中的 C=O 基如何促进取代反应 ch10
- 带有邻位双键的 C=O 基 ch22

## 分子轨道对羰基反应性的解释

我们先抛开上一章中您遇到的大多数反应——我们将在今后的内容中继续讨论它们。而本章我们则会聚焦于它们其中的一个——也许是有机反应中最简单的一个——羰基的亲核加成。羰基，出现于醛、酮以及很多其他化合物中，它无疑是有机化学中最重要的官能团，这也是我们选择它作为第一个详细研究的主题的另一个原因。

您在 pp. 115 和 121 曾遇到过羰基的亲核加成，当时我们展示的是氰化物与醛反应制备醇。作为回顾，我们在下面再次提到了这个反应和它的机理，不过这次换成了酮。



反应分两个步骤进行：首先是氰根的亲核进攻，接着是阴离子的质子化。事实上，这是所有羰基亲核加成的普遍特征。

我们将频繁地使用这样的图示，表示反应的过程和机理。箭头上是反应试剂和条件。图示的上半部分表示反应过程，即如何实施这个反应；下半部分表示反应机理，即反应在实际上如何发生。

● 羰基亲核加成的两个步骤：

- 亲核试剂进攻羰基；
- 氧负离子的质子化。

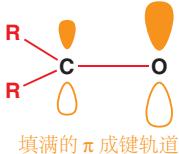
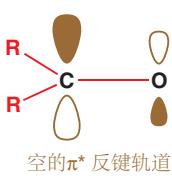
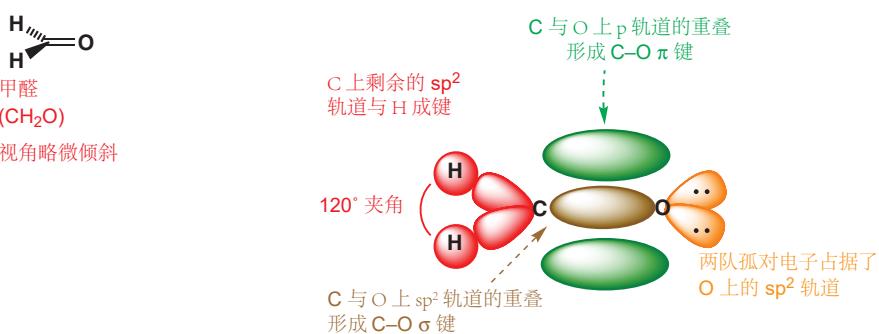
其中更为重要的是加成的一步，它形成了一个新的 C–C σ 键，并且断开了一个 C=O π 键。而质子化的步骤则对 HCN 对 C=O π 键的加成反应做了收尾。

至于为什么氰根，通常像其他亲核试剂一样进攻羰基官能团？而且为什么它会进攻羰基中的碳原子？想要解决这个问题，我们需要详细地了解一般羰基化合物的结构，尤其是 C=O 的分子轨道。

羰基中的双键，就像烯烃中的一样（我们在 Chapter 4 中提过），包括两个部分：一根 σ 键和一根 π 键。其中的 σ 键位于两个  $sp^2$  杂化的原子之间——碳原子和氧原子——它通过两个  $sp^2$  轨道的头碰头重叠成键。碳上的其他两个  $sp^2$  轨道与取代基形成两个 σ 键，而氧上的其他两个轨道则被两对孤对电子填满。 $sp^2$  杂化意味着整个羰基是平面性的，碳上两个取代基的键角接近  $120^\circ$ 。这张图展示了最简单的羰基化合物，甲醛 (formaldehyde, methanal, CH<sub>2</sub>O) 的上述信息。π 键则由两个剩余的/未参与杂化的 p 轨道肩并肩形成——您同样可以在下图中看到。

Interactive bonding orbitals in formaldehyde

► 我们在 Chapter 4 中向您介绍了轨道的极化作用，在 p. 104 有针对于羰基的讨论。



我们在 Chapter 4 中讲羰基的成键时，解释了 π 键的极化，即键偏向氧的原因；这是因为氧相比于碳具有更大的电负性；未填充的  $\pi^*$  反键轨道所偏向的方向与之相反，在碳原子的一端有更大的占比。如上所述，很难用像上图的一个大电子云来详细地描述 π 键，而分别绘制 π 和  $\pi^*$  轨道，并将它们都拆分成 C 和 O 上分开的两个部分反而是更直观的。左图就是用这种方式表现的 π 和  $\pi^*$  轨道。

电负性、键长、键能数据

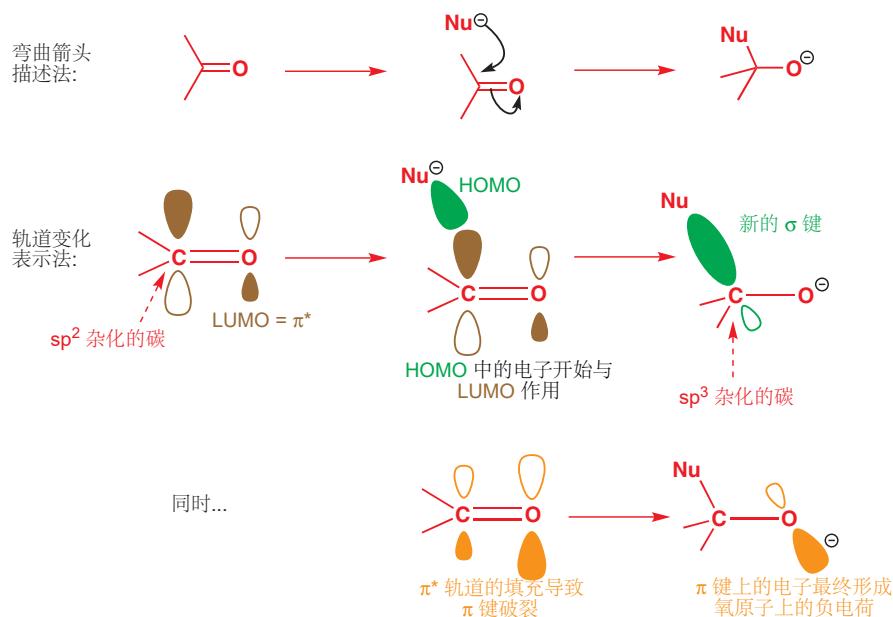
代表性的键能, kJ mol <sup>-1</sup>	代表性的键长, Å	电负性
C–O	351	C
C=O	720	O

因为 C 和 O 之间有两种成键方式，C=O 双键的键长往往短于 C–O 单键，键能也是其两倍多——那么为什么它那么活泼呢？极化是其中的关键。极化后的 C=O 键给予碳原子更大程度的正电性，正电荷对亲核试剂（像氰根）的吸引促成了反应。 $\pi^*$  反键轨道的极化也很重要，当羰基与亲核

试剂反应时，电子由亲核试剂的 HOMO 轨道（氰离子的 sp 轨道）流入亲电试剂的 LUMO 轨道——换句话说，C=O 键的  $\pi^*$  轨道。 $\pi^*$  轨道在碳原子上的占比越大，就意味着 HOMO-LUMO 的相互作用越好，因此碳是亲核进攻的位点。

当我们的亲核试剂——我们在此处用 “Nu<sup>-</sup>” 表示——接近碳原子时，它 HOMO 上的孤对电子就开始与 LUMO ( $\pi^*$  反键轨道) 相互作用并形成一个新的  $\sigma$  键。填充一根共价键的反键轨道会断裂该键：当这对电子流入羰基的  $\pi^*$  反键轨道时， $\pi$  键就断了，并且留下了只留下了 C–O  $\sigma$  键。但电子总不能凭空消失，因此原来在  $\pi$  成键轨道上的电子移动到了电负性更强的氧原子上，这就完成了亲核试剂上负电荷的整个流向。您可以在下面的图中看到全过程。

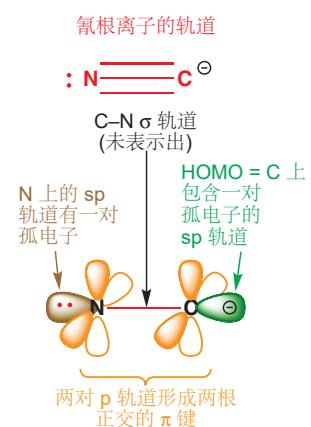
■ 亲核试剂的 HOMO 轨道取决于亲核试剂到底是什么；我们将会遇到其他例子，例如在 sp 或  $sp^3$  轨道上包含孤对电子的，或  $\beta$ -H  $\sigma$  轨道，或金属–碳  $\sigma$  轨道。我们马上将讨论氰离子作为亲核试剂的情况；氰离子的 HOMO 是碳上的 sp 轨道。



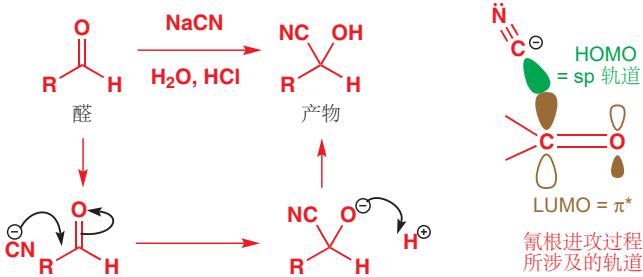
请注意羰基原本平面三角形的  $sp^2$  碳原子，是如何转变为产物中的四面体型的  $sp^3$  碳的。对于您在本章遇到的每一类亲核试剂，我们都将向您展示其中包含的 HOMO-LUMO 相互作用。这些相互作用也向您展示了在反应过程中，化合物轨道的变化。而本章最重要的轨道作用，就是亲核试剂的孤对电子与羰基的  $\pi^*$  结合形成产物中新键的过程。

## 氰根对醛酮的加成

现在我们已经了解了羰基上亲核加成的反应机理，让我们回到本章开始时的例子：羰基化合物和氰化钠生成氰醇 (cyanohydrin)。氰根含有  $sp$  杂化的 C 和 N 原子，并且它的 HOMO 轨道是碳上的一个  $sp$  轨道。该反应是一个典型的羰基上的亲核加成反应：CN<sup>-</sup> HOMO 轨道（碳上的一个  $sp$  轨道）上的电子对流入 C=O 的  $\pi^*$  轨道；C=O  $\pi$  轨道上的电子转移到氧原子上。这个反应通常是在酸性条件下进行的，酸的作用便是使烷氧基阴离子质子化，从而形成产物中的羟基。这个反应对酮和醛都适用，下面将展示普通醛的反应机理。如您所见，这个反应首先出现在 Chapter 5.

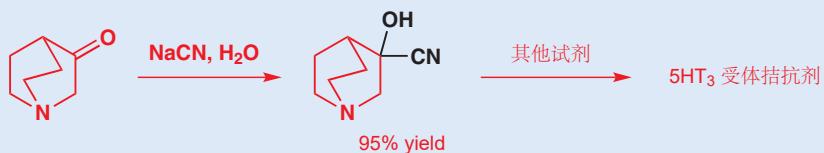


 Interactive mechanism for cyanohydrin formation



### 有机合成中的氰醇

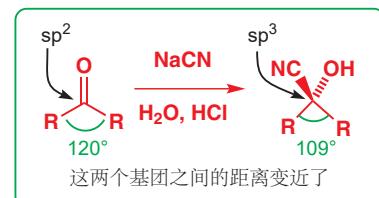
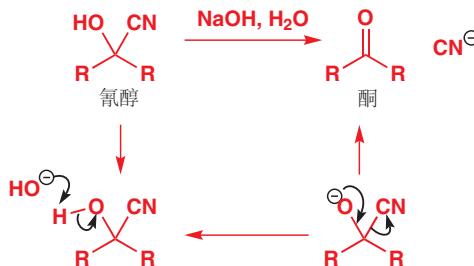
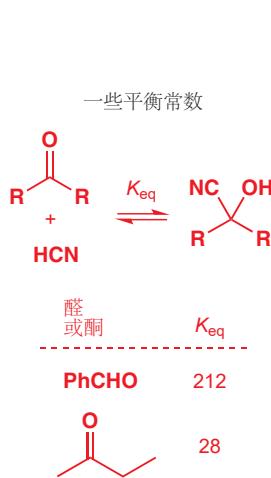
氰醇是重要的合成中间体。例如，通过环状氨基酮的亲核加成反应生成的氰醇，是一些药物在合成上的第一个中间态（如  $5HT_3$  受体拮抗剂）。这些药物大多用来减轻化疗带给患者的恶心。



氰醇也是许多天然和工业产品的组成部分，如杀虫剂氯氰菊酯（商品名“Ripcord”和“Barricade”）。



氰醇的生成是可逆的：只要把氰醇溶解在水中就能水解出作为原料的醛或酮，水体系中的碱通常能将氰醇完全水解。这是因为氰根是一个很好的离去基团——我们将在 Chapter 10 中更详细地讨论这类反应。



氰醇的生成与水解反应中，反应物与产物之间存在一个平衡，只有当这个平衡有利于产物生成时，我们才能得到好的产率。总体来说，醛比酮更容易发生反应，即平衡常数更大，原因在于连接在羰基碳原子上的另两个取代基的大小。随着羰基碳原子从  $sp^2$  变化到  $sp^3$ ，其键角从  $120^\circ$

左右变化到  $109^\circ$  左右——也就是说，产物中两个取代基靠得更近。键角的降低对醛来说不是问题，因为取代基中有一个（非常小的）氢原子，但对酮来说，尤其是所连的两个烷基较大的酮，这种影响就十分显著了。由取代基的大小和排斥所产生的效应称为空间位阻效应（简称空阻效应，steric effects），大取代基之间所产生的排斥力称为空间位阻（steric hindrance）。空间位阻（并不是“阻碍”）是烷基取代基上，占据充满轨道的电子之间排斥的结果。

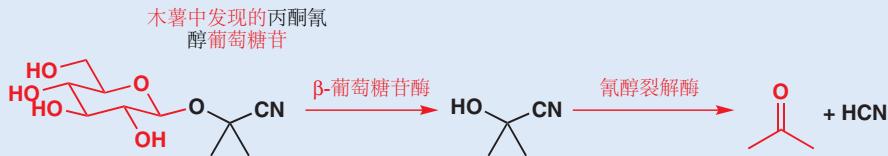
### 空间位阻

取代基的大小在很多有机反应中都起着重要影响——醛（有一个 H 与 C=O 相连）比酮更容易被加成的原因就是一个例子。空间位阻不仅影响反应速率，同时也可能使分子以一种完全不同的机理发生反应，正如您将在 Chapter 15 中会看到的一个发生取代反应的例子。您应当逐渐开始习惯考虑一个反应中是否有大取代基的存在，以及考虑它们所有的 C-H 和 C-C 键，是否对反应方向有所影响。

### 氰醇与木薯

氰醇形成的可逆不仅仅是理论上的。非洲部分地区以木薯作为主食，这种食物含有大量的亚麻仁苦苷（又称丙酮氰醇葡萄糖苷，葡萄糖苷是一种从葡萄糖中获得的缩醛）。我们将在本章后面讨论葡萄糖的结构，但现在，有一个事实是您需要知道的，它能够稳定分子中的氰醇结构。

这种葡萄糖苷本身没有毒性，但人体肠道中的酶会使其分解并释放 HCN。最终，每 100 克的木薯可以释放 50 毫克 HCN，一顿以未经处理的木薯为主食的饭足以杀死一个人。当地人通常将木薯碾碎并用水浸泡，在这个过程中木薯中的酶也会起到使亚麻仁苦苷分解的作用；于是在木薯煮熟并被食用之前，HCN 就会被冲洗掉。



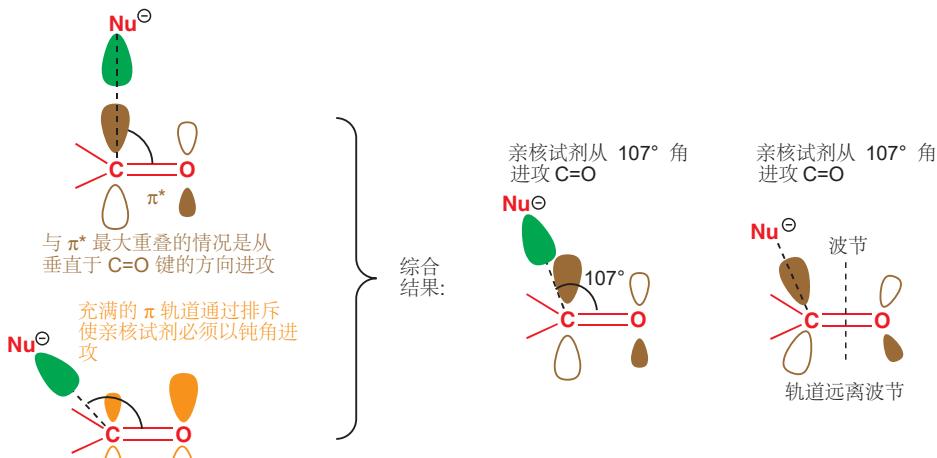
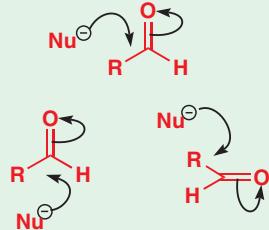
木薯现在可以安全食用，但仍然含有一些葡萄糖苷。在尼日利亚东部发现的一些疾病正是由于长期摄入 HCN 导致的。类似的葡萄糖苷也存在于苹果核、桃核、杏仁等水果的果核中。有些人喜欢吃这些食物，但一次食用过多是不明智的！

## 亲核试剂的进攻角度

上文已经介绍了的羰基上亲核进攻的步骤和顺序（HOMO 和 LUMO 的相互作用、新  $\sigma$  键的形成、 $\pi$  键的断裂），现在我们要更多地向您介绍亲核试剂进攻羰基的方向。亲核试剂不仅总是攻击羰基上的碳，而且它们总是从一个特定的角度靠近。一开始您可能会对这个角度感到惊讶，因为亲核试剂不是从垂直于羰基平面的方向进攻，而是从 C=O 键的  $107^\circ$  处进攻——也就是新键形成的角度。这种对进攻角度的要求被称为 Bürgi-Dunitz 轨道角，以通过美妙的晶体学方法揭示这一特点的两位科学家命名。您可以把进攻角度理解为使得 HOMO 在与空轨道  $\pi^*$  达到最大重叠时，与充满轨道  $\pi$  达到最小排斥的均衡结果。不过，更好的理解是由于波节的存在（Chapter 4），碳原子上的  $\pi^*$  轨道无法与相邻轨道保持平行，因此原子轨道本身已经成了一定的角度。而亲核试剂只是沿着 HOMO 中的大轨道方向进攻而已。

→ 我们曾在 Chapter 4 的 p. 104 中指明过。

纵使我们现在精确地知道了亲核试剂进攻 C=O 的方向，但我们在使用弯曲箭头表述时却不需要十分严格。Bürgi–Dunitz 轨道角的规则只需要记在您的头脑中，而绘制机理的时候则可以随心所欲。



分子中任何由于空阻对 Bürgi–Dunitz 轨迹角产生的阻碍都会大大地降低加成的速率，这也是醛比酮在亲核加成反应中更加活泼的另一原因。Bürgi–Dunitz 轨道角的重要性在今后会更加突出，尤其是在 Chapter 33.

Bürgi 与 Dunitz 通过研究一个既包含亲核氮原子又包含亲电羰基的化合物的晶体结构时，得出了轨道角的结论。他们发现，当这二者靠近得足够近，但无法达到可以发生反应的地步时，氮原子总是处在或接近  $107^\circ$  角。随后的理论计算给出了与之相同的最佳进攻角数值， $107^\circ$ .

## “氢负”在醛和酮上的亲核进攻

氢负离子 (hydride ion),  $\text{H}^-$ , 的亲核进攻，是一个几乎未知的反应。这种在氯化钠， $\text{NaH}$ ，其盐中存在的物种，有非常高的电荷密度，只能以碱的形式反应。原因在于，它充满的  $1s$  轨道，有与  $-\text{H}-\text{X}$  键 ( $\text{X}$  可以是任何原子) 的  $\sigma$  轨道中氢原子的贡献——理想的大小，并能与之相互作用；但相比于  $\text{C=O}$  基的 LUMO ( $\pi^*$ )  $2p$  轨道中碳较分散的轨道的贡献，就太小了，因而不能与之相互作用。



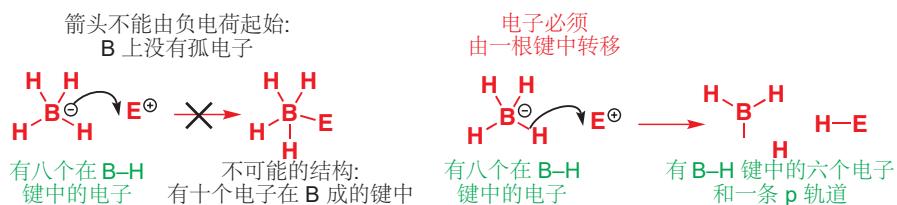
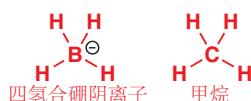
尽管如此，向  $\text{C=O}$  基碳添加  $\text{H}^-$  仍会是一个非常有用的反应，因为其结果会是醇的形成。这个过程会包含氧化程度由醛酮到醇的下降 (Chapter 2, p. 32) 并因而是一个还原反应。它不能通过  $\text{NaH}$  完成，但却可以通过与其他含有亲核氢原子的化合物完成。



这些化合物中最重要的是硼氢化钠 (四氢合硼酸钠, sodium borohydride),  $\text{NaBH}_4$ . 这是一个包含四面体型  $\text{BH}_4^-$  阴离子的水溶性盐，这种阴离子是甲烷的等电子体，但由于硼原子核比碳原子核

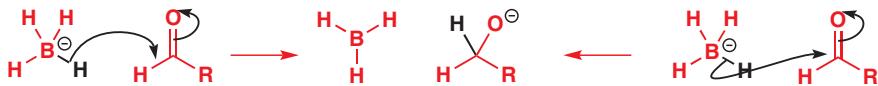
少一个质子，因而带一个负电荷。在 Chapter 4 中，我们考察了硼烷  $\text{BH}_3$  和甲基阳离子  $\text{CH}_3^+$  这一对等电子体。此时我们则是在二者上同时加入一个氢负离子。

当心！四氢合硼离子中，硼上没有孤对电子 (p. 115)：您的箭头不能出发于硼上的负电荷，以形成新键。如果您这样做了，那么就会得到一个五价的  $\text{B}(\text{V})$  化合物，外壳层中含有十个电子。这样的事是不可能的，因为第二周期元素仅含有四个可用的轨道 ( $1 \times 2s$  和  $3 \times 2p$ , 最多填入八个电子)。相反，由于所有的电子（包括负电荷所表示的）都位于  $\text{B}-\text{H}$   $\sigma$  轨道中，我们必须将箭头从其中一根  $\text{B}-\text{H}$  键出发，来表明  $\text{BH}_4^-$  在反应中做亲核试剂。通过这对电子的迁移，我们使硼原子变为电中性——带有六个电子的三价硼。



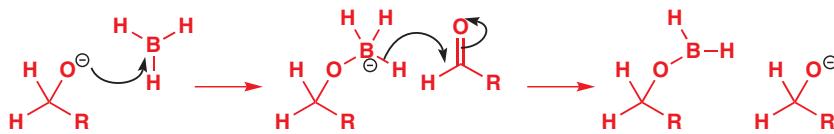
正如我们用  $\text{Nu}^-$  表示任何（未确定）的亲核试剂一样，此处的  $\text{E}^+$  意为任何（未确定）的亲电试剂。

当我们用一个羰基化合物作为这个反应的亲电试剂时，会有什么变化？带着  $\text{B}-\text{H}$  键中一对电子的氢原子，会被转移到  $\text{C}=\text{O}$  基的碳原子上。虽然反应不涉及真正的氢负离子， $\text{H}^-$ ，但带着一对电子的氢原子的转移可被视作“氢负迁移/氢负转移 (hydride transfer)” . 您会在本书中经常看到这样的描述。但要注意，不要将  $\text{BH}_4^-$  与氢负离子本身混淆。为了更加清晰地表达，是氢原子与 C 称新键，可以在绘制箭头时，令箭头穿过氢原子。

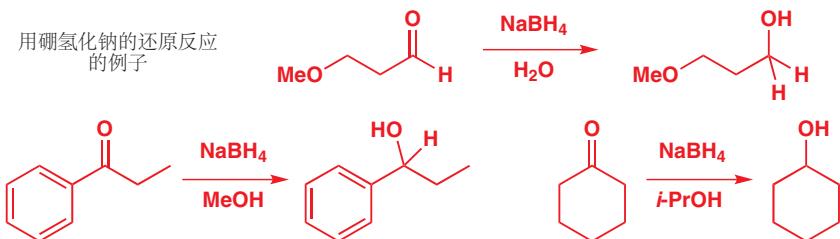


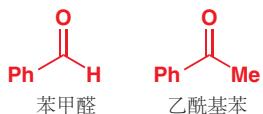
Interactive mechanism for borohydride reduction

后面的过程是您在 Chapter 5 中就学过的，但我们还有一些要说的。第一步形成的氧阴离子可以通过加成到其空  $p$  轨道以帮助稳定缺电子  $\text{BH}_3$  分子。现在我们再次得到了四价硼阴离子，继而可以将第二个氢原子（一并一对电子）转移到另一分子的醛上。



这个过程可以继续，因此，原则上四个氢原子都会被转移到醛分子中。在实践中，它则很少那么有效，但用水或醇溶液中的硼氢化钠，通常可将醛和酮以好的产率还原为对应的醇。水或醇溶液提供了由烷氧基形成醇所需的质子。



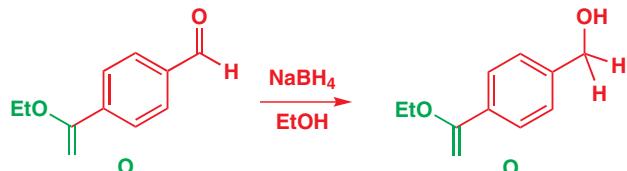


铝的电正性(金属性)比硼强，因而无论对于羰基还是水，都更愿意放弃氢原子(与和氢原子关联的负电荷)。氯化铝锂剧烈而危险地与水发生放热反应，并产生高度易燃的氢气。

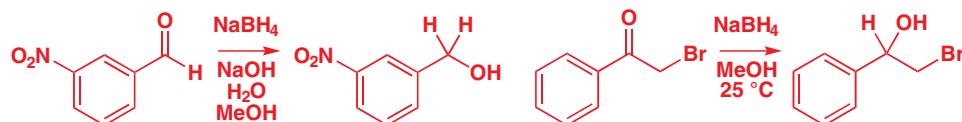


硼氢化钠是较弱的氢负供体中的一种。它可以在水中使用的事实在证明了这一点：更强的氢负供体，例如氯化铝锂(lithium aluminium hydride),  $\text{LiAlH}_4$ , 会剧烈地与水反应。硼氢化钠与醛和酮都可以反应，但与酮反应则较慢：例如，异丙烷中，苯甲醛的还原比乙酰基苯的还原快400倍。这是由于空阻所致(见左侧)。

硼氢化钠并不会与活性较弱的羰基化合物，例如酯或酰胺反应：如果一个分子同时包含醛基和酯基，那么仅醛基会被还原。



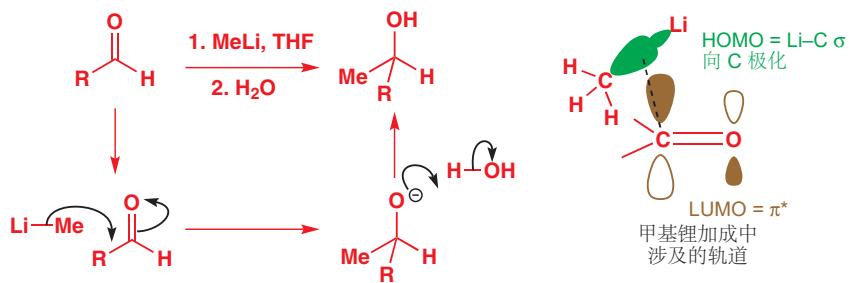
接下来的两个例子说明了醛和酮在其他活性官能团存在下的还原反应。第一个例子中，硝基不发生反应；第二个中，卤代烷不发生反应。



## 有机金属试剂对醛和酮的加成

有机金属化合物(Organometallic compounds)含有碳-金属键。锂和镁都是非常正电性的金属，并且有机锂和有机镁试剂中的 $\text{Li}-\text{C}$ 或 $\text{Mg}-\text{C}$ 键也高度像碳极化。因而它们是很强的亲核试剂，可进攻羰基已给出醇，同时形成新的 $\text{C}-\text{C}$ 键。作为第一个例子，我们将选择最简单的有机锂，在市面上可以其 $\text{Et}_2\text{O}$ 溶液出售的甲基锂与醛的反应。加成步骤的轨道图示显示了 $\text{C}-\text{Li}$ 键有多么极化，这意味着亲核试剂是其中的碳原子，它进攻亲电试剂的碳原子使我们得到一根新 $\text{C}-\text{C}$ 键。我们在 p. 113 中阐释了碳和其他负电性元素间键的极化。 $\text{C} 2.5$ ,  $\text{Li} 1.0$ ,  $\text{Mg} 1.2$ , 两种金属都比碳的电负性大得多。 $\text{MeLi}$ 的轨道已在 Chapter 4 中讨论。

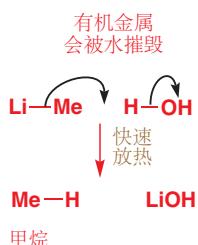
Interactive mechanism for methylolithium addition



反应的过程，与一般的对羰基的亲核加成一样，但我们需要作中强调反应图示中出现的一些差异。首先，反应条件未“1.  $\text{MeLi}$ , THF; 2.  $\text{H}_2\text{O}$ ”。这意味着，首先，在 THF 溶剂中，向醛中加入  $\text{MeLi}$ 。反应发生： $\text{MeLi}$  加成到醛上，得到一个烷氧基阴离子。然后，才能加入水，使烷氧基阴离子质子化。“2.  $\text{H}_2\text{O}$ ”的意思是，仅当  $\text{MeLi}$  已经反应完，才能加入水：与氰离子的反应，一些硼氢化物加成的反应不同，水在反应的开始并不存在。事实上，在  $\text{MeLi}$ (或其他有机金属试剂)对羰基的加成反应中，必须不能有水的存在，因为水会非常快速地通过将有机金属试剂质子化为烷烃(有

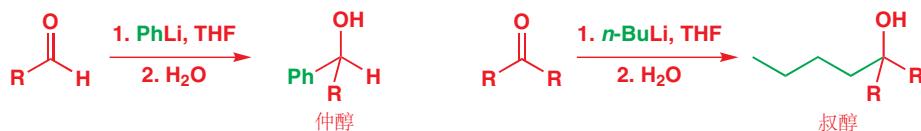
机锂、有机镁既是强亲核试剂，又是强碱) 来摧毁它们。反应结束后，水，或稀酸，或氯化铵的加入，被称为后处理 (work-up)。

由于有机锂太过活泼，经常需要在低温，通常是  $-78^{\circ}\text{C}$  (固态  $\text{CO}_2$  / 干冰的升华温度) 下，在非质子溶剂 (aprotic solvents) 例如  $\text{Et}_2\text{O}$  或 THF 中使用。水、醇等质子溶剂都含有酸性质子，而非质子溶剂，如醚则没有。有机锂也会与氧气反应，因此它们的处理需要在干燥、惰性气氛的氮气或氩气中进行。其他常用，并可购买的有机锂试剂还包括正丁基锂，它们也都可以与醛和酮反应。注意，对醛的加成给出仲醇；而对酮的加成给出叔醇。



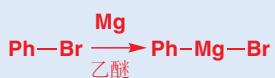
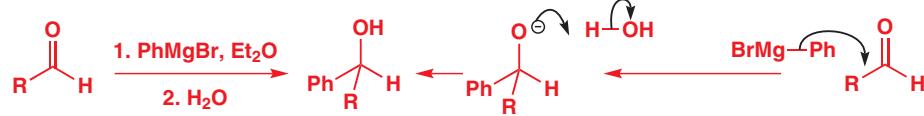
### 低温浴 (Low-temperature baths)

冷却反应混合物的工作，即低温浴通常分为两种：在  $0^{\circ}\text{C}$  左右的冰水浴，和在有机溶剂，例如不同、乙醇中的固体  $\text{CO}_2$  / 干冰浴，在大约  $-78^{\circ}\text{C}$ 。向溶剂中缓慢地加入小块的固态  $\text{CO}_2$ ，直到剧烈的冒泡停下来。少有化学家会去测量浴槽温度，它可能在  $-50$  到  $-80^{\circ}\text{C}$  间的任何值。出版物中给出的温度通常是  $-78^{\circ}\text{C}$ ，这是干冰浴的下限温度。更低的温度需要液氮实现。实践手册会给出详细说明。



被称为格氏试剂 (格林尼雅试剂，Grignard reagents) 的有机镁试剂 ( $\text{RMgX}$ )，也以相似的方式反应。一些简单的格氏试剂，例如氯化甲基镁， $\text{MeMgCl}$ ，和溴化苯基镁， $\text{PhMgBr}$ ，在市面上都是可购买的。下图展示了  $\text{PhMgBr}$  与醛的反应。这两类有机金属试剂——有机锂和格氏试剂——与羰基化合物的反应，都是构建 碳–碳 键最重要的反应之一，我们将在 Chapter 9 中更详细地考察它们。

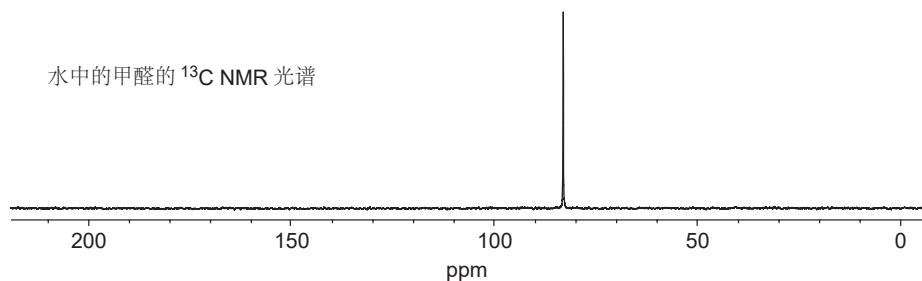
格氏试剂由 Victor Grignard (1871–1935) 在里昂大学发现，因为这个发现，它获得了 1912 年的诺贝尔奖。它们通过卤代烃与镁“旋转的”反应制取。



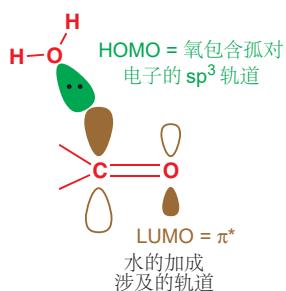
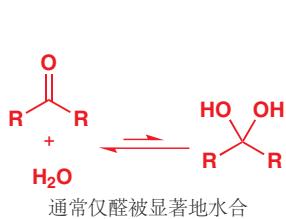
Interactive mechanism for Grignard addition

### 水对醛和酮的加成

与醛和酮反应的亲核试剂不必是高度极化，或带有负电荷的：中性亲核试剂也是很好的。我们如何知道？下面的将甲醛， $\text{H}_2\text{C}=\text{O}$ ，溶解在水中所获得的  $^{13}\text{C}$  NMR 光谱。您在 Chapter 3 中了解，羰基碳原子的  $^{13}\text{C}$  信号通常在 150–200 ppm 的区域内。那么甲醛羰基的峰值在哪里呢？相反，我们在 83 ppm 处得到了一个信号——我们会认为它是与氧成单键的四面体型碳原子显现出的。



所发生的，正是水加成到羰基上，得到了一个被称为水合物 (hydrate) 或 1,1-二醇的化合物。

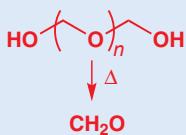


#### Interactive mechanism for hydrate formation

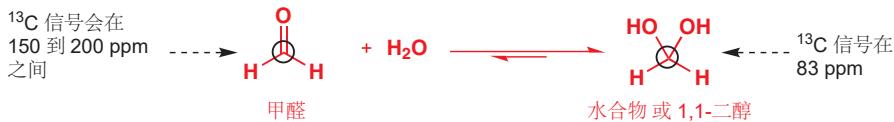
#### 单体甲醛

甲醛会被水合的属性为它的化学提出了一个问题，即它像我们刚刚谈论过的有机金属一样，要求无水环境。幸运的是，在无水溶液中断裂聚合物“多聚甲醛 (paraformaldehyde)”(加热以使之分解) 可提供甲醛单体。

聚合的“多聚甲醛”

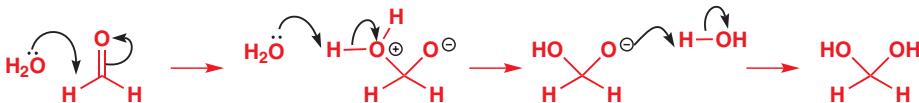


水合氯醛是阿加莎·克里斯蒂小说中臭名昭著的“knockout drops”，也是法外黑帮所用的“Mickey Finn”。(昏睡剂)



这个反应，与本章开始讨论的氰离子的加成反应一样，是以个平衡，并且对于醛和酮相当普遍。但就像氰醇一样，平衡的位置取决于羰基化合物的结构。通常，与之相同的空间因素 (p. 129) 意味着简单醛会在一定程度上水合，而简单酮则不会。然而，还有特殊的因素将平衡转向被水合的方向，即使是酮都是如此，尤其是当羰基化合物活泼而不稳定时。

甲醛是一个尤其活泼的醛，没有取代基阻碍进攻——它非常活泼，以至于相当容易聚合 (polymerization)。它非常乐意由  $sp^2$  转为  $sp^3$  杂化时，因为伴随进行的键角由  $120^\circ$  到  $109^\circ$  (p. 129) 对两个氢原子的空阻增加的非常少。这就是为什么甲醛的水溶液中基本上不含  $CH_2O$ ——它被彻底水合。水合反应的机理如下所示。注意观察，一个质子需要由一个氧原子转移到另一个氧原子上，这一过程被水分子促成。

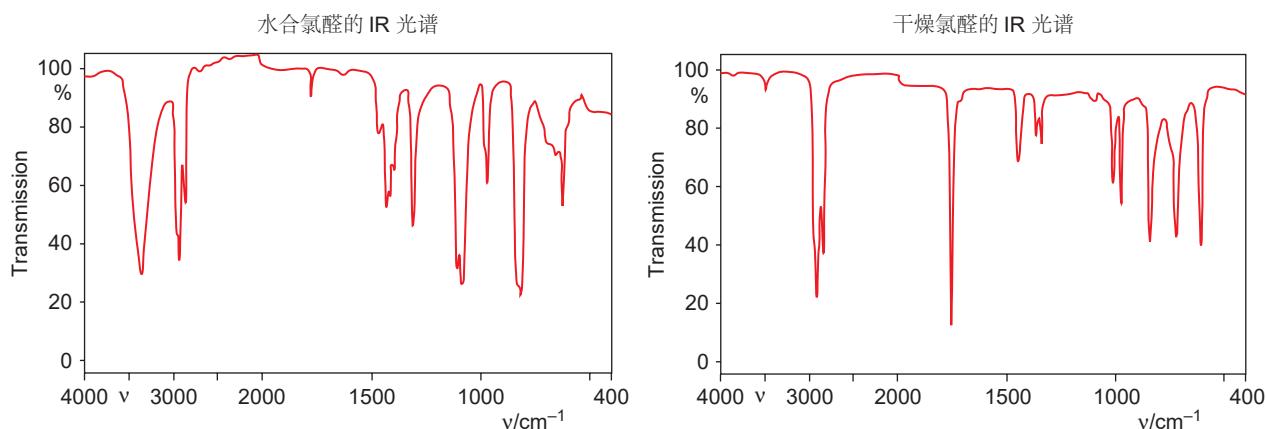


甲醛很容易与水反应，是因为它的取代基非常小：空间因素也非常小。电子效应同样可以使与亲核试剂的反应有利——在羰基旁边的碳上附着负电性原子，例如卤素，可与根据卤素取代基的数量和吸电子能力所导致的诱导效应强弱，相应地增加水合的程度。它们使羰基更加极化，并使羰基碳原子更加正电性，进而易于遭受水的进攻。三氯甲醛 (俗称氯醛，chloral,  $Cl_3CHO$ ) 在水中被彻底水合，产物“水合氯醛 (chloral hydrate)”可被分离为晶体，并用于麻醉。从下一页的两幅 IR 光谱中，您可以清晰地看出这一点。第一幅是仍在瓶中的水合氯醛的光谱——注意，在  $1700$  和  $1800\text{ cm}^{-1}$  之间 (我们认为  $C=O$  会出现的位置) 没有强吸收，相反，在  $3400\text{ cm}^{-1}$  处的  $O-H$  宽峰可以说明问题。加热以除去水，第二幅是所得的干燥氯醛的 IR 光谱： $C=O$  峰重新在  $1770\text{ cm}^{-1}$  出现，并且  $O-H$  峰消失了。

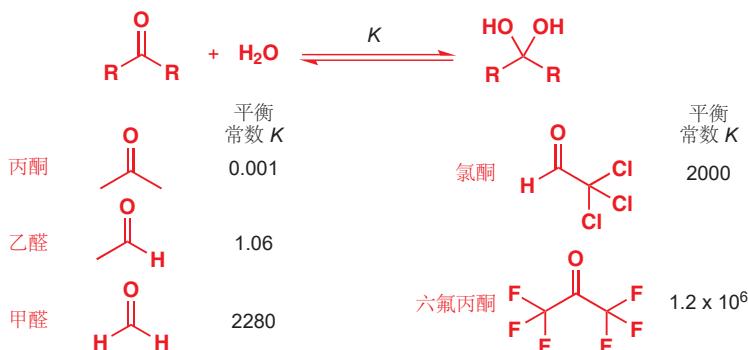
#### ● 空间效应和电子效应

- 空间效应关心分子内基团的大小和形状。
- 电子效应由分子内原子间电负性的差异所对电子分布造成的影响引起。它们可以分为诱导效应 (*inductive effects*)，电负性差异所导致的  $\sigma$  键的极化；和共轭效应 (*conjugation*, 有时被称为中介效应 *mesomorphic effects*)，影响的是  $\pi$  键中电子的分布，我们将在下一章讨论。

空间效应和电子效应是主宰亲核试剂与亲电试剂反应性的两个主要因素。

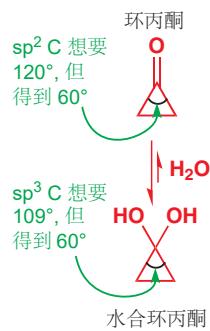


下面的图表显示了几种对羰基化合物的选择，所得的（在水中）的水合程度：六氟丙酮大概是最易水合的羰基化合物！平衡常数越大，平衡越偏向右侧。



Interactive structures of carbonyl compounds and hydrates

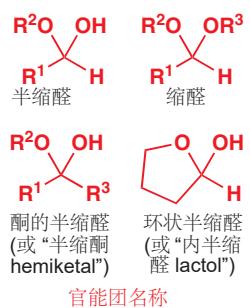
环丙酮——三元环酮——也同样会显著程度地水解，但这是不同的原因所致。您之前已经观察到，非环状酮由  $\text{sp}^2$  变为  $\text{sp}^3$  杂化时，键角也会由  $120^\circ$  变为  $109^\circ$ ，因而空阻增加。而环丙酮（和其他小环酮），则更加喜欢小键角，因为它们的取代基依然被限定在一个环中。以这样的方式看：三元环的张力已经非常大了，其键角被迫处于  $60^\circ$ ；对于  $\text{sp}^2$  杂化的酮来说，这意味着相较于正常的  $120^\circ$ ，键被弯曲了  $60^\circ$ ；而若变为  $\text{sp}^3$  杂化，扭曲则只有  $49^\circ (= 109^\circ - 60^\circ)$ 。因此对于  $\text{C=O}$  基的加成会释放一些小环中固有的张力——水合是有利的，并且环丙酮和环丁酮确实都是非常活泼的亲电试剂。



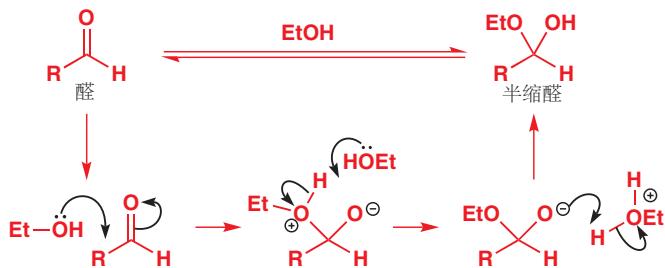
- 有利或无利于水合物形成的相同结构因素，在确定羰基对于其他亲核试剂，无论反应可逆与否的情况下都是重要的。越大的空阻和越多的烃基取代基，会令羰基化合物面对任何亲核试剂都是越不活泼的；吸电子基和小环则将使其更活泼。

## 醇与醛的反应得到半缩醛

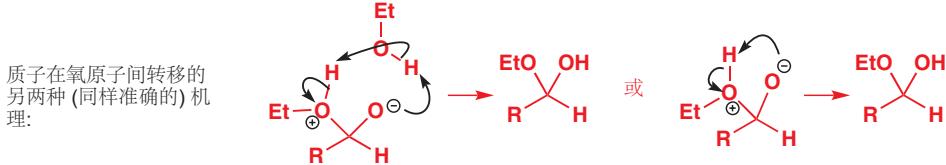
由于水可以加成到羰基化合物上（至少可以加成一点），醇同样可以就不会令人感到吃惊了。这个反应的产物被称为一个半缩醛（hemiacetal），由于它完成了缩醛（acetal）形成的一半，缩醛是您在



Interactive mechanism for hemiacetal formation



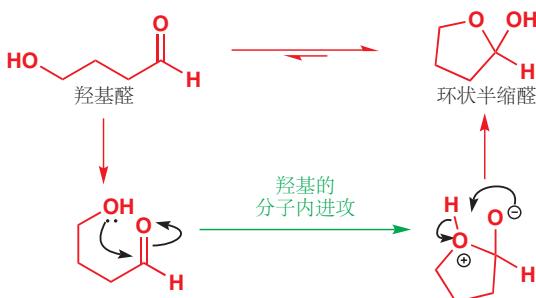
如上所示的机理中，也有一个质子，需要像 p. 134 的水合物形成机理中一样，由一个氧原子转移至另一个上。我们所展示的是一分子乙醇（或水）来完成这一工作，但其实我们无法准确地确定，质子在氧原子间迁移时究竟走什么样的路经。也许两个氧上出现的不是同一个质子：左下方所示的便是另一种可能的机理，乙醇分子同时送出一个质子，并得到另一个。最简单的写法则如右下所示，质子直接由一个氧原子跳到另一个上；这样表示机理并没有什么可耻的：它既不比其他机理准确，也不比它们更不准确。



可以肯定的是，质子在氧原子间的迁移是非常快并且可逆的，对于其原因来说，我们并不需要纠结细节——质子往往可以为机理的下一步的进行，前去任何需要它的位置。对于所有这些羰基化合物，真正重要的是加成的步骤，而不是质子的移动。

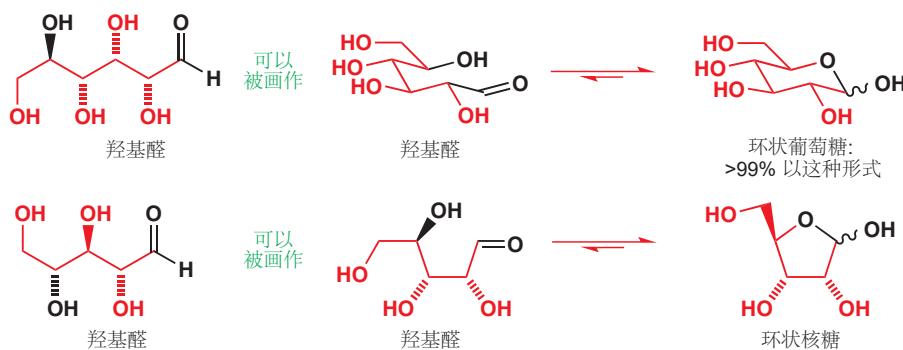
半缩醛的形成是可逆的，并且，半缩醛被与稳定水合物的相同的特定结构特征所稳定。然而，半缩醛还可以通过处于环中，而得到稳定型——当羰基进攻的羟基在同一分子中时，反应便是分子内的 (intramolecular) 加成，与我们之前在考察的分子间的 (intermolecular) 加成相对。

分子间反应在两个分子间发生。分子内反应在同一分子内部发生。我们将在 Chapters 11 和 12 中讨论为什么分子内反应有利，以及为什么环状半缩醛、环状缩醛更稳定。



虽然环状半缩醛（也被称作内半缩醛 lactol）产物更加稳定，它仍然与一些开链形态处在平衡中。

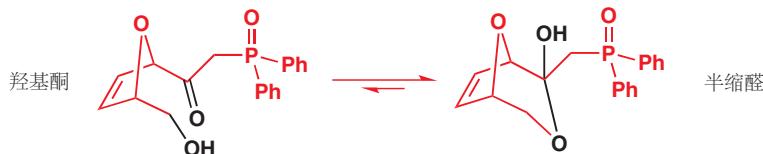
它的稳定性，和它形成时的容易性，取决于环的大小：五元和六元环不受环张力的束缚（它们的键可以自由地采取  $109^\circ$  或  $120^\circ$  角——对比 p. 135 中的三元环），五六元的内半缩醛是常见的。许多糖就是最重要的例子。例如葡萄糖（glucose），就是一个主要以六元环半缩醛的形式存在的羟基醛（>99% 的葡萄糖在溶液中成环存在），核糖（ribose）则以五元环半缩醛存在。



■ 我们绘制这些分子中的某些方式可能让您感到不熟悉，我们在 Chapter 2 中首次提过：我们需要展示立体化学 stereochemistry (键沿纸面向上，还是向下——用波浪线表示二者的混合)，对于环状葡萄糖，还需要展示构象 conformation (分子真正采取的形状)。它们对于糖是非常重要的：我们将在 Chapter 14 中学习立体化学，Chapter 16 中学习构象。

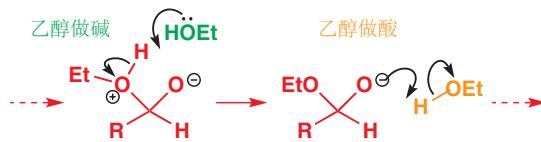
## 酮也可形成半缩醛

羟基酮也可形成半缩醛，但如您所料，它们通常不如羟基醛容易。但下面的羟基酮必须以环状半缩醛形式存在，因为没有 C=O 伸缩出现在它的 IR 光谱中，原因是什么？这个羟基酮已经是环状的了，其中 OH 基已经在准备进攻酮的位置上了——它不能离开，因而环化是高度有利的。



## 酸和碱催化半缩醛和水合物的形成

在 Chapter 8 中，我们将会详细地考察酸和碱，但在此处，我们需要介绍给您它们在化学上扮演的一个重要角色：它们可以作为很多羰基加成反应的催化剂，包括半缩醛和水合物的形成反应。为了观察为什么，我们需要重回 p. 138 的半缩醛形成机理，以及 p. 134 的水合物形成机理。它们都包含质子转移步骤，我们可以这样表述：

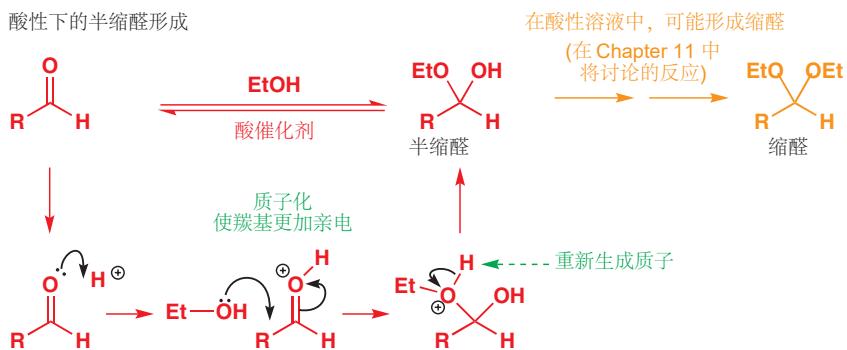


在第一个质子转移中，乙醇做碱，用于移去质子；而在第二个中，则作酸，来提供质子。您在 Chapter 5 观察过，水既可以做酸也可以做碱。强酸和强碱（例如 HCl 或 NaOH）可以加速半缩醛、水合物形成的原因，便是因为它们可以在羰基被加成前，分别先完成这两种质子转移步骤。

在酸中（比如说稀 HCl），机理在细节上有一些区别。第一步是羰基孤对电子的质子化，随之带上的正电荷使之更加亲电，因此加成反应变快。注意，开始时加上的质子在反应结束后还会失去——

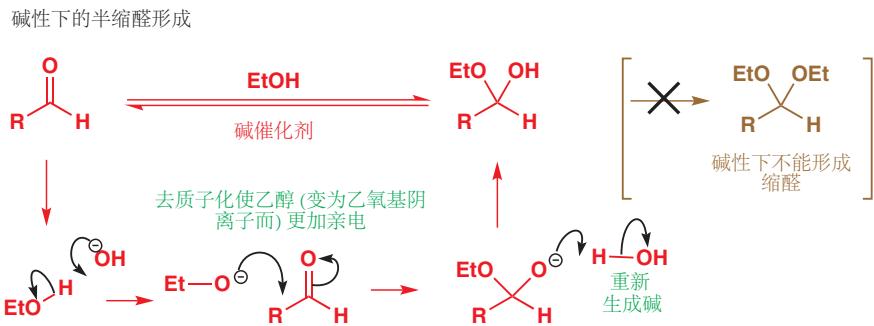
酸真的是催化剂。

■ 在酸性下，半缩醛还可能继续反应变为缩醛，但是这是 Chapter 11 中要处理的问题，您目前还不需要担心。



在碱性溶液中的机理又有些许不同。第一步是乙醇被氢氧根的去质子化，这个过程通过使乙醇更加亲核，而加速加成反应。再一次，碱(氢氧根)会在最后一步中重新生成，整个过程是碱催化的反应。

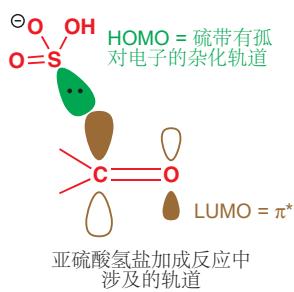
■ 如您会在 Chapter 11 中观察到，碱性下的反应往往在停止于半缩醛——缩醛绝不能在碱中形成。



最后一步也可以等价地表述为乙醇被烷氧基阴离子去质子——烷氧基阴离子也可以很好地作为反应的催化剂(做碱)。事实上，您会经常遇到，在机理中以“B<sup>-</sup>”表示碱，这意味着碱是什么并不重要。

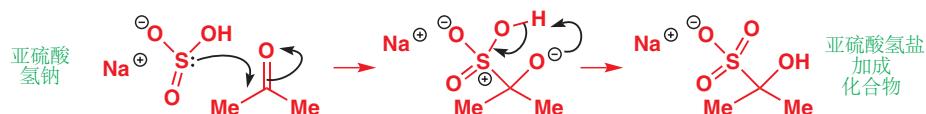
#### ● 对羰基的亲核加成反应：

- 酸催化剂通过使羰基更亲电而工作；
- 碱催化剂通过亲核试剂更亲核而工作；
- 两种催化剂都在反应结束时重新生成。



## 亚硫酸氢盐加成化合物

本章的最后一一种亲核试剂，亚硫酸氢钠 sodium bisulfite ( $\text{NaHSO}_3$ ) 对醛和一些酮的加成会给出通常被称为**亚硫酸氢盐加成化合物** (bisulfite addition compound) 的产物。反应通过硫的孤对电子对羰基的亲核进攻发生，与氰离子的相似。这会使硫原子带正电，但通过简单的质子转移则可得到产物。

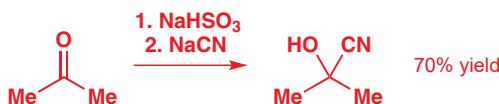


产物是实用的，有两点原因。第一，它们通常是晶体，因此可以通过重结晶来纯化液态的醛。

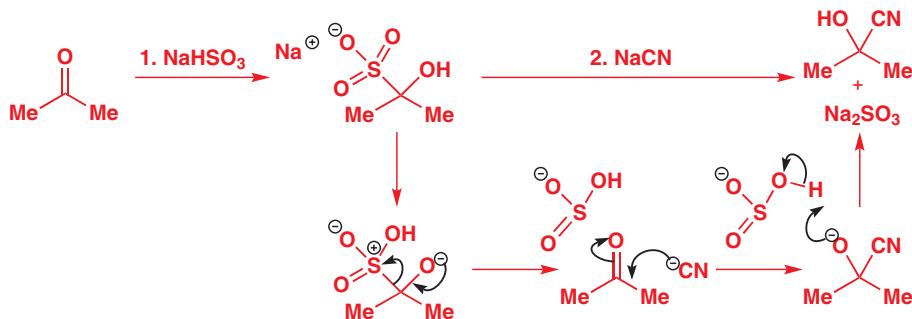
这种价值，建立在这个反应是可逆的上，如您在本章中遇到的许多反应一样。亚硫酸氢盐化合物可以通过将醛或酮与饱和亚硫酸氢钠水溶液在冰浴中混合，震荡，并重结晶而制得。亚硫酸氢盐加成化合物经过纯化后，可以通过在稀酸或碱的水溶液中水解，重新得到醛。



反应的可逆性，使亚硫酸氢盐化合物成为由醛或酮合成其他加合物时，有用的中间体。例如，制取氰醇的一种实践方法就涉及亚硫酸氢盐化合物。著名的实践书“Vogel”建议，先用丙酮与亚硫酸氢钠反应，然后再与氰化钠反应，可以以好的产率(70%)得到氰醇。



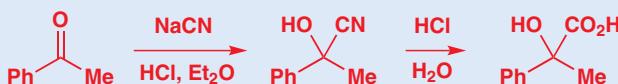
过程中发生了什么？首先形成亚硫酸氢盐化合物，但仅作为到氰醇途径中的中间体。当添加了氰根后，亚硫酸氢盐化合物的形成逆向进行，所得的亚硫酸氢根还可提供反应结束时回到羟基所需的一个质子。相比于用从酸中得到质子，这种方法不会释放危险的 HCN (氰离子和酸同时存在时往往都是危险的)。



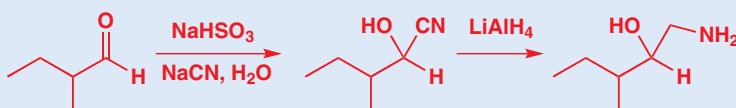
### 其他由氰醇制取的化合物

氰醇可以提供简单的反应，转化为羟基酸或氨基醇。下面是这两个过程的例子，但对于反应机理，您将要等到 Chapter 10 再学习。注意，第一个氰醇通过最简单的方法—— $\text{NaCN}$  和酸制得——而第二个则通过我们刚刚讨论的亚硫酸氢盐路线得到。

#### 通过氰醇中 CN 的水解得到羟基酸



#### 通过氰醇中 CN 的还原得到氨基醇

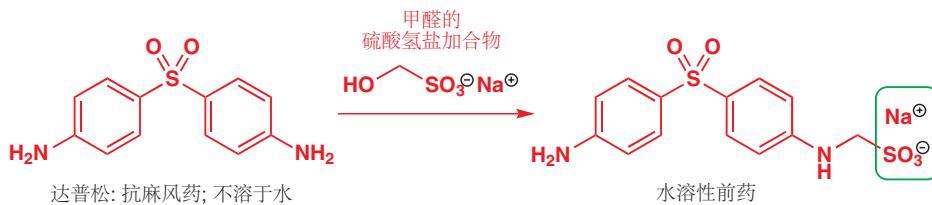


亚硫酸氢盐化合物有用的第二个原因在于，它们可溶于水。只有分子量低的醛和酮，例如丙酮是水溶的；超过四个左右碳原子的都是不溶的。这对于大多数化学家来说不成问题，因为我们通常在

■  $\text{NaHSO}_3$  亚硫酸氢钠的结构，相当有趣。它是一种硫(IV)化合物的氧阴离子，在其硫原子的 HOMO 上具有一个孤对电子，但形式电核却在更加负电性的氧上。作为第三周期元素(元素周期表的第三行)，硫可具有多于八个电子——S 或 P，不像 B 或 O 一样，它们可以成四、五，或六根键。第三周期元素除了 s 和 p 轨道，还有 d 轨道，可容纳更多电子。

有机溶剂中，而不是水中完成反应。但这却会困扰药物化学家，因为它们制取的化合物需要与生物体系共存。而在这个情形中，亚硫酸氢盐加合物的水溶性就委实至关重要了。

达普松/氨苯砜 (Dapsone) 是一种抗麻风药，特别是当与另外两种药物 (注：利福平和氯苯吩嗪) 在“cocktail”中联合使用时，非常有效，使用时无需任何特殊设备，可以直接以水溶液形式饮用。但有一个问题！达普松在水中不溶。解决方法是制取它的亚硫酸氢盐化合物。您可能会问，达普松没有醛基和酮基——只有两个氨基和一个砜基——该如何实现这一点呢。所用的诡计，是先制取甲醛的亚硫酸氢盐化合物，再用达普松中的氨基取代其中的 OH 基。



现在这个化合物便可溶于水了，并且可在患者体内释放达普松。这类化学的细节将在 Chapter 11 中展开，您会看到亚胺做中间体。在此阶段，我们只想让您明白，即使是在本章中这些相对简单的化学，在合成、商业，和医药上都是有用的。

## 延伸阅读

S. Warren, *Chemistry of the Carbonyl Group*, Wiley, Chichester, 1974 中的 Section 1, “Nucleophilic addition to the carbonyl group”，和 P. Sykes, *A Guidebook to Mechanism in Organic Chemistry*, 6th edn, Longman, Harlow, 1986, pp. 203–219. 想了解更多理论性内容，建议查阅 J. Keeler and P. Wothers, *Why Chemical Reactions Happen*, OUP, Oxford, 2003, especially pp. 102–106.

关于木薯–HCN 问题更深入、更先进、更细致的讨论: D. Siritunga, D. Arias-Garzon, W. White, and R. T. Sayre, *Plant Biotechnology Journal*, 2004, 2, 37. 用亚硫酸钠形成氰醇的细节: B. S. Furniss, A. J. Hannaford, P. W. G. Smith, and A. T. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, 5th edn, Longman, Harlow, 1989, pp. 729–730.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 离域与共振

## 联系

### 基础

- Orbitals and bonding ch4
- Representing mechanisms by curly arrows ch5
- Ascertaining molecular structure spectroscopically ch3

### 目标

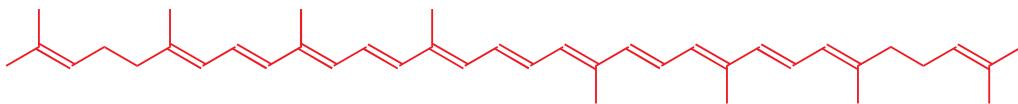
- Interaction between orbitals over many bonds
- Stabilization by the sharing of electrons over more than two atoms
- Where colour comes from
- Molecular shape and structure determine reactivity
- Representing one aspect of structure by curly arrows
- Structure of aromatic compounds

### 展望

- Acidity and basicity ch8
- How conjugation affects reactivity ch10, ch11, & ch15
- Conjugate addition and substitution ch22
- Chemistry of aromatic compounds ch21 & ch22
- Enols and enolates ch20, ch24–ch27
- Chemistry of heterocycles ch29 & ch30
- Chemistry of dienes and polyenes ch34 & ch35
- Chemistry of life ch42

## Introduction

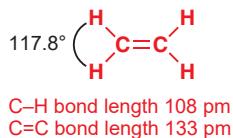
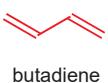
As you look around you, you will be aware of many different colours—from the greens and browns outside to the bright blues and reds of the clothes you are wearing. All these colours result from the interaction of light with the pigments in these different things—some frequencies of light are absorbed, others scattered. Inside our eyes, chemical reactions detect these different frequencies and convert them into electrical nerve impulses sent to the brain. All these pigments have one thing in common—lots of double bonds. For example, the pigment responsible for the red colour in tomatoes, lycopene, is a long-chain polyalkene.



lycopene, the red pigment in tomatoes, rose hips, and other berries

Lycopene contains only carbon and hydrogen; many pigments contain other elements. But nearly all contain double bonds—and many of them. This chapter is about the properties, including colour, of molecules that have several double bonds. These properties depend on the way the double bonds join up, or *conjugate*, and the resulting *delocalization* of the electrons within them.

In earlier chapters we talked about carbon skeletons made up of  $\sigma$  bonds. In this chapter we shall see how, in some cases, we can also have a large  $\pi$  framework spread over many atoms and how this dominates the chemistry of such compounds. We shall see how this  $\pi$  framework is responsible for the otherwise unexpected *stability* of certain cyclic polyunsaturated



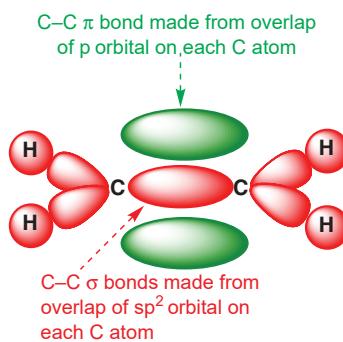
Interactive bonding orbitals in ethene

► We described the structure of ethene in Chapter 4 (p. 101)

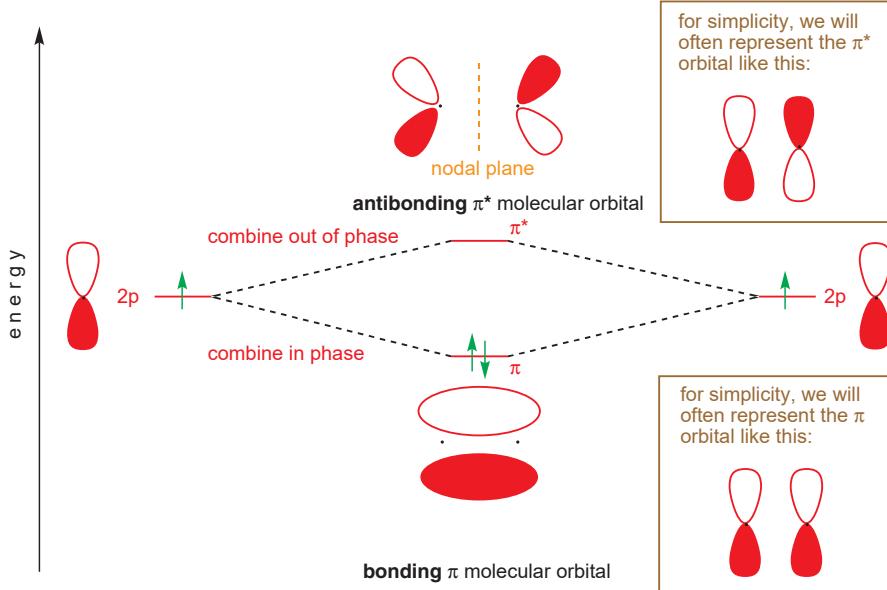
compounds, including benzene, but also *reactivity* in others, such as butadiene. We shall also see how this  $\pi$  framework gives rise to colour. To understand such molecules properly, we need to start with the simplest of all unsaturated compounds, ethene.

## The structure of ethene (ethylene, $\text{CH}_2=\text{CH}_2$ )

The structure of ethene (ethylene) is well known. It has been determined by electron diffraction and is **planar** (all atoms are in the same plane), with the bond lengths and angles shown on the left. The carbon atoms are roughly trigonal and the C=C bond distance is shorter than that of a typical C–C single bond. The electronic structure of ethene, you will recall from Chapter 4, can be considered in terms of two  $\text{sp}^2$  hybridized C atoms with a  $\sigma$  bond between them and four  $\sigma$  bonds linking them each to two H atoms. The  $\pi$  bond is formed by overlap of a p orbital on each carbon atom.



*Ethene* is chemically more interesting than *ethane* because of the  $\pi$  system. As you saw in Chapter 5, alkenes can be nucleophiles because the electrons in the  $\pi$  bond are available for donation to an electrophile. But remember that when we combine *two* atomic orbitals we get *two* molecular orbitals, from combining the p orbitals either in phase or out of phase. The in-phase combination accounts for the bonding molecular orbital ( $\pi$ ), whilst the out-of-phase combination accounts for the antibonding molecular orbital ( $\pi^*$ ). The shapes of the orbitals as they were introduced in Chapter 4 are shown below, but in this chapter we will also represent them in the form shown in the brown boxes—as the constituent p orbitals.



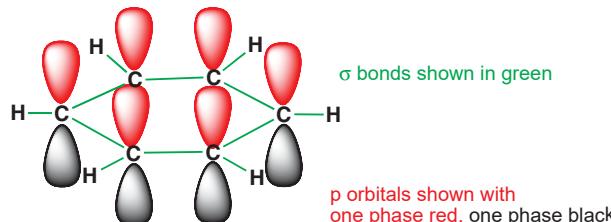
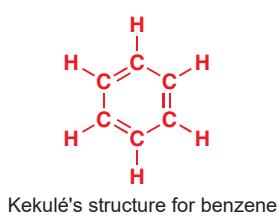
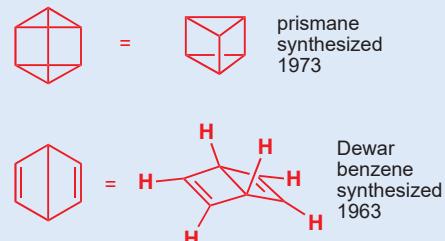
## Molecules with more than one C=C double bond

### Benzene has three strongly interacting double bonds

The rest of this chapter concerns molecules with more than one C=C double bond and what happens to the  $\pi$  orbitals when they interact. To start, we shall take a bit of a jump and look at the structure of benzene. Benzene has been the subject of considerable controversy since its discovery in 1825. It was soon worked out that the formula was  $C_6H_6$ , but how were these atoms arranged? Some strange structures were suggested until Kekulé proposed the correct structure in 1865.

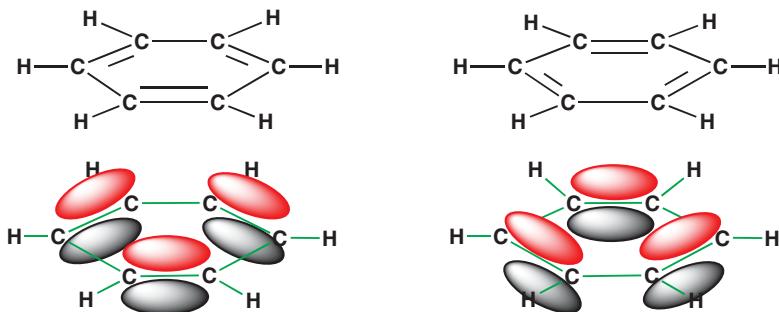
Shown below are the molecular orbitals for Kekulé's structure. As in simple alkenes, each of the carbon atoms is  $sp^2$  hybridized, leaving the remaining p orbital free.

The two early proposals for the structure of benzene were wrong, but nonetheless are stable isomers of benzene (they are both  $C_6H_6$ ) which have since been synthesized. For more on the Kekulé structure, see p. 24.



The  $\sigma$  framework of the benzene ring is like the framework of an alkene, and for simplicity we have just represented the  $\sigma$  bonds as green lines. The difficulty comes with the p orbitals—which pairs do we combine to form the  $\pi$  bonds? There seem to be two possibilities.

combining different pairs of p orbitals puts the double bonds in different positions

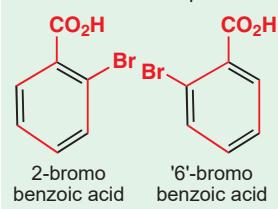


With benzene itself, these two forms are identical but, if we had a 1,2- or a 1,3-disubstituted benzene compound, these two forms would be different. A synthesis was designed for the two compounds in the box on the right but it was found that both compounds were identical. This posed a problem to Kekulé—his structure didn't seem to work after all. His solution—which we now know to be incorrect—was that benzene rapidly equilibrates, or 'resonates', between the two forms to give an averaged structure in between the two.

The molecular orbital answer to this problem is that all six p orbitals can combine to form (six) new molecular orbitals, and the electrons in these orbitals form a ring of electron density above and below the plane of the molecule. Benzene *does not resonate* between the two Kekulé structures—the electrons are in molecular orbitals spread equally over all the carbon atoms. However, the term 'resonance' is still sometimes used (but not in this book) to describe the averaging effect of this mixing of molecular orbitals. We shall describe the  $\pi$  electrons in benzene as **delocalized**, that is, no longer localized in specific double bonds between two particular carbon atoms but spread out, or delocalized, over all six atoms in the ring.

For example, if the double bonds were localized then these two compounds would be chemically different. (The double bonds are drawn shorter than the single bonds to emphasize the difference.)

in reality these are the same compound

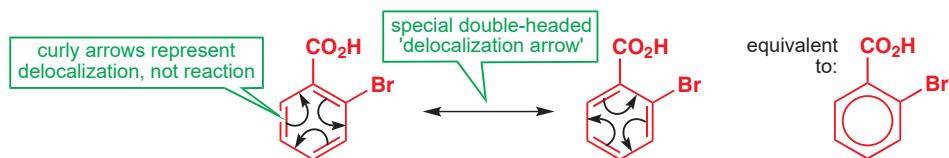




the circle represents the delocalized system

The alternative drawing on the left shows the  $\pi$  system as a ring and does not put in the double bonds: you may feel that this is a more accurate representation, but it does present a problem when it comes to writing mechanisms. As you saw in Chapter 5, the curly arrows we use represent two electrons. The circle here represents six electrons, so in order to write reasonable mechanisms we still need to draw benzene *as though* the double bonds were localized. However, when you do so, you must keep in mind that the electrons are delocalized, and it does not matter which of the two arrangements of double bonds you draw.

If we want to represent delocalization using these ‘localized’ structures, we can do so using curly arrows. Here, for example, are the two ‘localized’ structures corresponding to 2-bromo-carboxylic acid. The double bonds are not localized, and the relationship between the two structures can be represented with curly arrows which indicate how one set of bonds map onto the other.

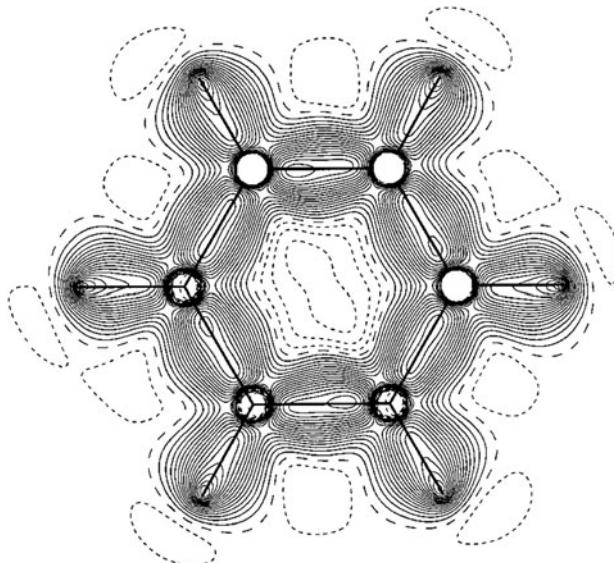


■ The delocalization arrow is used to connect two representations of the same structure. Don’t get it confused with an equilibrium arrow, which is used to show two structures interconverting. In an equilibrium, at least one  $\sigma$  bond must change place.

delocalization arrow  
  
 equilibrium arrow

These curly arrows are similar to the ones we introduced in Chapter 5, but there is a crucial difference: here, there is no reaction taking place. In a real reaction, electrons move. Here, they do not: the only things that ‘move’ are the double bonds in the structures. The curly arrows just show the link between alternative representations of exactly the same molecule. You must not think of them as showing ‘movement round the ring’. To emphasize this difference we also use a different type of arrow connecting them—a delocalization arrow made up of a single line with an arrow at each end. Delocalization arrows remind us that our simple fixed-bond structures do not tell the whole truth and that the real structure is a mixture of both.

The fact that *the  $\pi$  electrons are not localized in alternating double bonds but are spread out over the whole system* in a ring is supported by theoretical calculations and confirmed by experimental observations. Electron diffraction studies show benzene to be a regular planar hexagon with all the carbon–carbon bond lengths identical (139.5 pm). This bond length is in between that of a carbon–carbon single bond (154.1 pm) and a full carbon–carbon double bond (133.7 pm). A further strong piece of evidence for this ring of electrons is revealed by proton NMR and discussed in Chapter 13.



Electron diffraction image of a molecule of benzene

### How to describe delocalization?

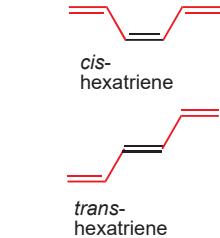
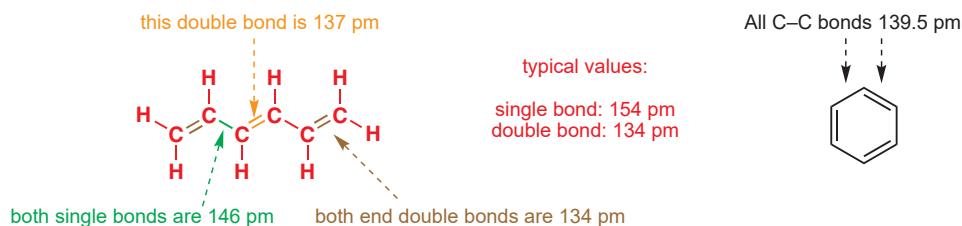
What words should be used to describe delocalization is a vexed question. Terms such as *resonance*, *mesomerism*, *conjugation*, and *delocalization* are only a few of the ones you will find in books. You will already have noticed that we're avoiding *resonance* because it carries a suggestion that the structure is somehow oscillating between localized structures. We shall use the words *conjugation* and *delocalization*: conjugation focuses on the way that double bonds link together into a single  $\pi$  system, while delocalization focuses on the electrons themselves. Adjacent double bonds, as you will see, are *conjugated*; the electrons in them are *delocalized*.

### Multiple double bonds not in a ring

Are electrons still delocalized even when there is no ring? To consider this, we'll look at hexatriene—three double bonds and six carbons, like benzene, but without the ring. There are two isomers of hexatriene, with different chemical and physical properties, because the central double bond can adopt a *cis* or a *trans* geometry. The structures of both *cis*- and *trans*-hexatriene have been determined by electron diffraction and two important features emerge:

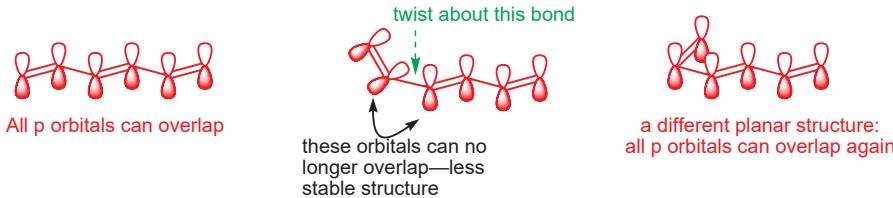
- Both structures are essentially planar.
- Unlike benzene, the double and single bonds have different lengths, but the central double bond in each case is slightly longer than the end double bonds and the single bonds are slightly shorter than a 'standard' single bond.

Here's the most stable structure of *trans*-hexatriene, with benzene shown for comparison.

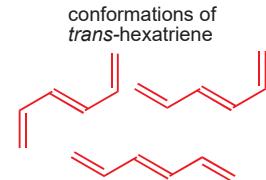


The terminal double bonds can't have two forms because they have only one substituent.

The reason for the deviation of the bond lengths from typical values and the preference for planar structures is again due to the molecular orbitals which arise from the combination of the six p orbitals. Just as in benzene, these orbitals can combine to give one molecular orbital stretching over the whole molecule. The p orbitals can overlap and combine only if the molecule is planar.



If the molecule is twisted about one of the single bonds, then some overlap is lost, making it harder to twist about the single bonds in this structure than in a simple alkene. Other planar arrangements are stable, however, and *trans*-hexatriene can adopt any of the planar conformations shown in the margin.



Conformation is the topic of Chapter 16.

### Conjugation

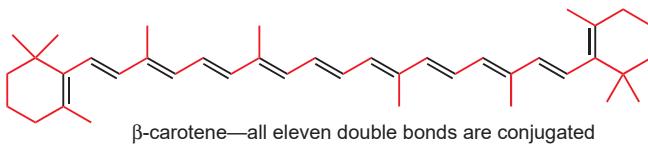
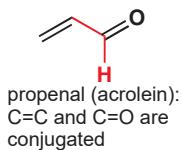
In benzene and hexatriene every carbon atom is  $sp^2$  hybridized with one p orbital available to overlap with its neighbours. The uninterrupted chain of p orbitals is a consequence of having alternate double and single bonds. When two double bonds are separated by just one single bond, the two double bonds are said to be *conjugated*. Conjugated double bonds have different properties from isolated double bonds, both physically (they are often longer, as you have just seen) and chemically (see Chapters 22).

You have already met several conjugated systems: lycopene at the start of this chapter and  $\beta$ -carotene in Chapter 3, for example. Each of the 11 double bonds in  $\beta$ -carotene is separated

### Conjugation

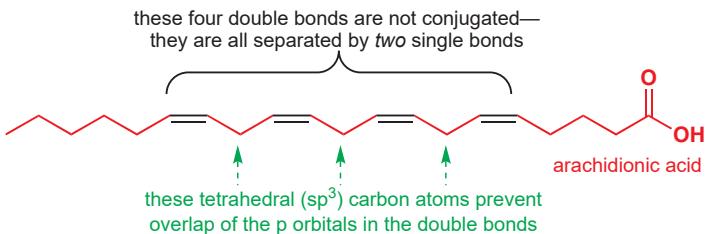
In the dictionary 'conjugated' is defined, among other ways, as 'joined together, especially in pairs' and 'acting or operating as if joined'. This does indeed fit very well with the behaviour of such conjugated double bonds, since the properties of a conjugated system are different from those of the component parts.

from its neighbour by only one single bond. We again have a long chain in which all the p orbitals can overlap to form molecular orbitals.

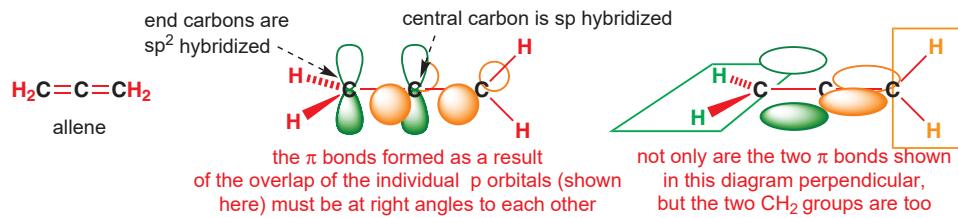


The chemistry of such conjugated carbonyl compounds is significantly different from the chemistry of the component parts. The alkene in propenal, for example, is electrophilic and not nucleophilic. This will be explained in Chapter 22.

It is not necessary to have two C=O double bonds in order to have a conjugated system—the C=C and C=O double bonds of propenal (acrolein) are also conjugated. What is important is that the double bonds are separated by *one and only one* single bond. Here's a counter-example: arachidonic acid is one of the fabled 'polyunsaturated' fatty acids. None of the four double bonds in this structure are conjugated since in between any two double bonds there is an  $sp^3$  carbon. This means that there is no p orbital available to overlap with the ones from the double bonds. The saturated carbon atoms 'insulate' the double bonds from each other and prevent conjugation.



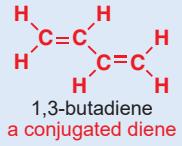
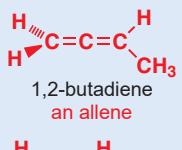
If an atom has two double bonds directly attached to it, that is, there are no single bonds separating them, again no conjugation is possible. The simplest compound with such an arrangement is allene. The arrangement of the p orbitals in allene means that no delocalization is possible because the two  $\pi$  bonds are perpendicular to each other.



Interactive bonding orbitals in allene

### Isomers of butadiene

Butadiene normally refers to 1,3-butadiene. It is also possible to have 1,2-butadiene, which is another example of an allene.



### Requirements for conjugation

- Conjugation requires double bonds separated by one single bond.
- Double bonds separated by two single bonds or no single bonds are not conjugated.

## The conjugation of two $\pi$ bonds

To understand the effects of conjugation on molecules, we need now to look at their molecular orbitals. We'll concentrate only on the electrons in  $\pi$  orbitals—you can take it that all the C–C and C–H  $\sigma$  bonds are essentially the same as those of all the other molecules you met in Chapter 4. We'll start with the simplest compound that can have two conjugated  $\pi$  bonds: butadiene. As you would expect, butadiene prefers to be planar to maximize overlap between its p orbitals. But exactly how does that overlap happen, and how does it give rise to bonding?

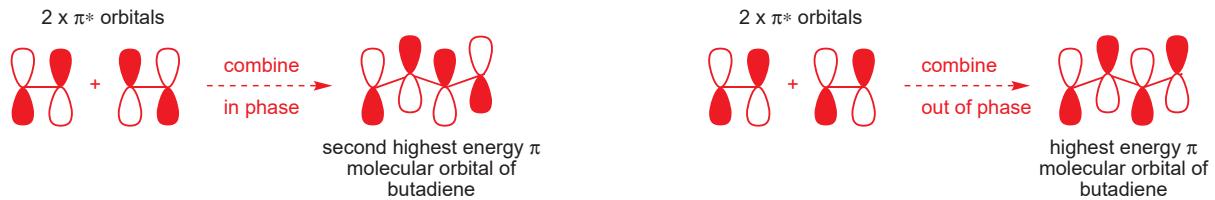
### The molecular orbitals of butadiene

Butadiene has two  $\pi$  bonds, each made up of two p orbitals: a total of four atomic orbitals. We'd therefore expect four molecular orbitals, housing four electrons. Just like

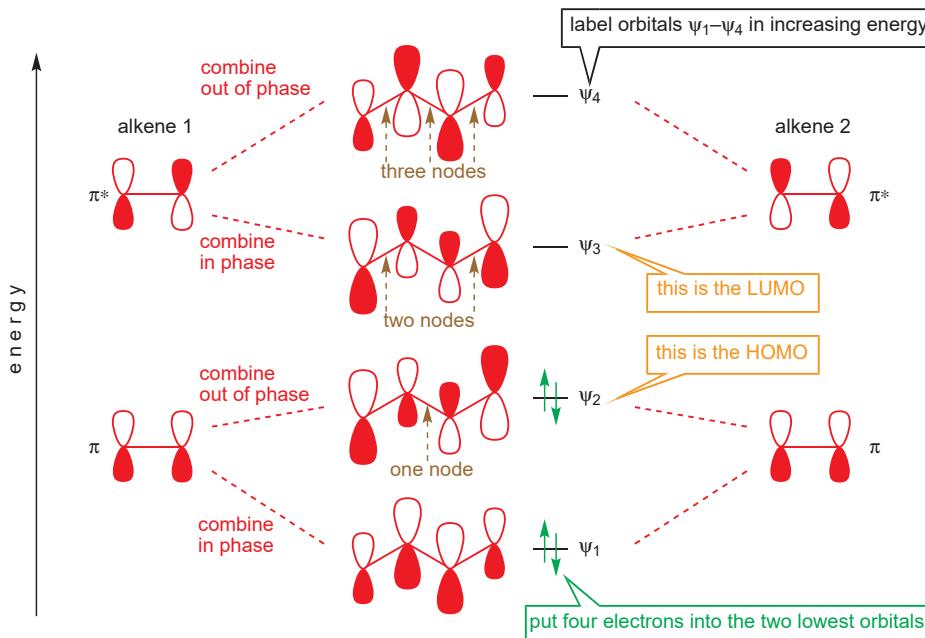
hexatriene above, these orbitals extend over the whole molecule, but we can easily work out what these molecular orbitals look like simply by taking the orbitals of two alkenes and interacting them side by side. We have two  $\pi$  orbitals and two  $\pi^*$  orbitals, and we can interact them in phase or out of phase. Here are the first two, made by interacting the two  $\pi$  orbitals:



and the next two, made from two  $\pi^*$  orbitals:



We can represent all four molecular orbitals like this, stacked up in order of their energy in a molecular orbital energy level diagram. With four orbitals, we can't just use '\*' to represent antibonding orbitals, so conventionally they are numbered  $\psi_1$ – $\psi_4$  ( $\psi$  is the Greek letter psi).



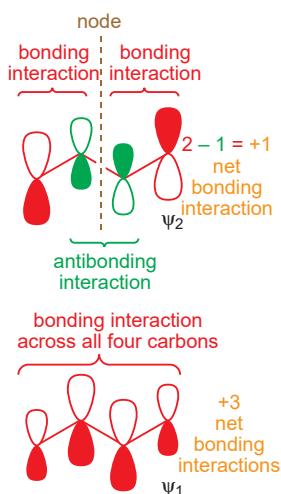
Interactive bonding orbitals in butadiene

→ The idea that higher energy orbitals have more nodes is familiar to you from Chapter 4—see p. 88.

It's worth noticing a couple of other things about the way we have represented these four molecular orbitals before we move on. Firstly, the number of nodes (changes in phase as you move from one orbital to the next) increases from zero in  $\psi_1$  to three in  $\psi_4$ . Secondly, notice that the p orbitals making up the  $\pi$  system are not all shown as the same size—their *coefficients* vary according to the orbital they are in. This is a mathematical consequence of the way the orbitals sum together, and you need not be concerned with the details, just the general principle that  $\psi_1$  and  $\psi_4$  have the largest coefficients in the middle;  $\psi_2$  and  $\psi_3$  the largest coefficients at the ends.

Now for the electrons: each orbital holds two electrons, so the four electrons in the  $\pi$  system go into orbitals  $\psi_1$  and  $\psi_2$ .

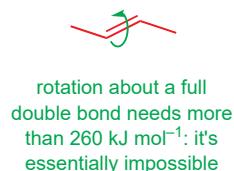
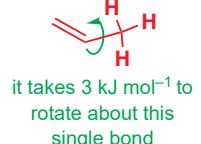
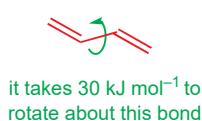
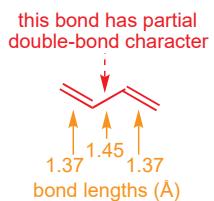
The term 'coefficient' describes the contribution of an individual atomic orbital to a molecular orbital. It is represented by the size of the lobes on each atom.



In our glimpse of hexatriene earlier in this chapter we saw similar effects: a tendency to be planar and restriction to rotation about the slightly shortened single bonds.

A closer look at these filled orbitals shows that in  $\psi_1$ , the lowest energy bonding orbital, the electrons are spread out over all four carbon atoms (above and below the plane) in one continuous orbital. There is bonding between all four C atoms—three net bonding interactions.  $\psi_2$  has bonding interactions between carbon atoms 1 and 2, and also between 3 and 4 but an *antibonding* interaction between carbons 2 and 3—in other words,  $2 - 1 = 1$  net bonding interaction. For the unoccupied orbitals there is a net -1 antibonding interaction in  $\psi_3$  and a net -3 antibonding interaction in  $\psi_4$ .

Overall, in both the occupied  $\pi$  orbitals there are electrons between carbons 1 and 2 and between 3 and 4, but the antibonding interaction between carbons 2 and 3 in  $\psi_2$  partially cancels out the bonding interaction in  $\psi_1$ . Only ‘partially’, because the coefficients of the antibonding pair of orbitals in  $\psi_2$  are smaller than the coefficients of the bonding pair in  $\psi_1$ . This explains why all the bonds in butadiene are not the same, and also why the middle bond is like a single bond but with a little bit of double-bond character. Its double-bond character extends to its preference for planarity, the fact that it takes more energy to rotate about this bond than about a typical single bond, and the fact that it is slightly shorter (1.45 Å) than a typical C–C single bond (around 1.54 Å).



The molecular orbital diagram also helps us explain some aspects of the reactivity of butadiene. Notice that we have marked on for you the HOMO ( $\psi_2$ ) and the LUMO ( $\psi_3$ ). On either side you can see the equivalent HOMO ( $\pi$  orbital) and LUMO ( $\pi^*$  orbital) for the isolated alkene (i.e. ethene). Some relevant features to note:

- The overall energy of the two bonding butadiene molecular orbitals is lower than that of the two molecular orbitals for ethene. This means that conjugated butadiene is more thermodynamically stable than just two isolated double bonds.
- The HOMO of butadiene is *higher* in energy than the HOMO for ethene. This is consistent with the fact that butadiene is *more* reactive than ethene towards electrophiles.
- The LUMO for butadiene is *lower* in energy than the LUMO for ethene. This is consistent with the fact that butadiene is *more* reactive than ethene towards nucleophiles.

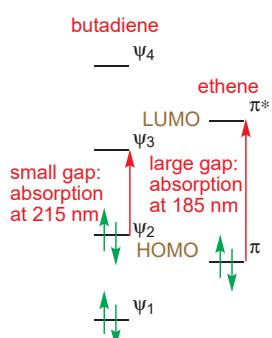
So conjugation makes butadiene more stable, but it also makes it more reactive to both nucleophiles and electrophiles! This superficially surprising result is revisited in detail in Chapter 19.

## UV and visible spectra

In Chapter 2 you saw how, if given the right amount of energy, electrons can be promoted from a low-energy atomic orbital to a higher energy one and how this gives rise to an atomic absorption spectrum. Exactly the same process can occur with molecular orbitals: energy of the right wavelength can promote an electron from a filled orbital (for example the HOMO) to an unfilled one (for example the LUMO), and plotting the absorption of energy against wavelength gives rise to a new type of spectrum called, for obvious reasons which you will see in a moment, a UV-visible spectrum.

You have just seen that the energy difference between the HOMO and LUMO for butadiene is less than that for ethene. We would therefore expect butadiene to absorb light of longer

To understand this section well you will need to remember the formulae linking energy and wavelength,  $E = h\nu$ , and energy and frequency,  $E = hc/\lambda$ . See p. 53 for more on these.



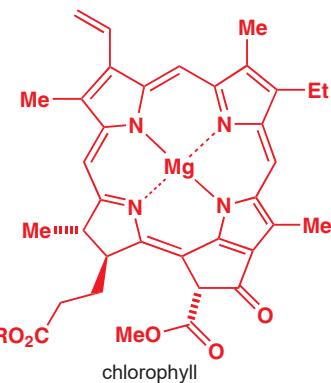
wavelength than ethene (the longer the wavelength the lower the energy). This is indeed the case: butadiene absorbs at 215 nm compared to 185 nm for ethene. The conjugation in butadiene means it absorbs light of a longer wavelength than ethene. One of the consequences of conjugation is to lessen the gaps between filled and empty orbitals, and so allow absorption of light of a longer wavelength.



UV absorption in ethene and butadiene

- The more conjugated a compound is, the smaller the energy transition between its HOMO and LUMO, and hence the longer the wavelength of light it can absorb. UV-visible spectroscopy can tell us about the conjugation present in a molecule.

Both ethene and butadiene absorb in the UV region of the electromagnetic spectrum. If we extend the conjugation further, the gap between HOMO and LUMO will eventually be small enough to allow the compound to absorb visible light and hence have a colour. Lycopene, the pigment in tomatoes, which we introduced at the start of the chapter, has 11 conjugated double bonds (plus two unconjugated ones). It absorbs blue-green light at about 470 nm: consequently tomatoes are red. Chlorophyll, in the margin, has a cyclic conjugated system: it absorbs at long wavelengths and is green.



### The colour of pigments depends on conjugation

It is no coincidence that these and many other highly conjugated compounds are coloured. All dyes and pigments based on organic compounds are highly conjugated.

The table below shows the approximate wavelengths of light absorbed by a polyene conjugated system containing various numbers  $n$  of double bonds. Note that the colour absorbed is complementary to the colour transmitted—a red compound must absorb blue and green light to appear red.

Approximate wavelengths for different colours

Absorbed frequency, nm	Colour absorbed	Colour transmitted	$R(CH=CH)_nR, n =$
200–400	ultraviolet	—	< 8
400	violet	yellow-green	8
425	indigo-blue	yellow	9
450	blue	orange	10
490	blue-green	red	11
510	green	purple	
530	yellow-green	violet	
550	yellow	indigo-blue	
590	orange	blue	
640	red	blue-green	
730	purple	green	

In colour chemistry, *dye* is a soluble colorant while a *pigment* is made of insoluble coloured particles. In biology the word pigment is used for any coloured compound. Dyeing pigments are often inorganic compounds, which are coloured for reasons other than conjugation, but nonetheless to do with the gaps between orbitals.

Fewer than about eight conjugated double bonds, and the compound absorbs only in the UV. With more than eight conjugated double bonds, the absorption creeps into the visible and, by the time it reaches 11, the compound is red. Blue or green polyenes are rare, and dyes of these colours rely on more elaborate conjugated systems.



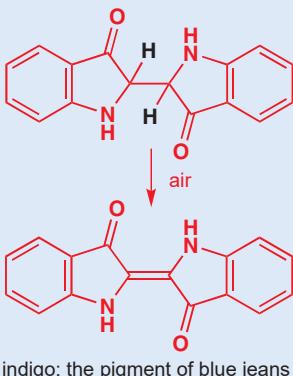
UV absorption in linear conjugated polyenes

### Blue jeans

Transitions from bonding to antibonding  $\pi$  orbitals are called  $\pi \rightarrow \pi^*$  transitions. If electrons are instead promoted from a non-bonding lone pair ( $n$  orbital) to a  $\pi^*$  orbital (an  $n \rightarrow \pi^*$  transition) smaller energy gaps may be available, and many dyes make use of  $n \rightarrow \pi^*$  transitions to produce colours throughout the whole spectrum. For example, the colour of blue jeans comes from the pigment indigo. The two nitrogen atoms provide the lone pairs that can be excited into the  $\pi^*$  orbitals of the rest of the molecule. These are low in energy because of the two carbonyl groups. Yellow light is absorbed by this pigment and indigo-blue light is transmitted.

Jeans are dyed by immersion in a vat of reduced indigo, which is colourless since the conjugation is interrupted by the central single bond. When the cloth is hung up to dry, the oxygen in the air oxidizes the pigment to indigo and the jeans turn blue.

colourless precursor to indigo



indigo: the pigment of blue jeans



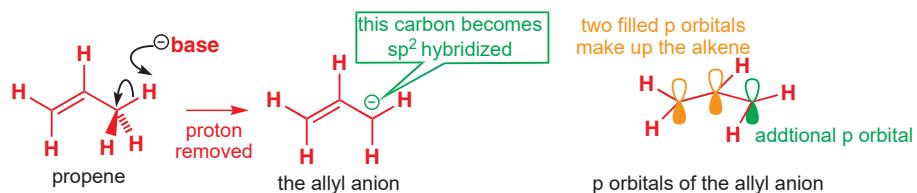
## The allyl system

### The allyl anion

► You will meet such super-strength bases in the next chapter.

In butadiene, four atomic p orbitals interact to make four molecular orbitals; in hexatriene (and you will soon see benzene too) six atomic orbitals interact to make six molecular orbitals. We are now going to consider some common conjugated systems made up of *three* interacting p orbitals. We'll start with the structure we get from treating propene with a very strong base—one strong enough to remove one of the protons from its methyl group.  $H^+$  is removed, so the product must have a negative charge, which formally resides on the carbon of what was the methyl group. That carbon atom started off  $sp^3$  hybridized (i.e. tetrahedral: it had four substituents), but after it has been deprotonated it must become trigonal ( $sp^2$ ), with only three substituents plus a p orbital to house the negative charge.

Of course the anion doesn't really exist 'free' like this; it will most likely have a metal cation to which it is coordinated in some way. The arguments we are going to apply about its structure are still valid whether or not there is a metal associated with it.

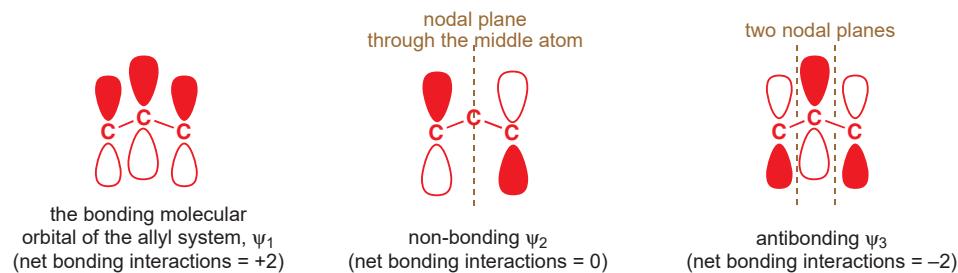


p orbitals of the allyl anion

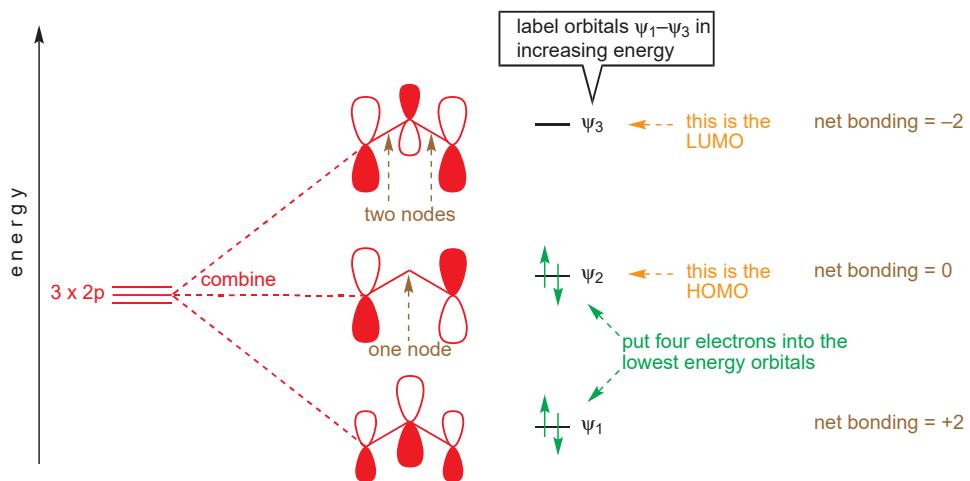
We could work out the orbitals of the allyl anion by combining this p orbital with a ready-made  $\pi$  bond, but instead this time we will start with the three separate p atomic orbitals and combine them to get three molecular orbitals. At first we are not concerned about where the electrons are—we are just building up the molecular orbitals.

The lowest energy orbital ( $\psi_1$ ) will have them all combining in phase. This is a bonding orbital since all the interactions are bonding. The next orbital ( $\psi_2$ ) requires one node, and the only way to include a node and maintain the symmetry of the system is to put the node through the central atom. This means that when this orbital is occupied there will be no electron density on this central atom. Since there are no interactions between adjacent atomic orbitals (either bonding or antibonding), this is a non-bonding orbital. The final molecular

orbital ( $\psi_3$ ) must have two nodal planes. All the interactions of the atomic orbitals are out of phase so the resulting molecular orbital is an antibonding orbital.



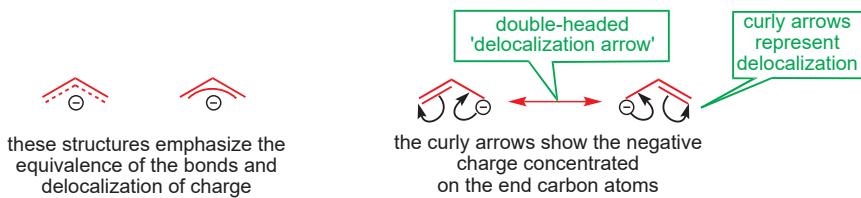
We can summarize all this information in a molecular orbital energy level diagram, and at the same time put the electrons into the orbitals. We need four electrons—two from the alkene  $\pi$  bond and two more for the anion (these were the two in the C–H bond, and they are still there because only a proton, H<sup>+</sup>, was removed). The four electrons go into the lowest two orbitals,  $\psi_1$  and  $\psi_2$ , leaving  $\psi_3$  vacant. Notice too that the energy of two of the electrons is lower than it would have been if they had remained in unconjugated p orbitals: conjugation lowers the energy of filled orbitals and makes compounds more stable.



This diagram shows only the  $\pi$  orbitals of the allyl system. We have ignored all the molecular orbitals from the  $\sigma$  framework because the bonding  $\sigma$  orbitals are considerably lower in energy than the molecular orbitals of the  $\pi$  system and the vacant antibonding  $\sigma^*$  orbitals are much higher in energy than the  $\pi$  antibonding molecular orbital.

Interactive bonding orbitals in the allyl anion

Where is the electron density in the allyl anion  $\pi$  system? We have two filled  $\pi$  molecular orbitals and the electron density comes from a sum of both orbitals. This means there is electron density on all three carbon atoms. However, the coefficients of the end carbons are of a significant size in both orbitals, but in  $\psi_2$  the middle carbon has no electron density at all—it lies on a node. So overall, even though the negative charge is spread over the whole molecule, the end carbons carry more of the electron density than the middle one. We can represent this in two ways—the first structure below emphasizes the delocalization of the charge over the whole molecule, but fails to get across the important point that the negative charge resides principally at the ends. Curly arrows do this much better: we can use them to show that the negative charge is not localized, but principally divided between the two end carbons.



A reminder: this is not an equilibrium—the arrows do not represent the movement of charge. The two structures are alternative, imperfect representations of an 'averaged' structure, and they are linked by a double-headed delocalization arrow.

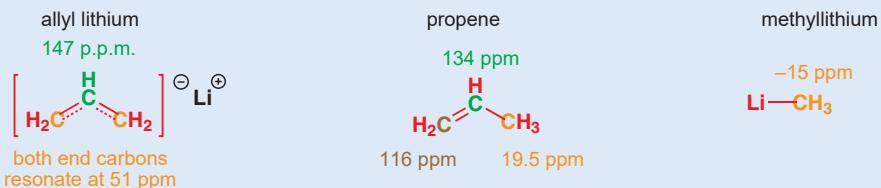


The problem with these structures carrying curly arrows is that they seem to imply that the negative charge (and the double bond for that matter) is jumping from one end of the molecule to the other. This, as we have seen, is just not so. Another and perhaps better picture uses dotted lines and partial charges. But the structure with the dotted bonds, as with the representation of benzene with a circle in the middle, is no good for writing mechanisms. Each of the representations has its strong and weak points: we shall use each as the occasion demands.

### Using NMR to study delocalization

Delocalization of the allyl anion, and the localization of the negative charge mainly on the end carbons, is clear from its  $^{13}\text{C}$  NMR spectrum as well. In Chapter 3 we explained that  $^{13}\text{C}$  NMR gives us a good measure of the amount of electron density around a C atom—the extent to which it is deshielded and therefore exposed to the applied magnetic field. If you need reminding about the terminology, theory, and practice of NMR, turn back now to Chapter 3, pp. 52–63.

It is possible to record a  $^{13}\text{C}$  NMR spectrum of an allyl anion with a lithium counterion. The spectrum shows only two signals: the middle carbon at 147 ppm and the two end carbons both at 51 ppm. This confirms two things: (i) both end carbons are the same and the structure is delocalized, and (ii) most of the negative charge is on the end carbons—they are more shielded (have a smaller chemical shift) as a result of the greater electron density. In fact, the central carbon's shift of 147 ppm is not far from that of a normal double-bond carbon (compare the signals in propene). The end carbons' shift is in between that of a double bond and a saturated carbon directly bonded to a metal (e.g. methylolithium, whose negative chemical shift results from the highly polarized Li–C bond).

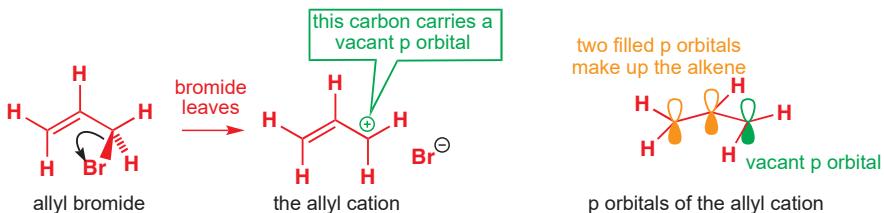


### The allyl cation

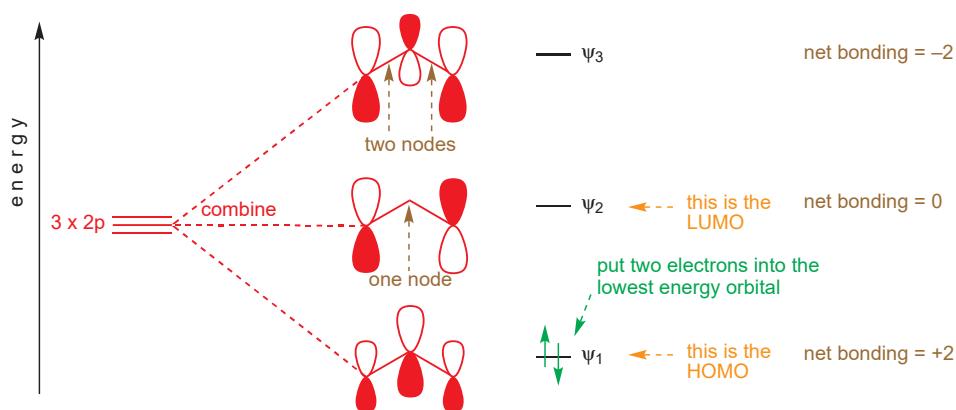


What if, instead of taking just a proton, we had also taken away two electrons from propene? In reality we can get such a structure quite straightforwardly from allyl bromide (prop-2-enyl bromide or 1-bromoprop-2-ene). Carbon 1 in this compound has four atoms attached to it (a carbon, two hydrogens, and a bromine atom) so it is tetrahedral (or  $\text{sp}^3$  hybridized).

Bromine is more electronegative than carbon and so the C–Br bond is polarized towards the bromine. It is quite easy to break this bond completely, with the bromine keeping both electrons from the C–Br bond to become bromide ion,  $\text{Br}^-$ , leaving behind an *allyl cation*. The positively charged carbon now has only three substituents so it becomes trigonal ( $\text{sp}^2$  hybridized). It must therefore have a vacant p orbital.



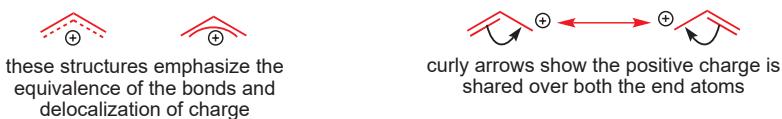
Like the allyl anion, the orbitals in the allyl cation are a combination of three atomic p orbitals, one from each carbon. So we can use the same molecular orbital energy level diagram as we did for the anion, simply by adjusting the number of electrons we put into the orbitals. This time, there are only two electrons, from the alkene, as those which were in the C–Br bond have left with anionic bromide.



The two electrons in the filled orbital are in a lower energy orbital than they would have been if they had stayed in an unconjugated  $p$  orbital: as with the anion, *conjugation* leads to *stabilization*.

The two electrons are spread over three carbon atoms. Overall, the allyl cation has a positive charge. But where is the positive charge concentrated? What we need to do is look to see where there is a *deficit* of charge. The only orbital with any electrons in it is the bonding molecular orbital  $\Psi_1$ . From the relative sizes of the coefficients on each atom we can see that the middle carbon has more electron density on it than the end ones, so the end carbons must be more positive than the middle one.

We expect both end carbons to be identical, and  $^{13}\text{C}$  NMR tells us that this is so (see below). Again we need a way of showing this delocalization, either on a single structure or as a pair of localized structures linked by a delocalization arrow.

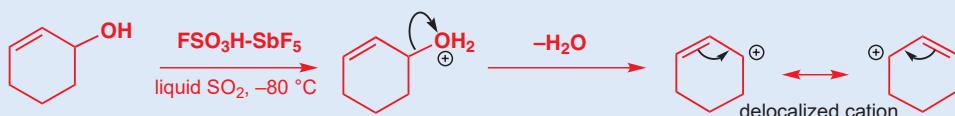


Notice how we draw the curly arrows here: we want to show the positive charge 'moving', and it is tempting to draw a curly arrow starting from the positive charge. But curly arrows must always start on something representing a pair of electrons. So we must move the positive charge as a consequence of the movement of the electrons in the double bond: as we pull them away from one end, they leave behind a positive charge.

► The guidelines for drawing curly arrows are given on p. 123.

### The NMR spectrum of a delocalized cation

The reaction below shows the formation of a cation close in structure to the allyl cation. A very strong acid (called 'super-acid'—see Chapter 15) protonates the OH group of 3-cyclohexenol, which can then leave as water. The resulting cation is, not surprisingly, unstable and would normally react rapidly with a nucleophile. However, at low temperatures and if there are no nucleophiles present, the cation is relatively stable and it is even possible to record a  $^{13}\text{C}$  NMR spectrum (at  $-80^\circ\text{C}$ ).



The  $^{13}\text{C}$  NMR spectrum of this allylic cation reveals a plane of symmetry, which confirms that the positive charge is spread over two carbons. The large shift of 224 ppm for these carbons indicates very strong deshielding (that is, lack of electrons) but is nowhere near as large as that of a localized cation (which would resonate at about 330 ppm). The middle carbon's shift of 142 ppm is almost typical of a normal double bond, indicating that it is neither significantly more nor less electron-rich than normal. In fact, it is interesting to note that the middle carbon of this cation and the allyl anion we described above have almost exactly the same chemical shift—proof that the charge lies mainly on the ends of the allyl system.

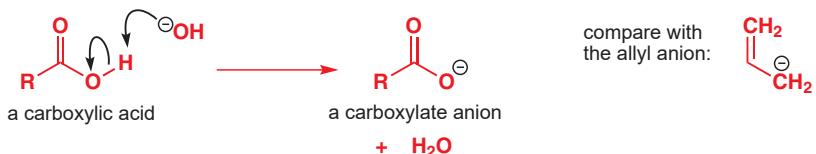
$^{13}\text{C}$  NMR shifts in ppm—notice the plane of symmetry down the middle



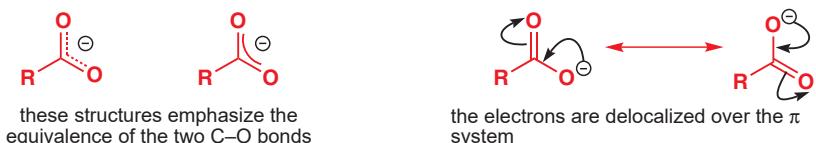
## Delocalization over three atoms is a common structural feature

### The carboxylate anion

You may already be familiar with one anion very much like the allyl anion—the carboxylate ion, which forms when a carboxylic acid reacts with a base. In this structure we again have a negatively charged atom separated from a double bond by a single bond adjacent to a single bond: it's analogous to an allyl anion with oxygen atoms replacing two of the carbon atoms.



X-ray crystallography shows both carbon–oxygen bond lengths in this anion to be the same (136 pm), in between that of a normal carbon–oxygen double bond (123 pm) and single bond (143 pm). The negative charge is spread out equally over the two oxygen atoms, and we can represent this in two ways—as before, the one on the left shows the equivalence of the two C–O bonds, but you would use the one on the right for writing mechanisms. The delocalization arrow tells us that both localized forms contribute to the real structure.



### The nitro group

The nitro group consists of a nitrogen bonded to two oxygen atoms and a carbon (for example an alkyl group). There are two ways of representing the structure: one using formal charges, the other (which we suggest you avoid) using a dative bond. Notice in each case that one oxygen is depicted as being doubly bonded, the other singly bonded. Drawing both oxygen atoms doubly bonded is incorrect—*nitrogen cannot participate in five bonds*: this would require ten bonding electrons around the N atom, and there are not enough s and p orbitals to put them in.



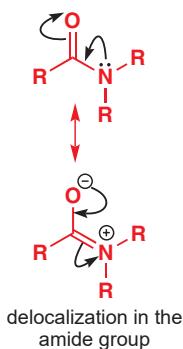
The problem even with the ‘correct’ structure on the left is that the equivalence of the two N–O bonds is not made clear. The nitro group has exactly the same number of electrons as a carboxylate anion (although it’s neutral of course because nitrogen already has one more electron than carbon) and the delocalized structure can be shown with curly arrows in the same way.

We have not shown molecular orbital energy level diagrams for the carboxylate and nitro groups, since they are similar to that of the allyl anion. Only the absolute energies of the molecular orbitals are different since different elements with different electronegativities are involved in each case.

### The amide group

Life is built of amides, because the amide group is the link through which amino acids join together to form the proteins which make up much of the structural features of living systems.

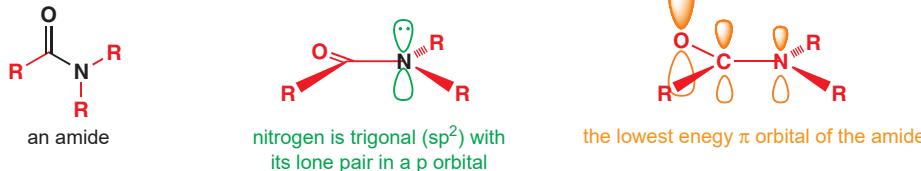
We call structures such as a nitro and a carboxylate group *isoelectronic*: the atoms may be different but the number of and arrangement of the bonding electrons are the same.



Nylon is a synthetic polyamide, and shares with many proteins the property of durability. The structure of this deceptively simple functional group has an unexpected feature which is responsible for much of the stability it confers.

The allyl anion, carboxylate, and nitro groups have four electrons in a  $\pi$  system spread out over three atoms. The nitrogen in the amide group also has a pair of electrons that can conjugate with the  $\pi$  bond of the carbonyl group. For effective overlap with the  $\pi$  bond, this lone pair of electrons must be in a p orbital. This in turn means that the nitrogen must be  $sp^2$  hybridized.

Contrast this with the lone pair of a typical amine, which lies in an  $sp^3$  orbital (see p. 103): an amine N is pyramidal ( $sp^3$ ) while an amide N is trigonal planar ( $sp^2$ ).



In the carboxylate ion, a negative charge is shared (equally) between two oxygen atoms. In an amide there is no charge as such—the lone pair on nitrogen is shared between the nitrogen and the oxygen. The delocalization can be shown as usual by using curly arrows, as shown in the margin.

This representation suffers from the usual problems. Curly arrows usually show electron movement, but here they do not: they simply show how to get from one of the alternative representations to the other. The molecular orbital picture of the amide tells us that the electrons are unevenly distributed over the three atoms in the  $\pi$  system with a greater electron density on the oxygen: you can see this in the delocalized structure on the right, which has a full negative charge on O and a positive charge on N. (We also indicated this in the diagram of the lowest energy  $\pi$  orbital above, which has a greatest coefficient, and therefore greatest electron density, on O.) Another aspect of the structure of the amide group that this pair of structures indicates correctly is that there is partial double bond character between the C atom and the N atom. We will come back to this shortly.

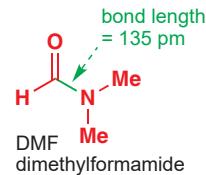
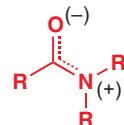
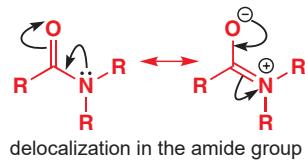
The real structure of the amide group lies in between the two extreme structures linked by the delocalization arrow: a better representation might be the structure on the right. The charges in brackets indicate substantial, although not complete, charges, maybe about a half plus or minus charge. However, we cannot draw mechanisms using this structure.

We can summarize several points about the structure of the amide group, and we will then return to each in a little more detail

- The amide group is planar—this includes the first carbon atoms of the R groups attached to the carbonyl group and to the nitrogen atom.
- The lone pair of electrons on nitrogen is delocalized into the carbonyl group.
- The C–N bond is strengthened by this interaction—it takes on partial double bond character. This also means that we no longer have free rotation about the C–N bond, which we would expect if it were only a single bond.
- The oxygen is more electron-rich than the nitrogen. Hence we might expect the oxygen rather than the nitrogen to be the site of electrophilic attack.
- The amide group as a whole is made more stable as a result of the delocalization.

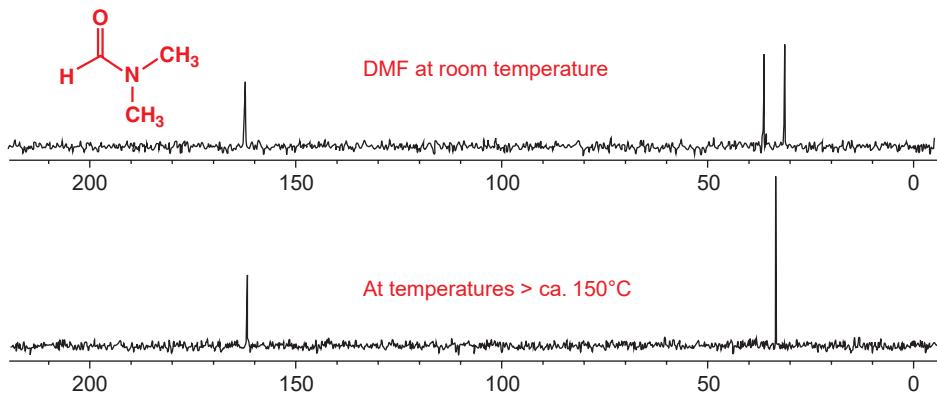
How do we know the amide group is planar? X-ray crystal structures are the simplest answer. Other techniques such as electron diffraction also show that simple (non-crystalline) amides have planar structures. *N,N*-Dimethylformamide (DMF) is an example.

The N–CO bond length in DMF (135 pm) is closer to that of a standard C–N double bond (127 pm) than to that of a single bond (149 pm). This partial double bond character, which the delocalized structures led us to expect, is responsible for restricted rotation about this C–N bond. We must supply 88 kJ mol<sup>-1</sup> if we want to rotate the C–N bond in DMF (remember a single bond only takes about 3 kJ mol<sup>-1</sup>, while a full C–C double bond takes about 260 kJ mol<sup>-1</sup>). The amount of energy available at room temperature is only enough to allow this bond



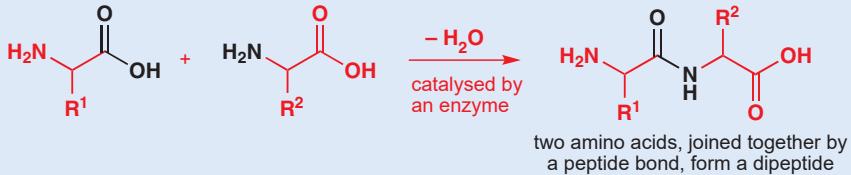
to rotate slowly, and the result is quite clear in the  $^{13}\text{C}$  NMR spectrum of DMF. There are three carbon atoms altogether and three signals appear—the two methyl groups on the nitrogen are different. If free rotation were possible about the C–N bond, we would expect to see only two signals, since the two methyl groups would become identical.

■ In fact, if we record the spectrum at higher temperatures, we do indeed only see two signals since now there is sufficient energy available to overcome the rotational barrier and allow the two methyl groups to interchange.



### Amides in proteins

Proteins are composed of many amino acids joined together with amide bonds. The amino group of one can combine with the carboxylic acid group of another to give an amide known as a peptide—two amino acids join to form a dipeptide; many join to give a polypeptide.



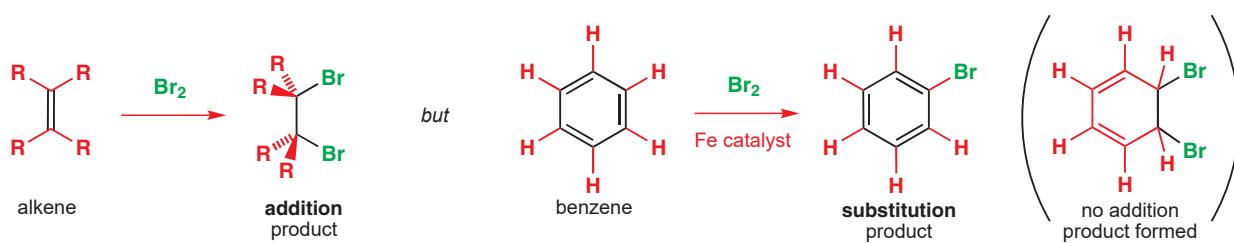
The peptide unit so formed is a planar, rigid structure because of restricted rotation about the C–N bond. This rigidity confers organizational stability on protein structures.

### Conjugation and reactivity: looking forward to Chapter 10

Just as delocalization stabilizes the allyl cation and anion (at least some of the electrons in conjugated systems end up in lower energy orbitals than they would have done without conjugation) so too is the amide group stabilized by the conjugation of the nitrogen's lone pair with the carbonyl group. This makes an amide C=O one of the least reactive carbonyl groups (we shall discuss this in Chapter 10). Furthermore, the nitrogen atom of an amide group is very different from that of a typical amine. Most amines are easily protonated. However, since the lone pair on the amide's nitrogen is conjugated into the  $\pi$  system, it is less available for protonation or, indeed, reaction with any electrophile. As a result, when an amide is protonated (and it is not protonated easily, as you will see in the next chapter) it is protonated on oxygen rather than nitrogen. The consequences of conjugation for reactivity extend far and wide, and will be a running theme through many chapters in this book.

## Aromaticity

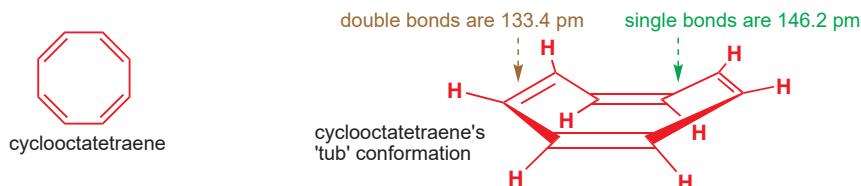
It's now time to go back to the structure of benzene. Benzene is unusually stable for an alkene and is not normally described as an alkene at all. For example, whereas normal alkenes (whether conjugated or not) readily react with bromine to give dibromoalkane *addition* products, benzene reacts with bromine only with difficulty—it needs a catalyst (iron will do) and then the product is a *monosubstituted* benzene and not an addition compound.



Bromine reacts with benzene in a substitution reaction (a bromine atom replaces a hydrogen atom), *keeping the benzene structure intact*. This ability to retain its conjugated structure through all sorts of chemical reactions is one of the important differences between benzene and other alkenes.

### What makes benzene special?

You might assume benzene's special feature is its ring structure. To see whether this is the case, we'll look at another cyclic polyene, cyclooctatetraene, with four double bonds in a ring. Given what we have explained about the way that  $\pi$  systems gain stability by allowing overlap between their p orbitals, you may be surprised to find that cyclooctatetraene, unlike benzene, is *not* planar. There is no conjugation between any of the double bonds—there are indeed alternate double and single bonds in the structure, but conjugation is possible only if the p orbitals of the double bonds can overlap and here they do not. The fact that there is no conjugation is shown by the alternating C–C bond lengths in cyclooctatetraene—146.2 and 133.4 pm—which are typical for single and double C–C bonds. If possible, make a model of cyclooctatetraene for yourself—you will find the compound naturally adopts the shape on the right below. This shape is often called a 'tub'.



Interactive structures of cyclooctatetraene, the dianion and dication

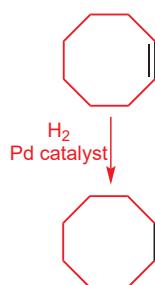
Chemically, cyclooctatetraene behaves like an alkene, not like benzene. With bromine, for example, it forms an addition product and not a substitution product. So benzene is not special just because it is cyclic—cyclooctatetraene is cyclic too but does not behave like benzene.

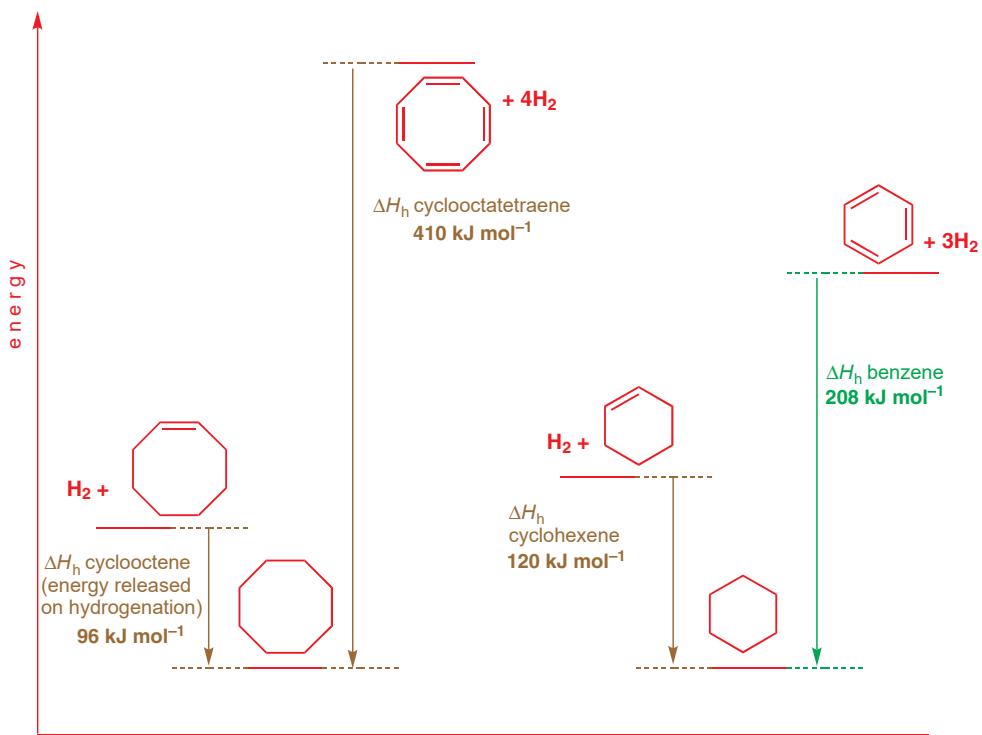
### Heats of hydrogenation of benzene and cyclooctatetraene

$\text{C}=\text{C}$  double bonds can be reduced using hydrogen gas and a metal catalyst (usually nickel or palladium) to produce fully saturated alkanes. This process is called hydrogenation and it is exothermic (that is, energy is released) since a thermodynamically more stable product, an alkane, is produced.

More on this in Chapter 23.

When *cis*-cyclooctene is hydrogenated to cyclooctane, 96  $\text{kJ mol}^{-1}$  of energy is released. Cyclooctatetraene releases 410  $\text{kJ mol}^{-1}$  on hydrogenation. This value is approximately four times one double bond's worth, as we might expect. However, whereas the heat of hydrogenation for cyclohexene is 120  $\text{kJ mol}^{-1}$ , on hydrogenating benzene only 208  $\text{kJ mol}^{-1}$  is given out, which is much less than the 360  $\text{kJ mol}^{-1}$  that we would have predicted by multiplying the figure for cyclohexene by 3. Benzene has something to make it stable which cyclooctatetraene does not have.



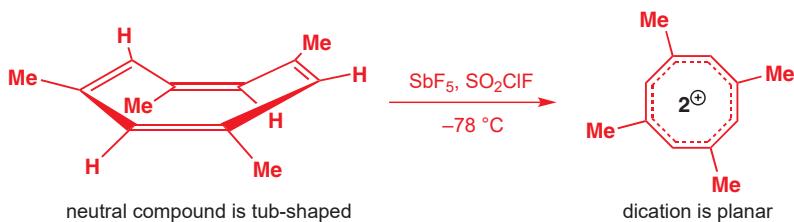


### Varying the number of electrons

The mystery deepens when we look at what happens when we treat cyclooctatetraene with powerful oxidizing or reducing agents. If 1,3,5,7-tetramethylcyclooctatetraene is treated at low temperature (-78 °C) with SbF<sub>5</sub>/SO<sub>2</sub>ClF (strongly oxidizing conditions) a dication is formed. This cation, unlike the neutral compound, is *planar* and all the C–C bond lengths are the same.

Interactive structures of cyclooctatetraene, the dianion and dication

This dication still has the same number of atoms as the neutral species, only fewer electrons. The electrons have come from the  $\pi$  system, which is now two electrons short. We could draw a structure showing two localized positive charges, but the charge is in fact spread over the whole ring.



It is also possible to *add* electrons to cyclooctatetraene by treating it with alkali metals and a *dianion* results. X-ray structures reveal this dianion to be planar, again with all C–C bond lengths the same (140.7 pm). The difference between the anion and cation of cyclooctatetraene on the one hand and cyclooctatetraene on the other is the number of electrons in the  $\pi$  system. Neutral, non-planar, cyclooctatetraene has eight  $\pi$  electrons, the planar dication has six  $\pi$  electrons (as does benzene), and the planar anion has ten.

Can you see a pattern forming? The important point is not the number of conjugated atoms but the *number of electrons in the  $\pi$  system*.

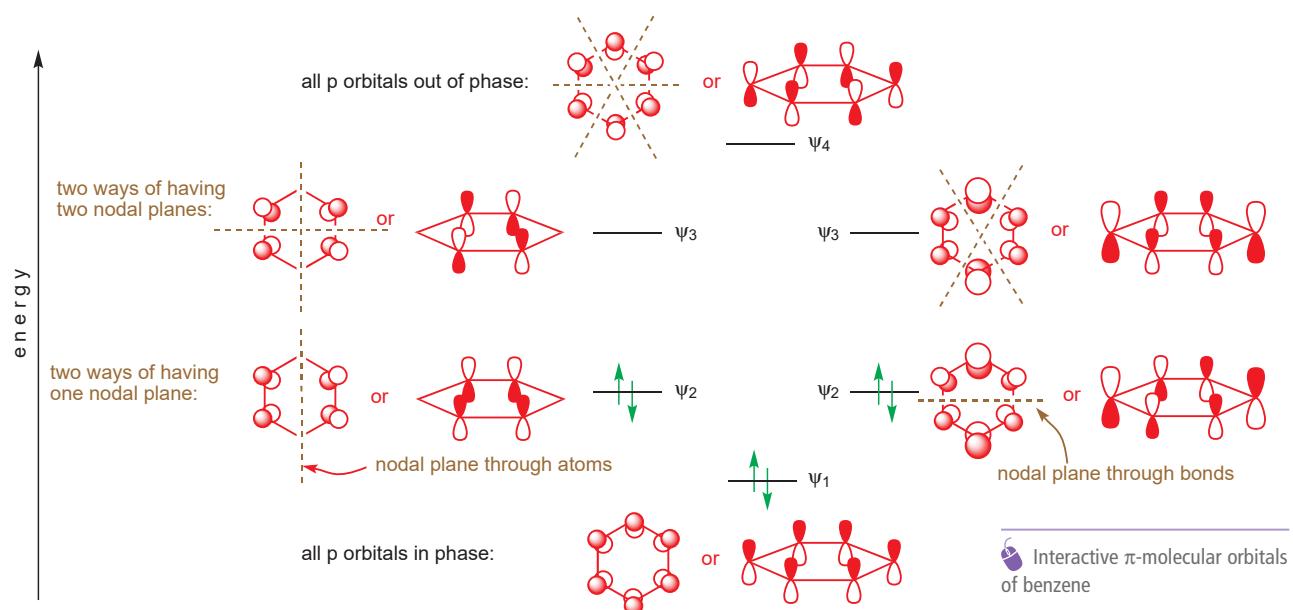
- When they have four or eight  $\pi$  electrons, both six- and eight-membered rings adopt non-planar structures; when they have six or ten  $\pi$  electrons, a planar structure is preferred.

If you made a model of cyclooctatetraene, you might have tried to force it to be flat. If you managed this you probably found that it didn't stay like this for long and that it popped back into the tub shape. The strain in planar cyclooctatetraene can be overcome by the molecule

adopting the tub conformation. The strain is due to the numbers of atoms and double bonds in the ring—it has nothing to do with the number of electrons. The planar dication and dianion of cyclooctatetraene still have this strain. The fact that these ions do adopt planar structures must mean there is some other form of stabilization that outweighs the strain of being planar. This extra stabilization is called *aromaticity*.

### Benzene has six $\pi$ molecular orbitals

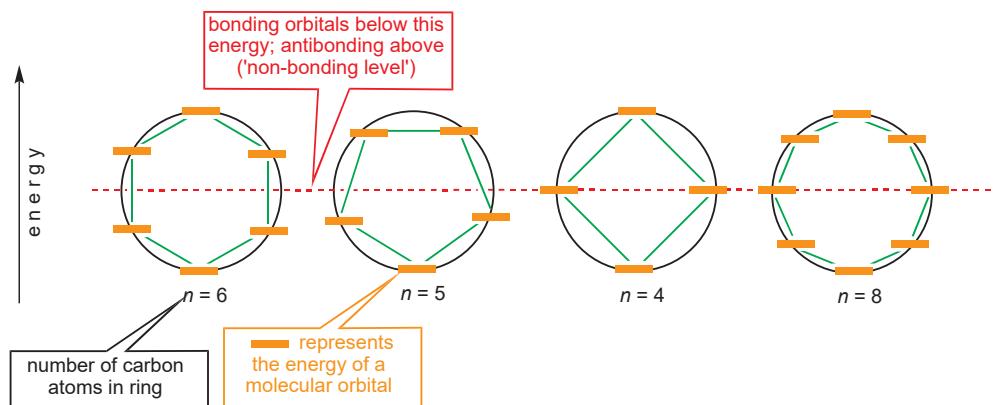
The difference between the amount of energy we expect to get from benzene on hydrogenation ( $360 \text{ kJ mol}^{-1}$ ) and what is observed ( $208 \text{ kJ mol}^{-1}$ ) is about  $150 \text{ kJ mol}^{-1}$ . This represents a crude measure of just how extra stable benzene really is relative to what it would be like with three localized double bonds. In order to understand the origin of this stabilization, we must look at the molecular orbitals. We can think of the  $\pi$  molecular orbitals of benzene as resulting from the combination of the six p orbitals in a ring and, as with butadiene, each successively higher energy orbital contains one more node. This is what we get for benzene:



The molecular orbital lowest in energy,  $\psi_1$ , has no nodes, with all the orbitals combining in phase. The next lowest molecular orbital will have one nodal plane, which can be arranged in two ways depending on whether or not the nodal plane passes through a bond or an atom. It turns out that these two different molecular orbitals both have exactly the same energy, that is, they are degenerate, and we call them both  $\psi_2$ . There are likewise two ways of arranging two nodal planes and again there are two degenerate molecular orbitals  $\psi_3$ . The final molecular orbital  $\psi_4$  will have three nodal planes, which must mean all the p orbitals combining out of phase. Six electrons slot neatly into the three lowest energy bonding orbitals.

### The $\pi$ molecular orbitals of other conjugated cyclic hydrocarbons

Notice that the layout of the energy levels in benzene is a regular hexagon with its apex pointing downwards. It turns out that the energy level diagram for the molecular orbitals resulting from the combination of *any* regular cyclic arrangement of p orbitals can be deduced from the appropriately sided polygon with an apex pointing downwards. The horizontal diameter (the red line) represents the energy of a carbon p orbital and any energy levels on this line represent non-bonding molecular orbitals. All molecular orbitals with energies below this line are bonding; all those above are antibonding.



### Aromaticity of cyclic polyenes

It's worth noting a few points about these energy level diagrams:

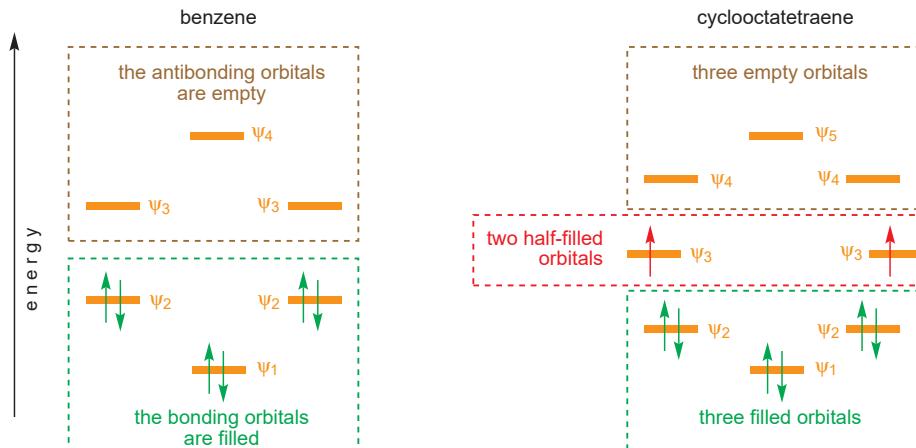
- The method predicts the energy levels for the molecular orbitals of planar, cyclic arrangements of identical atoms (usually all C) only.
- There is always one single molecular orbital lower in energy than all the others. This is because there is always one molecular orbital where all the p orbitals combine in phase.
- If there is an even number of atoms, there is also a single molecular orbital highest in energy; otherwise there will be a pair of degenerate molecular orbitals highest in energy.
- All the molecular orbitals come in degenerate pairs except the one lowest in energy and (for even-numbered systems) the one highest in energy.

### Molecular orbitals and aromaticity

Now we can begin to put all the pieces together and make sense of what we know so far. We'll compare the way that the electrons fit into the energy level diagrams for benzene and planar cyclooctatetraene. We are not concerned with the actual shapes of the molecular orbitals involved, just their energies.

Benzene has six  $\pi$  electrons, which means that all its three bonding molecular orbitals are fully occupied, giving what we can call a 'closed shell' structure. Cyclooctatetraene's eight electrons, on the other hand, do not fit so neatly into its orbitals. Six of these fill up the bonding molecular orbitals but there are two electrons left. These must go into the degenerate pair of non-bonding orbitals. Hund's rule (Chapter 4) would suggest one in each. Planar cyclooctatetraene would not have the closed shell structure that benzene has—to get one it must either lose or gain two electrons. This is exactly what we have already seen—both the dianion and dication from cyclooctatetraene are planar, allowing delocalization all over the ring, whereas neutral cyclooctatetraene avoids the unfavourable arrangement of electrons shown below by adopting a tub shape with localized bonds.

■ You can draw an analogy here with the stability of 'closed shell' electronic arrangements in atoms.



## Hückel's rule tells us if compounds are aromatic

As we pointed out on the previous page, all the cyclic conjugated hydrocarbons have a single lowest energy molecular orbital, and then a stack of degenerate pairs of orbitals of increasing energy. Since the single low energy orbital holds two electrons, and then the successive degenerate pairs four each, a 'closed shell' arrangement in which all the orbitals below a certain level are filled will always contain  $(4n + 2)$  electrons (where  $n$  is an integer—0, 1, 2, etc.—corresponding to the number of degenerate orbital pairs). This is the basis of Hückel's rule.

### ● Hückel's rule

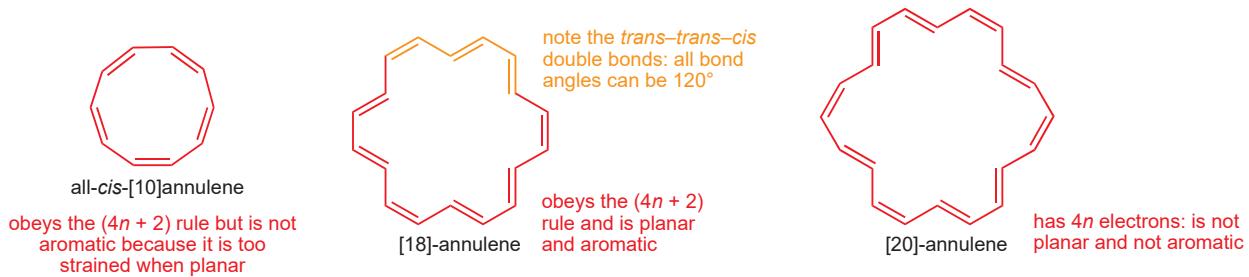
Planar, fully conjugated, monocyclic systems with  $(4n + 2) \pi$  electrons have a closed shell of electrons all in bonding orbitals and are exceptionally stable. Such systems are said to be **aromatic**.

Analogous systems with  $4n \pi$  electrons are described as **anti-aromatic**.

The next  $(4n + 2)$  number after six is ten so we might expect this cyclic alkene, [10]annulene, to be aromatic. But if a compound with five *cis* double bonds were planar, each internal angle would be  $144^\circ$ . Since a normal double bond has bond angles of  $120^\circ$ , this would be far from ideal. This compound can be made but it does *not* adopt a planar conformation and therefore is not aromatic even though it has ten  $\pi$  electrons.

This is not a strict definition of aromaticity: it is actually very difficult to define aromaticity precisely, but all aromatic systems obey Hückel's  $(4n + 2)$  rule.

**Annulenes** are compounds with alternating double and single bonds. The number in brackets tells us how many carbon atoms there are in the ring. Using this nomenclature, you could call benzene [6]annulene and cyclooctatetraene [8]annulene—but don't.

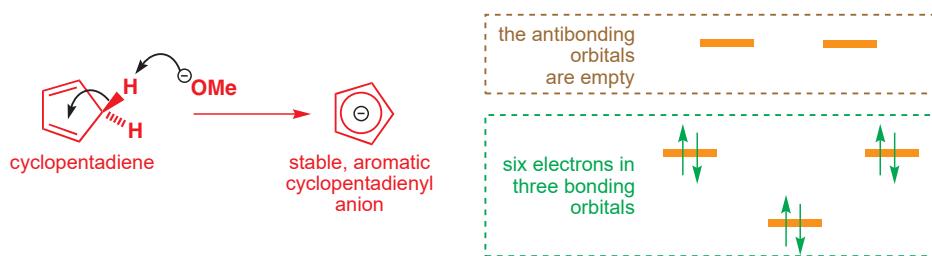


By contrast, [18]annulene, which is also a  $(4n + 2) \pi$  electron system ( $n = 4$ ), does adopt a planar conformation and *is* aromatic. The *trans-trans-cis* double bond arrangement allows all bond angles to be  $120^\circ$ . [20]Annulene presumably could become planar (it isn't quite) but since it is a  $4n \pi$  electron system rather than a  $4n + 2$  system, it is not aromatic and the structure shows localized single and double bonds.

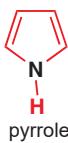
When the conjugated systems are not monocyclic, the situation becomes a little less clear. Naphthalene, for example, has ten electrons but you can also think of it as two fused benzene rings. From its chemistry, it is very clear that naphthalene has aromatic character (it does substitution reactions) but is less aromatic than benzene itself. For example, naphthalene can easily be reduced to tetralin (1,2,3,4-tetrahydronaphthalene), which still contains a benzene ring. Also, in contrast to benzene, all the bond lengths in naphthalene are not the same. 1,6-Methano[10]annulene is rather like naphthalene but with the middle bond replaced by a methylene bridging group. This compound is almost flat and shows aromatic character.



Hückel's rule helps us predict and understand the aromatic stability of numerous other systems. Cyclopentadiene, for example, has two conjugated double bonds but the conjugated system is not cyclic since there is an  $sp^3$  carbon in the ring. However, this compound is relatively easy to deprotonate to give a very stable anion in which all the bond lengths are the same.



Not only are most aromatic systems heterocyclic, but more than 50% of *all organic compounds* contain an aromatic heterocycle.



### Heterocyclic aromatic compounds

So far all the aromatic compounds you have seen have been hydrocarbons. However, most aromatic systems are heterocyclic—that is, they contain atoms other than just carbon and hydrogen. (In fact the majority of *all organic compounds* are aromatic heterocycles!) A simple example is pyridine, in which a nitrogen replaces one of the CH groups of benzene. The ring still has three double bonds and thus six  $\pi$  electrons.

Consider the structure shown on the left, pyrrole. This is also aromatic but it's not enough just to use the electrons in the double bonds: in pyrrole the nitrogen's lone pair contributes to the six  $\pi$  electrons needed for the system to be aromatic. Aromatic chemistry makes several more appearances in this book: in Chapter 21 we shall look at the chemistry of benzene and in Chapters 30 and 31 we shall discuss heterocyclic aromatic compounds in much more detail.

## 延伸阅读

*Molecular Orbitals and Organic Chemical Reactions: Student Edition* by Ian Fleming, Wiley, Chichester, 2009, gives an excellent account of delocalization.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 8

## 酸性、碱性和 $pK_a$

### 联系

#### 基础

- Conjugation and molecular stability ch7
- Curly arrows represent delocalization and mechanisms ch5
- How orbitals overlap to form conjugated systems ch4

#### 目标

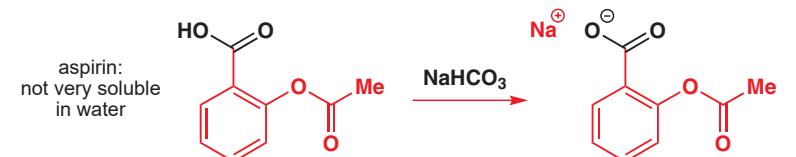
- Why some molecules are acidic and others basic
- Why some acids are strong and others weak
- Why some bases are strong and others weak
- Estimating acidity and basicity using pH and  $pK_a$
- Structure and equilibria in proton transfer reactions
- Which protons in more complex molecules are more acidic
- Which lone pairs in more complex molecules are more basic
- Quantitative acid/base ideas affecting reactions and solubility
- Effects of quantitative acid/base ideas on medicine design

#### 展望

- Acid and base catalysis in carbonyl reactions ch10 & ch11
- The role of catalysts in organic mechanisms ch12
- Making reactions selective using acids and bases ch23
- More details on acid and base catalysis ch39

### Organic compounds are more soluble in water as ions

Most organic compounds are insoluble in water. But sometimes it's necessary to make them dissolve, perhaps by converting them to anions or cations. Water can solvate both cations and anions, unlike some of the solvents you will meet later. A good way of dissolving an organic acid is to put it in basic solution: the base deprotonates the acid to give an anion. A simple example is aspirin: whilst the acid itself is not very soluble in water, the sodium salt is much more soluble. The sodium salt forms with the weak base, sodium hydrogencarbonate.



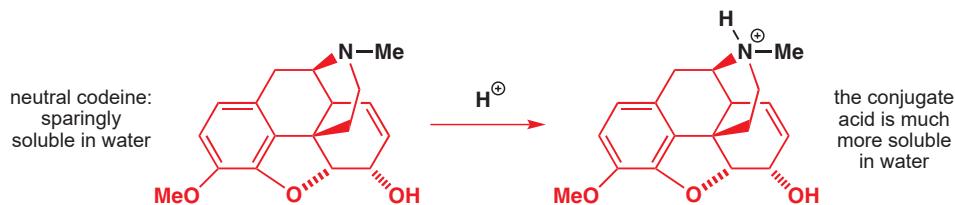
the sodium salt  
of aspirin is  
more soluble  
in water

Water is special for many reasons, and it falls into a class of solvents we call *polar protic* solvents. We will discuss other solvents in this class, as well as *polar aprotic* solvents (such as acetone and DMF) and *non-polar* solvents (such as toluene and hexane) in Chapter 12.



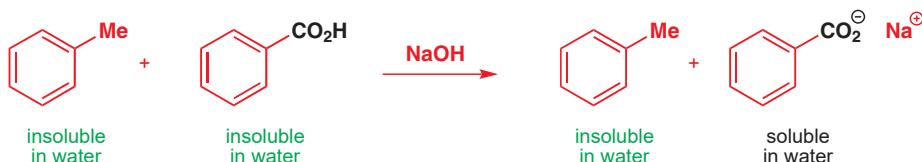
The sodium or calcium salt of 'normal' aspirin is sold as 'soluble aspirin'. But when the pH of a solution of aspirin's sodium salt is lowered, the amount of the 'normal' acidic form present increases and the solubility decreases. In the acidic environment of the stomach (around pH 1–2), soluble aspirin will be converted back to the normal acidic form and precipitate out of solution.

In the same way, organic bases such as amines can be dissolved by *lowering* the pH. Codeine (7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol) is a commonly used pain-killer. Codeine itself is not very soluble in water but it does contain a basic nitrogen atom that can be protonated to give a more soluble salt. It is usually encountered as a phosphate salt. The structure is complex, but that doesn't matter.

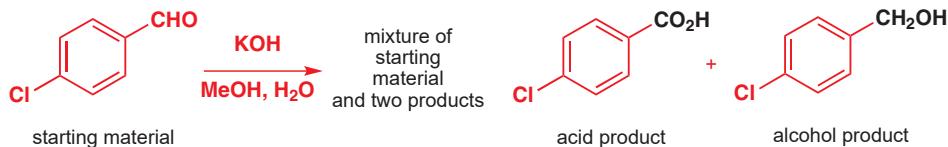


### Charged compounds can be separated by acid-base extraction

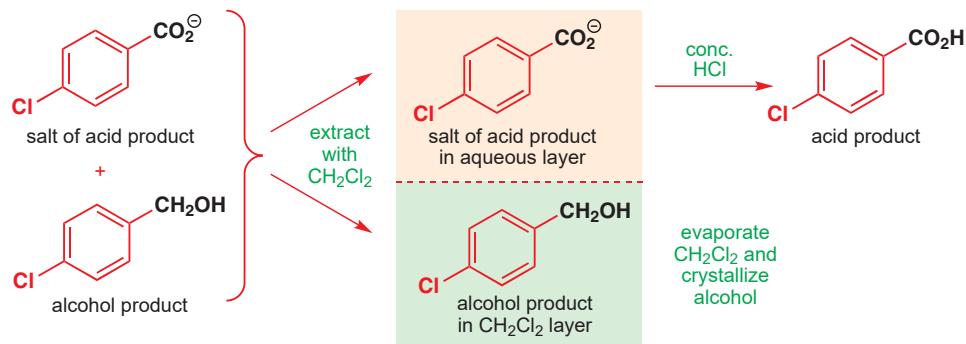
Adjusting the pH of a solution often provides an easy way to separate compounds. Separating a mixture of benzoic acid ( $\text{PhCO}_2\text{H}$ ) and toluene ( $\text{PhMe}$ ) is easy: dissolve the mixture in  $\text{CH}_2\text{Cl}_2$ , add aqueous NaOH, shake the mixture of solutions, and separate the layers. The  $\text{CH}_2\text{Cl}_2$  layer contains all the toluene. The aqueous layer contains the sodium salt of benzoic acid. Addition of HCl to the aqueous layer precipitates the insoluble benzoic acid.



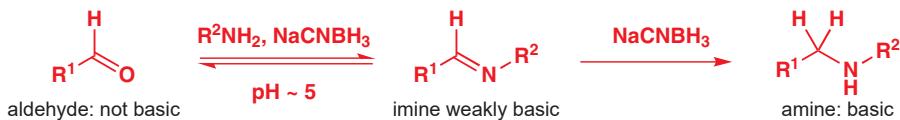
A more realistic separation is given in a modern practical book after a Cannizzaro reaction. You will meet this reaction in Chapters 26 and 39 but all you need to know now is that there are two products, formed in roughly equal quantities. Separation of these from starting material and solvent, as well as from each other, makes this a useful reaction.



The products under the basic reaction conditions are the *salt* of the acid (soluble in water) and the alcohol (not soluble in water). Extraction with dichloromethane removes the alcohol and leaves the salt in the aqueous layer along with solvent methanol and residual KOH. Rotary evaporation of the  $\text{CH}_2\text{Cl}_2$  layer gives crystalline alcohol and acidification of the aqueous layer precipitates the neutral acid.



In the same way, any basic compounds dissolved in an organic layer can be extracted by washing the layer with dilute aqueous acid and recovered by raising the pH, which will precipitate out the less soluble neutral compound. A general way to make amines is by ‘reductive amination.’ Ignore the details of this reaction for now (we come back to them in Chapter 11) but consider how the amine might be separated from starting material, by-products, and solvent.



As the reaction mixture is weakly acidic, the amine will be protonated and will be soluble in water. The starting material and intermediate (of which very little is present anyway) are soluble in organic solvents. Extracting the aqueous layer and neutralizing with NaOH gives the amine.

Whenever you do any extractions or washes in practical experiments, just stop and ask yourself: ‘What is happening here? In which layer is my compound and why?’ You will then be less likely to throw away the wrong layer (and your precious compound)!

## Acids, bases, and $pK_a$

If we are going to make use of the acid–base properties of compounds as we have just described, we are going to need a way of measuring *how acidic* or *how basic* they are. Raising the pH leads to deprotonation of aspirin and lowering the pH leads to protonation of codeine, but *how far* do we have to raise or lower the pH to do this? The measure of acidity or basicity we need is called  $pK_a$ . The value of  $pK_a$  tells us how acidic (or not) a given hydrogen atom in a compound is. Knowing about  $pK_a$  tells us, for example, that the amine product from the reaction just above will be protonated at weakly acidic pH 5, or that only a weak base (sodium hydrogen carbonate) is needed to deprotonate a carboxylic acid such as aspirin. It is also useful because many reactions proceed through protonation or deprotonation of one of the reactants (you met some examples in Chapter 6), and it is obviously useful to know what strength acid or base is needed. It would be futile to use too weak a base to deprotonate a compound but, equally, using a very strong base where a weak one would do risks the result of cracking open a walnut with a sledge hammer.

The aim of this chapter is to help you to understand *why* a given compound has the  $pK_a$  that it does. Once you understand the trends involved, you should have a good feel for the  $pK_a$  values of commonly encountered compounds and also be able to predict roughly the values for unfamiliar compounds.

### Benzoic acid preserves soft drinks

Benzoic acid is used as a preservative in foods and soft drinks (E210). Like acetic acid, it is only the acid form that is effective as a bactericide. Consequently, benzoic acid can be used as a preservative only in foodstuffs with a relatively low pH, ideally less than its  $pK_a$  of 4.2. This isn’t usually a problem: soft drinks, for example, typically have a pH of 2–3. Benzoic acid is often added as the sodium salt (E211), perhaps because this can be added to the recipe as a concentrated solution in water. At the low pH in the final drink, most of the salt will be protonated to give benzoic acid proper, which presumably remains in solution because it is so dilute.

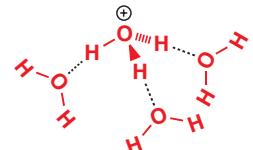
## Acidity

Let’s start with two simple, and probably familiar, definitions:

- An acid is a species having a tendency to lose a proton.
- A base is a species having a tendency to accept a proton.

'The proton is a unique chemical species, being a bare nucleus. As a consequence it has no independent existence in the condensed state and is invariably found bound by a pair of electrons to another atom.'

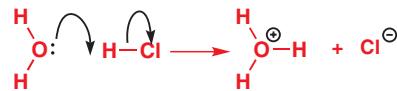
Ross Stewart, *The Proton: Applications to Organic Chemistry*, Academic Press, Orlando, 1985, p. 1.



a structure for a solvated hydronium ion in water:  
the dashed bonds represent hydrogen bonds

### An isolated proton is extremely reactive—formation of $\text{H}_3\text{O}^+$ in water

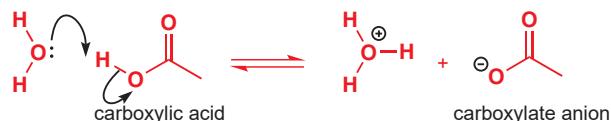
Gaseous HCl is not an acid at all—it shows no tendency to dissociate into  $\text{H}^+$  and  $\text{Cl}^-$  as the H–Cl bond is strong. But hydrochloric acid—that is, a solution of HCl in water—is a strong acid. The difference is that an isolated proton  $\text{H}^+$  is too unstable to be encountered under normal conditions, but in water the hydrogen of HCl is transferred to a water molecule and not released as a free species.



The chloride anion is the same in both cases: the only difference is that a very unstable naked proton would have to be the other product in the gas phase but a much more stable  $\text{H}_3\text{O}^+$  cation would be formed in water. In fact it's even better than that, as other molecules of water cluster round ('solvate') the  $\text{H}_3\text{O}^+$  cation, stabilizing it with a network of hydrogen bonds.

That is why HCl is an acid in water. But how strong an acid is it? This is where chloride plays a role: hydrochloric acid is a strong acid because chloride ion is a stable anion. The sea is full of it! Water is needed to reveal the acidic quality of HCl, and acidity is determined in water as the standard solvent. If we measure acidity in water, what we are really measuring is how much our acid transfers a proton to a water molecule.

HCl transfers its proton almost completely to water, and is a strong acid. But the transfer of protons to water from carboxylic acids is only partial. That is why carboxylic acids are weak acids. Unlike the reaction of HCl with water, the reaction below is an equilibrium.



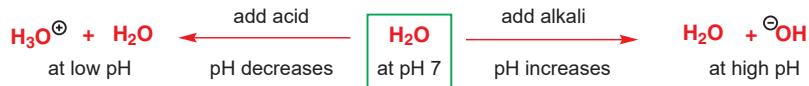
### The pH scale and $pK_a$

The amount of  $\text{H}_3\text{O}^+$  in any solution in water is described using the pH scale. pH is simply a measure of the concentration of  $\text{H}_3\text{O}^+$  on a logarithmic scale, and it is characteristic of any aqueous acid—it depends not only on what the acid is (hydrochloric, acetic, etc.) but also on how concentrated the acid is.

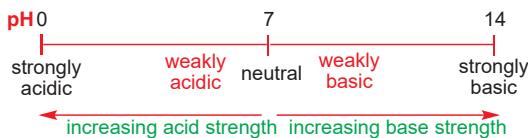
● pH is the negative logarithm of the  $\text{H}_3\text{O}^+$  concentration.

$$\text{pH} = -\log[\text{H}_3\text{O}^+]$$

You will already know that neutrality is pH 7 and that below pH 7 water is increasingly acidic while above pH 7 it is increasingly basic. At higher pH, there is little  $\text{H}_3\text{O}^+$  in the solution and more hydroxide ion, but at lower pH there is more  $\text{H}_3\text{O}^+$  and little hydroxide.



The reason that higher pH means less  $\text{H}_3\text{O}^+$  is because the arbitrary definition of pH is the negative logarithm (to the base 10) of the  $\text{H}_3\text{O}^+$  concentration. To summarize in a diagram:



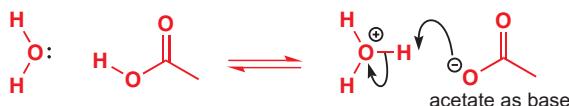
We will explain later why this scale seems to stop at pH 0 and 14—in fact these numbers are approximate, but easy to remember.

pH is used to measure the acidity of aqueous solutions, but what about the inherent tendency of an acidic compound to give up H<sup>+</sup> to water and form these acid solutions? A good way of measuring this tendency is to find the pH at which a solution contains exactly the same amount of the protonated, acidic form and its deprotonated, basic form. This number, which is characteristic of any acid, is known as the pK<sub>a</sub>. In the example just above, this would be the pH where the amount of the carboxylic acid is matched by the amount of its carboxylate salt—which happens to be at about pH 5: the pK<sub>a</sub> of acetic acid is 4.76.

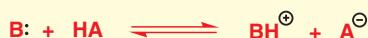
We'll come back to a more formal definition of pK<sub>a</sub> later, but first we need to look more closely at this pair of species—the protonated acid and its deprotonated, basic partner.

### Every acid has a conjugate base

Looking back at the equilibrium set up when acetic acid dissolves in water, but drawing the mechanism of the back reaction, we see acetate ion acting as a base and H<sub>3</sub>O<sup>+</sup> acting as an acid. In all equilibria involving just proton transfer a species acting as a base on one side acts as an acid on the other. We describe H<sub>3</sub>O<sup>+</sup> as the *conjugate acid* of water and water as the *conjugate base* of H<sub>3</sub>O<sup>+</sup>. In the same way, acetic acid is the conjugate acid of acetate ion and acetate ion is the conjugate base of acetic acid.



● For any acid and any base:



AH is an acid and A<sup>-</sup> is its conjugate base and B is a base and BH<sup>+</sup> is its conjugate acid. That is, **every acid has a conjugate base associated with it and every base has a conjugate acid associated with it.**

Water doesn't have to be one of the participants—if we replace water in the reaction we have been discussing with ammonia, we now have ammonia as the conjugate base of NH<sub>4</sub><sup>+</sup> (the ammonium cation) and the ammonium cation as the conjugate acid of ammonia. What is different is the position of equilibrium: ammonia is more basic than water and now the equilibrium will be well over to the right. As you will see, pK<sub>a</sub> will help us assess where equilibria like these lie.



The amino acids you met in Chapter 2 have carboxylic acid and amine functional groups within the same molecule. When dissolved in water, they transfer a proton from the CO<sub>2</sub>H group to the NH<sub>2</sub> group and form a *zwitterion*. This German term describes a double ion having positive and negative charges in the same molecule.



### Water can behave as an acid or as a base

So far we have seen water acting as a (very weak) base to form H<sub>3</sub>O<sup>+</sup>. If we added a strong base, such as sodium hydroxide, to water, the base would deprotonate the water to give hydroxide ion,

$\text{HO}^-$ , and here the water would be acting as an acid. It's amusing to notice that hydrogen gas is the conjugate acid of hydride ion, but more important to note that hydroxide ion is the conjugate base of water.



Water is a weak acid and a weak base so we need a strong acid like HCl to give much  $\text{H}_3\text{O}^+$ , and a strong base, like hydride ion, to give much hydroxide ion.

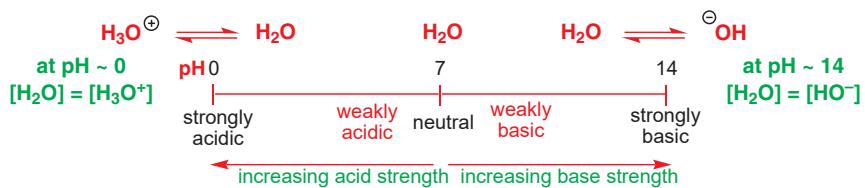
### The ionization of water

The concentration of  $\text{H}_3\text{O}^+$  ions in water is very low indeed at  $10^{-7}$  mol dm<sup>-3</sup>. Pure water at 25 °C therefore has a pH of 7.00. Hydronium ions in pure water can arise only from water protonating (and deprotonating) itself. One molecule of water acts as a base, deprotonating another that acts as an acid. For every  $\text{H}_3\text{O}^+$  ion formed, a hydroxide ion must also be formed, so that in pure water at pH 7 the concentrations of  $\text{H}_3\text{O}^+$  and hydroxide ions must be equal:  $[\text{H}_3\text{O}^+] = [\text{HO}^-] = 10^{-7}$  mol dm<sup>-3</sup>.



The product of these two concentrations is known as the *ionization constant* (or as the *ionic product*) of water,  $K_w$ , with a value of  $10^{-14}$  mol<sup>2</sup> dm<sup>-6</sup> (at 25 °C). This is a constant in aqueous solutions, so if we know the hydronium ion concentration (which we can get by measuring the pH), we also know the hydroxide concentration since the product of the two concentrations always equals  $10^{-14}$ .

So, roughly at what pH does water become mostly  $\text{H}_3\text{O}^+$  ions and at what pH mostly hydroxide ions? We can now add two additional pieces of information to the approximate chart we gave you before. At pH 7, water is almost entirely  $\text{H}_2\text{O}$ . At about pH 0, the concentrations of water and  $\text{H}_3\text{O}^+$  ions are about the same and at about pH 14, the concentrations of hydroxide ions and water are about the same.



### Acids as preservatives

Acetic acid is used as a preservative in many foods, for example pickles, mayonnaise, bread, and fish products, because it prevents bacteria and fungi growing. However, its fungicidal nature is not due to any lowering of the pH of the food-stuff. In fact, it is the undissociated acid that acts as a bactericide and a fungicide in concentrations as low as 0.1–0.3%. Besides, such a low concentration has little effect on the pH of the foodstuff anyway.

Although acetic acid can be added directly to a foodstuff (disguised as E260), it is more common to add vinegar, which contains between 10 and 15% acetic acid. This makes the product more 'natural' since it avoids the nasty 'E numbers'. Actually, vinegar has also replaced other acids used as preservatives, such as propionic (propanoic) acid (E280) and its salts (E281, E282, and E283).

### The definition of $pK_a$

When we introduced you to  $pK_a$  on p. 167, we said it is the pH at which an acid and its conjugate base are present in equal concentrations. We can now be more precise about the definition

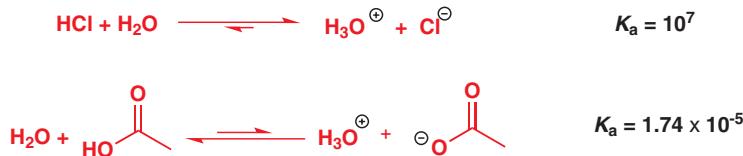
of  $pK_a$ ,  $pK_a$  is the log (to the base ten) of the equilibrium constant for the dissociation of the acid. For an acid HA this is:



The concentration of water is ignored in the definition because it is also constant (at 25 °C).

Because of the minus sign in the definition (it's there too in the definition of pH) the lower the  $pK_a$  the larger the equilibrium constant and the stronger the acid. You may find the way we introduced  $pK_a$  more helpful as a concept for visualizing  $pK_a$ : any acid is half dissociated in a solution whose pH matches the acid's  $pK_a$ . At a pH above the  $pK_a$  the acid exists largely as its conjugate base ( $\text{A}^-$ ) but at a pH below the  $pK_a$  the acid largely exists as HA.

With  $pK_a$  we can put figures to the relative strengths of hydrochloric and acetic acid we introduced earlier. HCl is a much stronger acid than acetic acid: the  $pK_a$  of HCl is around -7 compared to 4.76 for acetic acid. This tells us that in solution  $K_a$  for hydrogen chloride is  $10^7 \text{ mol dm}^{-3}$ . This is an enormous number: only one molecule in 10,000,000 is not dissociated, so it is essentially fully dissociated. But  $K_a$  for acetic acid is only  $10^{-4.76} = 1.74 \times 10^{-5} \text{ mol dm}^{-3}$  so it is hardly dissociated at all: only a few molecules in every million of acetic acid are present as the acetate ion.

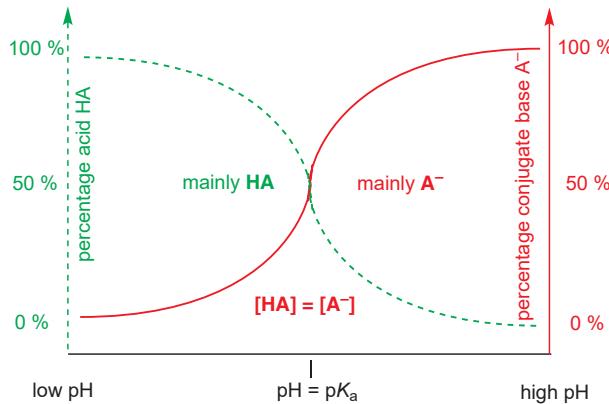


How concentrated is water? One mole of pure water has a mass of 18 g and occupies 18 cm<sup>3</sup>. So, in 1 dm<sup>3</sup>, there are  $1000/18 = 55.56$  mol. Water is a  $55.56 \text{ mol dm}^{-3}$  solution of water...in water.

What about the  $pK_a$  of water? You know the figures already:  $K_a$  for water is  $[\text{H}_3\text{O}^+] [\text{HO}^-]/[\text{H}_2\text{O}] = 10^{-14}/55.5$ . So  $pK_a = -\log[10^{-14}/55.5] = 15.7$ . Now you see why water isn't really quite half dissociated at pH 14—the concentration of water in the equation means that the two ends of the scale on p. 168 are not at 0 and 14, but at -1.7 and 15.7.

### A graphical description of the $pK_a$ of acids and bases

For both cases, adjusting the pH alters the proportions of the acid form and of the conjugate base. The graph plots the concentration of the free acid AH (green curve) and the ionized conjugate base A<sup>-</sup> (red curve) as percentages of the total concentration as the pH is varied. At low pH the compound exists entirely as AH and at high pH entirely as A<sup>-</sup>. At the  $pK_a$  the concentration of each species, AH and A<sup>-</sup>, is the same. At pHs near the  $pK_a$  the compound exists as a mixture of the two forms.



Now we have established why you need to understand acids and bases, we must move on to consider why some acids are stronger than other acids and some bases stronger than other bases. To do this we must be able to estimate the  $pK_a$  of common classes of organic compounds.

You do not need to learn exact figures for  $pK_a$  values, but you will certainly need to develop a feel for approximate values—we will guide you towards which figures are worth learning and which you can leave to be looked up when you need them.

### An acid's $pK_a$ depends on the stability of its conjugate base

The stronger the acid, the easier it is to ionize, which means that it must have a stable conjugate base. Conversely, a weak acid is reluctant to ionize because it has an *unstable* conjugate base. The other side of this coin is that unstable anions  $A^-$  make strong bases and their conjugate acids AH are weak acids.

#### ● Acid and conjugate base strength

**The stronger the acid HA, the weaker its conjugate base  $A^-$ .**

**The stronger the base  $A^-$ , the weaker its conjugate acid AH.**

For example, hydrogen iodide has a very low  $pK_a$ , about  $-10$ . This means that HI is a strong enough acid to protonate almost anything. Its conjugate base, iodide ion, is therefore not basic at all—it will not deprotonate anything. A very powerful base is methyl lithium, MeLi. Although it is actually a covalent compound, as we discuss in Chapter 9, for the purpose of the discussion here you can think of MeLi as  $\text{CH}_3\text{Li}^+$ .  $\text{CH}_3^-$  can accept a proton to become neutral methane,  $\text{CH}_4$ . Methane is therefore the conjugate acid. Clearly, methane isn't at all acidic—its  $pK_a$  is estimated to be 48. The table below gives a few inorganic compounds and their approximate  $pK_a$  values.

The approximate  $pK_a$  values of some inorganic compounds

Acid	$pK_a$	Conjugate base	Acid	$pK_a$	Conjugate base	Acid	$pK_a$	Conjugate base
$\text{H}_2\text{SO}_4$	-3	$\text{HSO}_4^-$	$\text{H}_3\text{O}^+$	-1.7	$\text{H}_2\text{O}$	$\text{NH}_4^+$	9.2	$\text{NH}_3$
HCl	-7	$\text{Cl}^-$	$\text{H}_2\text{O}$	15.7	$\text{HO}^-$	$\text{NH}_3$	33	$\text{NH}_2^-$
HI	-10	$\text{I}^-$	$\text{H}_2\text{S}$	7.0	$\text{HS}^-$			

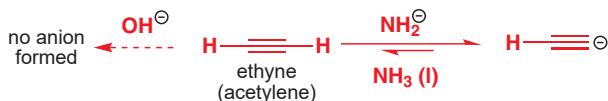
Notice that the lower down the periodic table we go, the stronger the acid. Notice also that oxygen acids are stronger than nitrogen acids. We have also put down more exact  $pK_a$  values for water but you need remember only the approximate values of 0 and 14. Over the next few pages we shall be considering the reasons for these differences in acid strength but we are first going to consider the simple consequences of mixing acids or bases of different strengths. Notice the vast range covered by  $pK_a$  values: from around  $-10$  for HI to nearly 50 for methane. This corresponds to a difference of  $10^{60}$  in the equilibrium constant.

### The choice of solvent limits the $pK_a$ range we can use

In water, we can measure the  $pK_a$  of an acid only if the acid does not completely protonate water to give  $\text{H}_3\text{O}^+$  or completely deprotonate it to give  $\text{HO}^-$ . We are restricted roughly to pH -1.7 to 15.7, beyond which water is more than 50% protonated or deprotonated. The strength of acids or bases we can use in any solvent is limited by the acidity and basicity of the solvent itself. Think of it this way: say you want to remove the proton from a compound with a high  $pK_a$ , say 25–30. It would be impossible to do this in water since the strongest base we can use is hydroxide. If you add a base stronger than hydroxide, it won't deprotonate your compound, it will just deprotonate water and make hydroxide anyway. Likewise, acids stronger than  $\text{H}_3\text{O}^+$  can't exist in water: they just protonate water completely to make  $\text{H}_3\text{O}^+$ . If you do need a stronger base than  $\text{OH}^-$  (or a stronger acid than  $\text{H}_3\text{O}^+$ , but this is rarer) you must use a different solvent.

Let's take acetylene as an example. Acetylene (ethyne) has  $pK_a$  25. This is remarkably low for a hydrocarbon (see below for why) but, even so, hydroxide (the strongest base we could have in aqueous solution,  $pK_a$  15.7) would establish an equilibrium where only 1 in  $10^{9.3}$  ( $10^{15.7}/10^{25}$ ), or about 1 in 2 billion, ethyne molecules are deprotonated. We can't use a stronger base than hydroxide, since, no matter what strong base we dissolve in water, we will only at best get hydroxide ions. So, in order to deprotonate ethyne to any appreciable extent, we must use a different solvent—one that does not have a  $pK_a$  less than 25.

Conditions often used to do this reaction are sodium amide ( $\text{NaNH}_2$ ) in liquid ammonia. Using the  $pK_a$  values of  $\text{NH}_3$  (ca. 33) and ethyne (25) we would estimate an equilibrium constant for this reaction of  $10^8 (10^{-25}/10^{-33})$ —well over to the right. Amide ions can be used to deprotonate alkynes.



Since we have an upper and a lower limit on the strength of an acid or base that we can use in water, this poses a bit of a problem: how do we know that the  $pK_a$  for  $\text{HCl}$  is more negative than that of  $\text{H}_2\text{SO}_4$  if both completely protonate water? How do we know that the  $pK_a$  of methane is greater than that of ethyne since both the conjugate bases fully deprotonate water? The answer is that we can't simply measure the equilibrium for the reaction in water—we can do this only for  $pK_a$  values that fall between the  $pK_a$  values of water itself. Outside this range,  $pK_a$  values are determined in other solvents and the results are extrapolated to give a value for what the  $pK_a$  in water might be.

Because the  $pK_a$  values for very strong acids and bases are so hard to determine, you will find that they often differ in different texts—sometimes the values are no better than good guesses! However, while the absolute values may differ, the relative values (which is the important thing because we need only a rough guide) are usually consistent.

## Constructing a $pK_a$ scale

We now want to look at ways to rationalize, and estimate, the different  $pK_a$  values for different compounds—we wouldn't want to have to memorize all the values. You will need to get a feel for the  $pK_a$  values of different compounds and if you know what factors affect them it will make it much easier to predict an approximate  $pK_a$  value, or at least understand why a given compound has the  $pK_a$  value that it does.



A number of factors affect the strength of an acid  $\text{AH}$ . These include:

1. The intrinsic stability of the conjugate base, anion  $\text{A}^-$ . Stability can arise by having the negative charge on an electronegative atom or by spreading the charge over several atoms (delocalization) groups. Either way, the more stable the conjugate base, the stronger the acid  $\text{HA}$ .
2. Bond strength A–H. Clearly, the easier it is to break this bond, the stronger the acid.
3. The solvent. The better the solvent is at stabilizing the ions formed, the easier it is for the reaction to occur.

### • Acid strength

The most important factor in the strength of an acid is the stability of the conjugate base—the more stable the conjugate base, the stronger the acid.

An important factor in the stability of the conjugate base is which element the negative charge is on—the more electronegative the element, the more stable the conjugate base.

## The negative charge on an electronegative element stabilizes the conjugate base

The  $pK_a$  values for the ‘hydrides’ of the first row elements  $\text{CH}_4$ ,  $\text{NH}_3$ ,  $\text{H}_2\text{O}$ , and  $\text{HF}$  are about 48, 33, 16, and 3, respectively. This trend is due to the increasing electronegativities across the period:  $\text{F}^-$  is much more stable than  $\text{CH}_3^-$  because fluorine is much more electronegative than carbon.

Acid	Conjugate base	$pK_a$
methane $\text{CH}_4$	$\text{CH}_3^-$	~48
ammonia $\text{NH}_3$	$\text{NH}_2^-$	~33
water $\text{H}_2\text{O}$	$\text{HO}^-$	~16
HF	$\text{F}^-$	3

### Weak A–H bonds make stronger acids

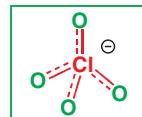
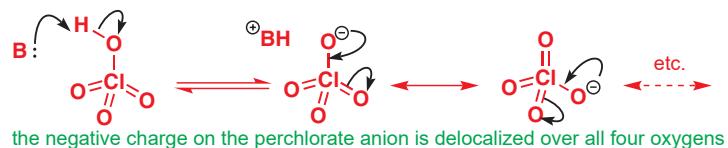
However, on descending group VII (group 17), the  $pK_a$  values for HF, HCl, HBr, and HI decrease: 3, -7, -9, and -10. Since the electronegativities decrease on descending the group we might expect an increase in  $pK_a$ . The decrease is due to the weakening bond strengths on descending the group and to some extent the way in which the charge can be spread over the increasingly large anions.

Acid	Conjugate base	$pK_a$
HF	fluoride ion $F^-$	3
HCl	chloride ion $Cl^-$	-7
HBr	bromide ion $Br^-$	-9
HI	iodide ion $I^-$	-10

### Delocalization of the negative charge stabilizes the conjugate base

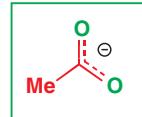
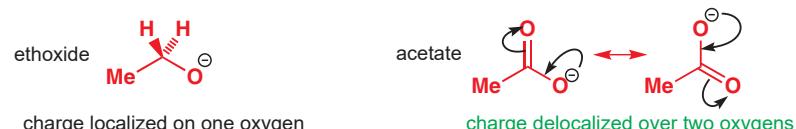
The acids  $HClO$ ,  $HClO_2$ ,  $HClO_3$ , and  $HClO_4$  have  $pK_a$  values 7.5, 2, -1, and about -10, respectively. In each case the acidic proton is on an oxygen attached to chlorine, that is, *we are removing a proton from the same environment in each case*. Why then is perchloric acid,  $HClO_4$ , some 17 orders of magnitude stronger in acidity than hypochlorous acid,  $HClO$ ? Once the proton is removed, we end up with a negative charge on oxygen. For hypochlorous acid, this is localized on the one oxygen. With each successive oxygen, the charge can be more delocalized, and this makes the anion more stable. For example, with perchloric acid, the negative charge can be delocalized over all four oxygen atoms.

Acid	Conjugate base	$pK_a$
hypochlorous acid $HO-Cl$	$ClO^-$	7.5
chlorous acid $HO-ClO$	$ClO_2^-$	2
chloric acid $HO-ClO_2$	$ClO_3^-$	-1
perchloric acid $HO-ClO_3$	$ClO_4^-$	-10

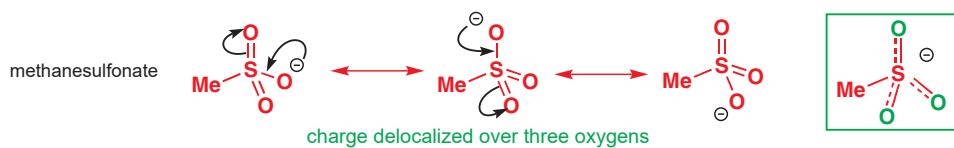


That the charge is spread out over all the oxygen atoms equally is shown by electron diffraction studies: whereas perchloric acid has two types of Cl–O bond, one 163.5 pm and the other three 140.8 pm long, in the perchlorate anion all Cl–O bond lengths are the same, 144 pm, and all O–Cl–O bond angles are  $109.5^\circ$ . Just to remind you: these delocalization arrows do not indicate that the charge is actually moving from atom to atom. We discussed this in Chapter 7. These structures simply show that the charge is spread out in the molecular orbitals and mainly concentrated on the oxygen atoms.

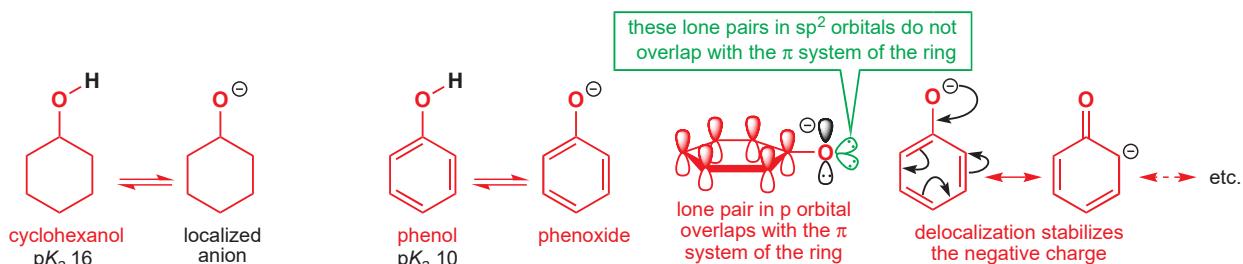
Looking at some organic acids, we might expect alcohols to have a  $pK_a$  not far from that of water, and for ethanol that is correct ( $pK_a$  15.9). If we allow the charge in the conjugate base to be delocalized over two oxygen atoms, as in acetate, acetic acid is indeed a much stronger acid ( $pK_a$  4.8). The difference is huge: the conjugation makes acetic acid about  $10^{10}$  times stronger.



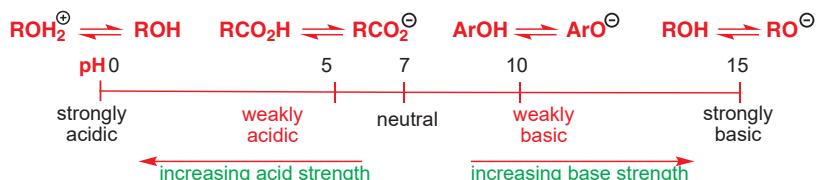
It is even possible to have a negative charge of an organic acid delocalized over *three* atoms—as in the anions of the sulfonic acids. Methanesulfonic acid has a  $pK_a$  of -1.9.



Even delocalization into a hydrocarbon part of the molecule increases acid strength. In phenol, PhOH, the OH group is directly attached to a benzene ring. On deprotonation, the negative charge can again be delocalized, not onto other oxygen atoms but into the aromatic ring itself. The effect of this is to stabilize the phenoxide anion relative to the conjugate base of cyclohexanol, where no delocalization is possible, and this is reflected in the  $pK_a$  values of the two compounds: 10 for phenol but 16 for cyclohexanol.



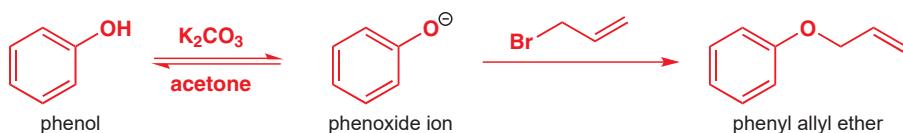
So now we can expand our chart of acid and base strengths to include the important classes of alcohols, phenols, and carboxylic acids. They conveniently, and memorably, have  $pK_a$  values of about 0 for the protonation of alcohols, about 5 for the deprotonation of carboxylic acids, about 10 for the deprotonation of phenols, and about 15 for the deprotonation of alcohols. The equilibria above each  $pK_a$  shows that at approximately that pH, the two species each form 50% of the mixture. You can see that carboxylic acids are weak acids, alkoxide ions ( $\text{RO}^-$ ) are strong bases, and that it will need a strong acid to protonate an alcohol.



■ equilibrium arrow:   
 delocalization arrow   
 Reminder: the equilibrium arrows mean two interconverting compounds.  
 The double-headed arrow means two ways of drawing a conjugated structure.

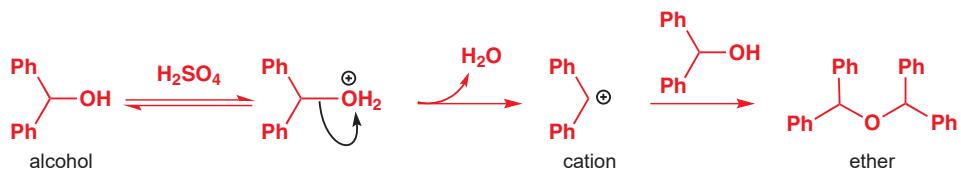
■ It is worthwhile learning these approximate values.

If we need to make the anion of a phenol, a base such as NaOH will be good enough, but if we want to make an anion from an alcohol, we need a stronger base. Vogel (p. 986) suggests potassium carbonate ( $\text{K}_2\text{CO}_3$ ) is strong enough to make an ether from phenol. The base strength of carbonate anion is about the same as that of phenoxide ion ( $\text{PhO}^-$ ) so the two will be in equilibrium but enough phenoxide ion will be present for the reaction.

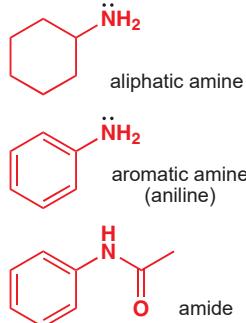


On the other hand, if we want to make the OH group into a good leaving group, we need to protonate it and a very strong acid will be needed. Sulfuric acid is used to make ethers from alcohols. Protonation of the OH groups leads to loss of water and formation of a cation. This reacts with more alcohol to give the ether. There is another example of this reaction in Chapter 5.

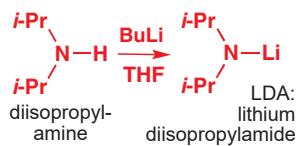
■ As you will discover in Chapters 10 and 15, a *leaving group* is simply a functional group that will leave the molecule, taking with it the pair of electrons that formed the bond. Leaving groups may be anions, such as bromide  $\text{Br}^-$ , or protonated groups such as the protonated alcohol in this example, which leaves as water.



## Nitrogen compounds as acids and bases



The most important organic nitrogen compounds are amines and amides. Amine nitrogens can be joined to alkyl or aryl groups (in which case the amines are called anilines). They all have lone pairs on nitrogen and may have hydrogen atoms on nitrogen too. As nitrogen is less electronegative than oxygen, you should expect amines to be less acidic and more basic than alcohols. And they are. The  $pK_a$  values for the protonated amines are about 10 (this value is about 0 for water and alcohol) and the  $pK_a$  values for amines acting as acids are very high, something like 35 (compared with about 15 for an alcohol). So ammonium salts are about as acidic as phenols and amines will be protonated at pH 7 in water. This is why amino acids (p. 167) exist as zwitterions in water.

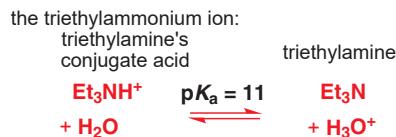


Removing a proton from an amine is very difficult as the anion (unfortunately called an ‘amide’ anion) is very unstable and very basic. The only way to succeed is to use a very strong base, usually an alkylolithium. The ‘anion’ then has an N–Li bond and is soluble in organic solvents. This example, known as LDA, is commonly used as a strong base in organic chemistry.

The basicity of amines as neutral compounds is measured by the  $pK_a$  of their conjugate acids—so, for example, the  $pK_a$  associated with the protonation of triethylamine, a commonly used tertiary amine, is 11.0.

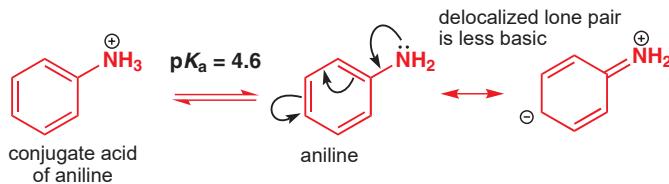
### The ‘ $pK_a$ s’ of bases

Chemists often say things like ‘the  $pK_a$  of triethylamine is about 10.’ (It’s actually 11.0 but 10 is a good number to remember for typical amines). This may surprise you as triethylamine has no acidic hydrogens. What they mean is of course this: ‘the  $pK_a$  of the conjugate acid of triethylamine is about 10.’ Another way to put this is to write ‘the  $pK_{aH}$  of triethylamine is about 10.’ The subscript ‘ $aH$ ’ refers to the conjugate acid.

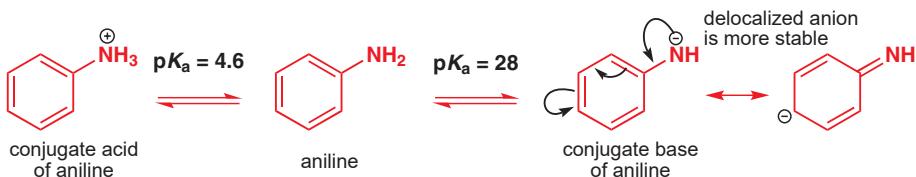


It's OK to say 'the  $pK_a$  of triethylamine is about 10'  
as long as you understand that what is really meant is  
'the  $pK_a$  of the triethylammonium ion is about 10',  
which can also be expressed thus:  
'the  $pK_{aH}$  of triethylamine is about 10'

When a molecule is both acidic and basic, as for example aniline, it is important to work out which  $pK_a$  is meant as again chemists will loosely refer to ‘the  $pK_a$  of aniline is 4.6’ when they mean ‘the  $pK_a$  of the conjugate acid of aniline is 4.6.’ Aniline is much less basic than ammonia or triethylamine because the lone pair on nitrogen is conjugated into the ring and less available for protonation.

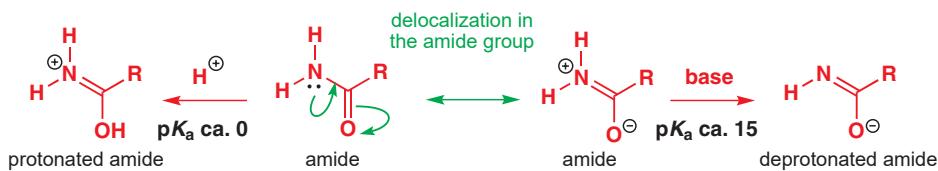
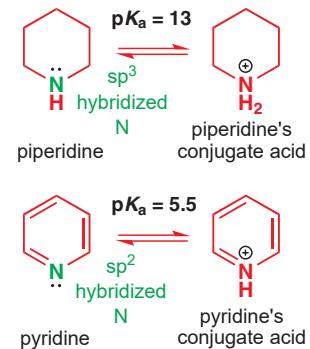


But for the same reason, aniline is also more acidic than ammonia ( $pK_a$  33) and has a genuine  $pK_a$  in which one of the protons on nitrogen is lost. So we can say correctly that 'the  $pK_a$  of aniline is about 28.' Just be careful to check which  $pK_a$  is meant in such compounds. The full picture is:



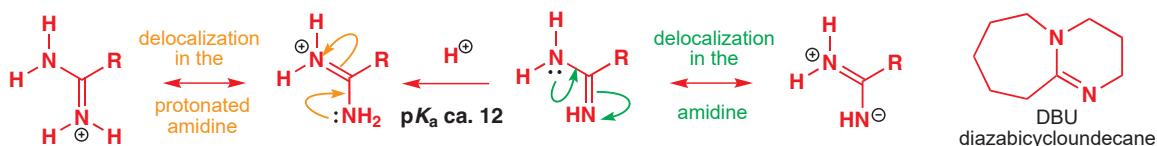
The  $pK_a$  associated for protonation of piperidine, a typical secondary amine, is about 13. The equivalent  $pK_a$  for protonation of pyridine—a compound with a similar heterocyclic structure, but with its lone pair in an  $sp^2$  rather than an  $sp^3$  orbital, is only 5.5: pyridine is a weaker base than piperidine (its conjugate acid is a stronger acid). Nitriles, whose lone pair is  $sp$  hybridized, are not basic at all. Lone pairs with more p character ( $sp^3$  orbitals are  $3/4$  p, while  $sp$  orbitals are  $1/2$  p) are higher in energy—they spend more time further from the nucleus—and are therefore more basic.

Amides are very different because of the delocalization of the lone pair into the carbonyl group. This makes amides more acidic but less basic and protonation occurs on oxygen rather than nitrogen. Amides have  $pK_a$  values of around 15 when they act as acids, making them some  $10^{10}$  times more acidic than amines. The  $pK_a$  of protonated amides is around 0, making them some  $10^{10}$  times weaker as bases.

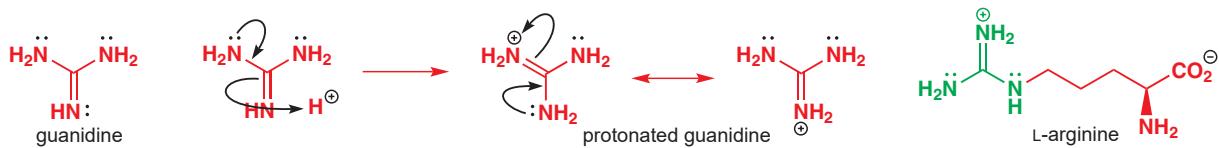


→ Delocalization in amides was discussed on p. 155.

If we replace the carbonyl oxygen atom in an amide by nitrogen we get an amidine. Amidines are conjugated, like amides, but unlike amides they are *stronger* bases than amines, by about 2–3 pK<sub>a</sub> units, because the two nitrogens work together to donate electron density onto each other. The bicyclic amidine DBU is often used as a strong organic base (see Chapter 17).



But the champions are the guanidines, with three nitrogens all donating lone pair electrons at once. A guanidine group (shown in green) makes arginine the most basic of the amino acids.

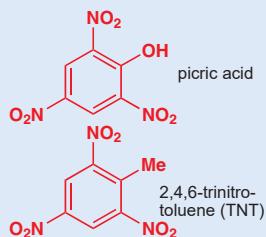


## Substituents affect the $pK_a$

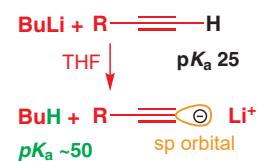
Substituents that are conjugated with the site of proton gain or loss, and even substituents that are electronegative but not conjugating, can have significant effects on  $pK_a$  values. Phenol has  $pK_a$  10 but phenols with anions stabilized by extra conjugation can have much lower  $pK_a$ s.

### Picric acid is a very acidic phenol

2,4,6-Trinitrophenol's more common name, picric acid, reflects the strong acidity of this compound ( $pK_a$  0.7 compared to phenol's 10.0). Picric acid used to be used in the dyeing industry but is little used now because it is also a powerful explosive when dry. (Compare its structure with that of TNT!)

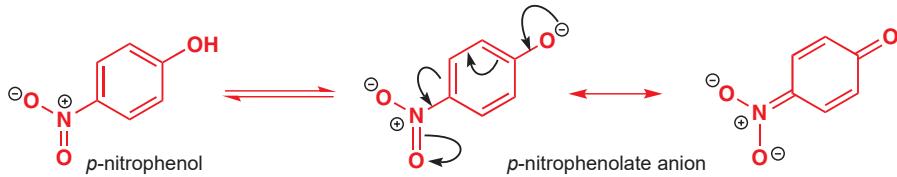


If you draw a carboxylate anion you will find that it is impossible to stabilize its negative charge any further by conjugation, other than between the two oxygens.

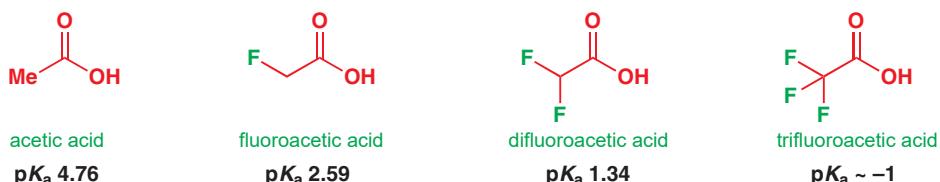


If you don't see why this is, think about the shapes of an s and a p orbital: the nucleus sits in the node of a p orbital, but in an s orbital the nucleus is in a region of high electron density. The more s character a negative charge has, the closer the electron density is to the nucleus, and the more stable it is.

One nitro group, as in *p*-nitrophenol, lowers the  $pK_a$  to 7.14, nearly a thousand-fold increase in acidity. This is because the negative charge on oxygen is delocalized into the very electrone-withdrawing nitro group. By contrast 4-chlorophenol, with only inductive withdrawal in the C–Cl bond, has  $pK_a$  9.38, hardly different from phenol itself.



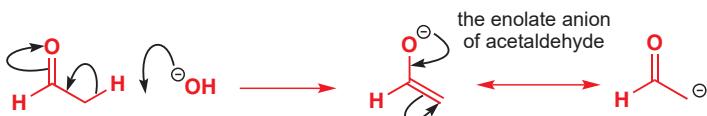
Inductive effects of nearby electronegative atoms can also have marked effects on the  $pK_a$  of acids. Adding fluorines to acetic acid reduces the  $pK_a$  from about 5 by smallish steps. Trifluoroacetic acid (TFA) is a very strong acid indeed, and is commonly used as a convenient strong acid in organic reactions. Inductive effects occur by polarization of  $\sigma$  bonds when the atom at one end is more electronegative than at the other. Fluorine is much more electronegative than carbon (indeed, F is the most electronegative element of all) so each  $\sigma$  bond is very polarized, making the carbon atom more electropositive and stabilizing the carboxylate anion.



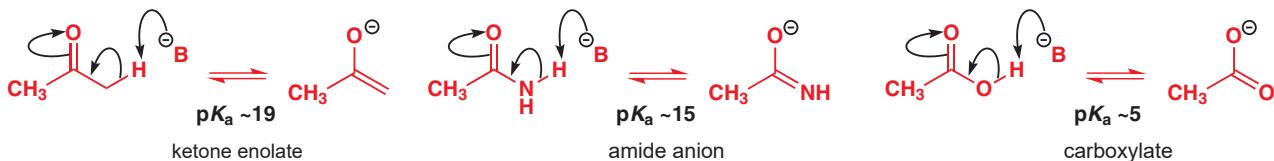
## Carbon acids

Hydrocarbons are not acidic. We have already established that methane has a  $pK_a$  of about 48 (p. 170 above)—it's essentially impossible to deprotonate. Alkylolithiums are for this reason among the strongest bases available. But some hydrocarbons *can* be deprotonated, the most important example being alkynes—you saw on p. 171 that acetylene has a  $pK_a$  of 25 and can be deprotonated by  $\text{NH}_2^-$  (as well as other strong bases such as  $\text{BuLi}$ ). The difference is one of hybridization—an idea we introduced with the nitrogen bases above. Making the acetylidy anion, whose negative charge resides in an sp orbital, is much easier than making a methyl anion, with a negative charge in an  $\text{sp}^3$  orbital, because electrons in sp orbitals spend a lot of their time closer to the nucleus than electrons in  $\text{sp}^3$  orbitals.

C–H bonds can be even more acidic than those of acetylene if stabilization of the resulting anion is possible by *conjugation*. Conjugation with a carbonyl group has a striking effect. One carbonyl group brings the  $pK_a$  down to 13.5 for acetaldehyde so that even hydroxide ion can produce the anion. You will discover in Chapter 20 that we call this the 'enolate anion' and that the charge is mostly on oxygen, although the anion can be drawn as a carbanion.

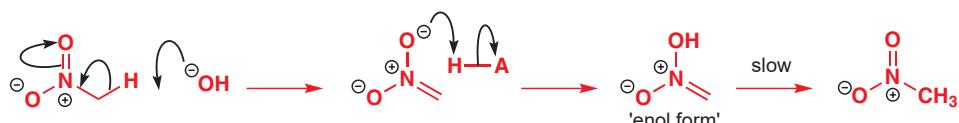


It is interesting to compare the strengths of the carbon, nitrogen, and oxygen acids of similar structure below. The ketone (acetone) is of course least acidic, the amide is more acidic, and the carboxylic acid most acidic. The oxyanion conjugate bases are all delocalized but delocalization onto a second very electronegative oxygen atom is much (~10 pH units) more effective than delocalization onto nitrogen, which is 4 pH units more effective than delocalization onto carbon.



Nevertheless, the effect of conjugation on the carbon acid compared with methane is enormous (~30 pH units) and brings proton removal from carbon within the range of accessible bases

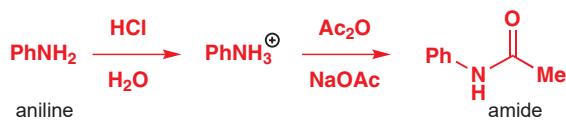
The nitro group is even more effective: nitromethane, with a  $pK_a$  of 10, dissolves in aqueous NaOH. The proton is removed from carbon, but the negative charge in the conjugate base is on oxygen. The big difference is that the nitrogen atom has a positive charge throughout. If the anion is protonated in water by some acid (HA) the ‘enol’ form of nitromethane is the initial product and this slowly turns into nitromethane itself. Whereas proton transfers between electronegative atoms (O, N, etc.) are fast, proton transfers to or from carbon can be slow.



Carbon acids are very important in organic chemistry as they allow us to make carbon–carbon bonds and you will meet many more of them in later chapters of this book.

### Why do we need to compare acid strengths of O and N acids?

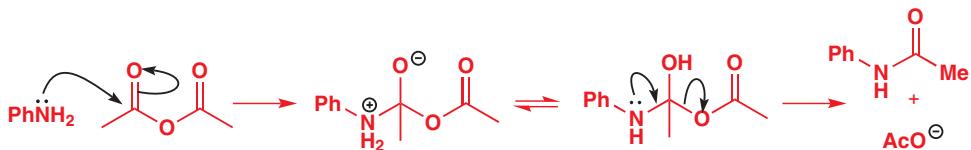
The rates of nucleophilic addition to carbonyl groups that you met in Chapter 6 depend on the basicity of nucleophiles. As nitrogen bases are much stronger than oxygen bases (or, if you prefer, ammonium ions are much weaker acids than  $H_3O^+$ ), amines are also much better nucleophiles than water or alcohols. This is dramatically illustrated in an amide synthesis from aniline and acetic anhydride in aqueous solution.



Aniline is not very soluble in water but addition of HCl converts it into the soluble cation by protonation at nitrogen. The solution is now warmed and equal amounts of acetic anhydride and aqueous sodium acetate are added. The  $pK_a$  of acetic acid is about 5, as is the  $pK_a$  of  $\text{PhNH}_3^+$ , so an equilibrium is set up and the solution now contains these species:



The only electrophile is acetic anhydride, with its two electrophilic carbonyl groups. The nucleophiles available are water, aniline, and acetate. Water is there in great abundance and does react with acetic anhydride but can't compete with the other two as they are more basic (by about  $10^5$ ). If acetate attacks the anhydride, it simply regenerates acetate. But if aniline attacks, the amide is formed as acetate is released.



The isolation of the product is easy as the amide is insoluble in water and can be filtered off. Environmental considerations suggest that we should not use organic solvents so much and should use water when possible. If we have some idea about  $pK_a$ s we can estimate whether water will interfere in a reaction we are planning and decide whether it is a suitable solvent or not. It is even possible to acylate amines with the more reactive acid chlorides in aqueous solution, and we will return in detail to acylation reactions such as these in Chapter 10.

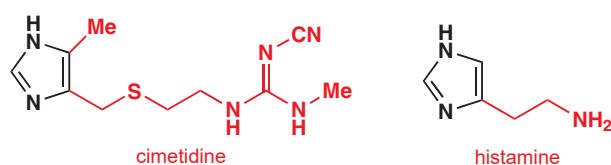
## $pK_a$ in action—the development of the drug cimetidine

Histamine is an agonist in the production of gastric acid. It binds to specific sites (receptor sites) in the stomach cells and triggers the production of gastric acid (mainly HCl).

An antagonist works by binding to the receptor but not stimulating acid secretion. It therefore inhibits acid secretion by blocking the receptor sites.

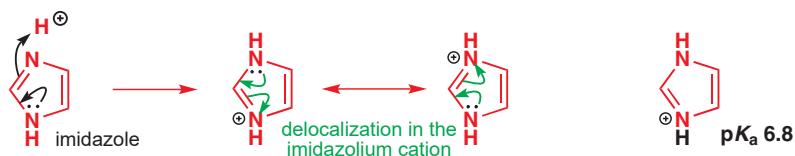
When the drug was invented, the company was called Smith, Kline and French (SKF) but after a merger with Beechams the company became SmithKline Beecham (SB). SB and GlaxoWelcome later merged to form GlaxoSmithKline (GSK). Things may have changed further by the time you read this book.

The development of the anti-peptic ulcer drug cimetidine gives a fascinating insight into the important role of  $pK_a$  in chemistry. Peptic ulcers are a localized erosion of the mucous membrane, resulting from overproduction of gastric acid in the stomach. One of the compounds that controls the production of the acid is histamine. (Histamine is also responsible for the symptoms of hay fever and allergies.)



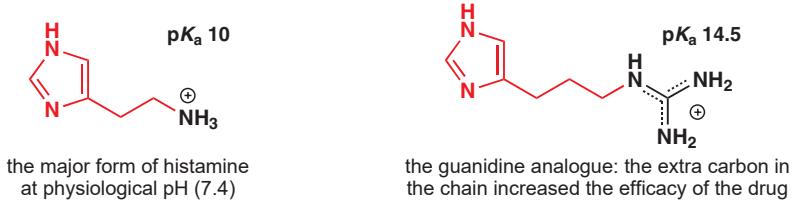
Histamine works by binding into a receptor in the stomach lining and stimulating the production of acid. What the developers of cimetidine at Smith, Kline and French wanted was a drug that would bind to these receptors without activating them and thereby prevent histamine from binding but not stimulate acid secretion itself. Unfortunately, the antihistamine drugs successfully used in the treatment of hay fever did not work—a different histamine receptor was involved.

Notice that cimetidine and histamine both have the same nitrogen-containing ring (shown in black) as part of their structures. This ring is known as an imidazole—imidazole itself is quite a strong base whose protonated form is delocalized as shown below. This is not coincidence—cimetidine's design was centred around the structure of histamine.



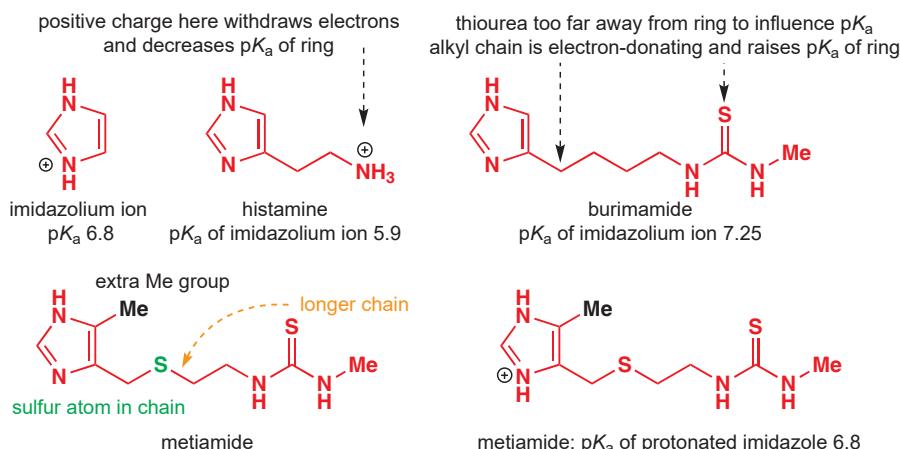
Guanidine was introduced to you on p. 175.

In the body, most histamine exists as a salt, being protonated on the primary amine and the early compounds modelled this. The guanidine analogue was synthesized and tested to see if it had any antagonistic effect (that is, if it could bind in the histamine receptors and prevent histamine binding). It did bind but unfortunately it acted as an *agonist* rather than an *antagonist* and stimulated acid secretion rather than blocking it. Since the guanidine analogue has a  $pK_a$  even greater than histamine (about 14.5 compared to about 10), it is effectively all protonated at physiological pH.

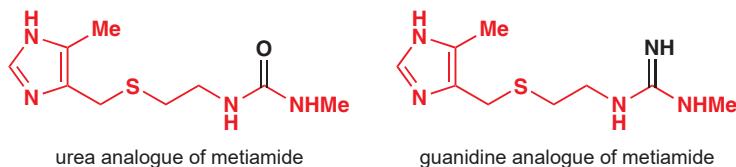


Remember that amidines and guanidines, p. 175, are basic but that amides aren't. The thiourea, and indeed a urea, is more like an amide.

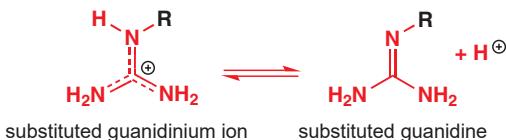
The agonistic behaviour of the drug clearly had to be suppressed. The thought occurred to the chemists that perhaps the positive charge made the compound agonistic, and so a polar but much less basic compound was sought. Eventually, they came up with burimamide. The most important change is the replacement of the C=NH in the guanidine compound by C=S. Now instead of a guanidine we have a thiourea, which is much less basic. Other adjustments were to increase the chain length, insert a second sulfur atom on the chain, and add methyl groups to the thiourea and the imidazole ring, to give metiamide with increased efficacy.



The new drug, metiamide, was ten times more effective than burimamide when tested in humans. However, there was an unfortunate side-effect: in some patients: the drug caused a decrease in the number of white blood cells, leaving the patient open to infection. This was eventually traced back to the thiourea group. The sulfur had again to be replaced by oxygen, to give a normal urea and, just to see what would happen, by nitrogen to give another guanidine.



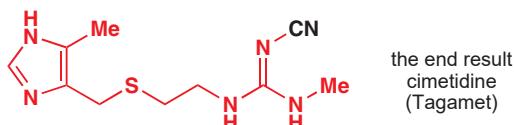
Neither was as effective as metiamide but the important discovery was that the guanidine analogue no longer showed the agonistic effects of the earlier guanidine. Of course, the guanidine would also be protonated so we had the same problem we had earlier—how to decrease the pK<sub>a</sub> of the guanidinium ion. A section of this chapter considered the effect of electron-withdrawing groups on pK<sub>a</sub> and showed that they make a base less basic. This was the approach now adopted—the introduction of electron-withdrawing groups on to the guanidine to lower its pK<sub>a</sub>. The table below shows the pK<sub>a</sub>s of various substituted guanidinium ions.



pK<sub>a</sub>s of substituted guanidinium ions

R	H	Ph	CH <sub>3</sub> CO	NH <sub>2</sub> CO	MeO	CN	NO <sub>2</sub>
pK <sub>a</sub>	14.5	10.8	8.33	7.9	7.5	-0.4	-0.9

Clearly, the cyano and nitro-substituted guanidines would not be protonated at all. These were synthesized and found to be just as effective as metiamide but without the side-effects. Of the two, the cyanoguanidine compound was slightly more effective and this was developed and named ‘cimetidine’.



The development of cimetidine by Smith, Kline and French from the very start of the project up to its launch on the market took 13 years. This enormous effort was well rewarded—Tagamet (the trade name of the drug cimetidine) became the best-selling drug in the world and the first to gross more than one billion dollars per annum. Thousands of ulcer patients worldwide no longer had to suffer pain, surgery, or even death. The development of cimetidine followed a rational approach based on physiological and chemical principles and it was for this that one of the scientists involved, Sir James Black, received a share of the 1988 Nobel Prize for Physiology or Medicine. None of this would have been possible without an understanding of  $pK_a$ s.

## Lewis acids and bases

Johannes Nicolaus Brønsted (1879–1947) was a Danish physical chemist who, simultaneous with Thomas Lowry, introduced the protic theory of acid–base reactions in 1923.

All the acids and bases we have been discussing so far have been protic, or *Brønsted*, acids and bases. In fact, the definition of an acid and a base we gave you on p. 165 is a definition of a Brønsted acid and a Brønsted base. When a carboxylic acid gives a proton to an amine, it is acting as a Brønsted acid while the amine is a Brønsted base. The ammonium ion produced is a Brønsted acid while the carboxylate anion is a Brønsted base.



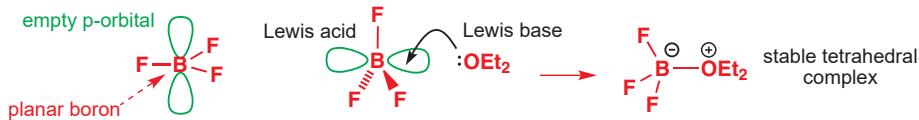
- Brønsted acids donate protons.
- Brønsted bases accept protons.

The American chemist Gilbert Lewis (1875–1946) introduced his electronic theory of acid–base interactions in 1924.

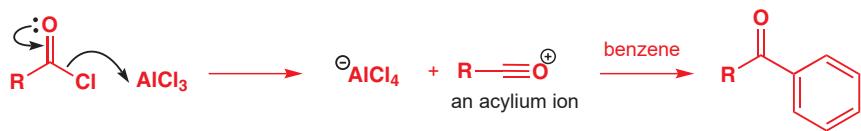
But there is another important type of acid: the Lewis acid. These acids don't donate protons—indeed they usually have no protons to donate. Instead they accept electrons. It is indeed a more general definition of acids to say that they accept electrons and of bases that they donate electrons. Lewis acids are usually halides of the higher oxidation states of metals, such as  $\text{BF}_3$ ,  $\text{AlCl}_3$ ,  $\text{ZnCl}_2$ ,  $\text{SbF}_5$ , and  $\text{TiCl}_4$ . By removing electrons from organic compounds, Lewis acids act as important catalysts in important reactions such as the Friedel–Crafts alkylation and acylation of benzene (Chapter 21), the  $\text{S}_{\text{N}}1$  substitution reaction (Chapter 15), and the Diels–Alder reaction (Chapter 34).

- Lewis acids accept electrons.
- Lewis bases donate electrons.

A simple Lewis acid is  $\text{BF}_3$ . As you saw in Chapter 5, monomeric boron compounds have three bonds to other atoms and an empty p orbital, making six electrons only in the outer shell. They are therefore not stable and  $\text{BF}_3$  is normally used as its ‘etherate’: a complex with  $\text{Et}_2\text{O}$ . Ether donates a pair of electrons into the empty p orbital of  $\text{BF}_3$  and this complex has tetrahedral boron with eight electrons. In this reaction the ether donates electrons (it can be described as a Lewis base) and  $\text{BF}_3$  accepts electrons: it is a Lewis acid. No protons are exchanged. The complex is a stable liquid and is the form usually available from suppliers.



Lewis acids often form strong interactions with electronegative atoms such as halides or oxygen. In the Friedel–Crafts acylation, which you will meet in Chapter 21, for example,  $\text{AlCl}_3$  removes the chloride ion from an acyl chloride to give a species, the acylium ion, which is reactive enough to combine with benzene.



Lewis acid–base interactions are very common in chemistry and are often rather subtle. You are about to meet, in the next chapter, an important way of making C–C bonds by adding organometallics to carbonyl compounds, and in many of these reactions there is an interaction at some point between a Lewis acidic metal cation and a Lewis basic carbonyl group.

## 延伸阅读

The quote at the start of the chapter comes from Ross Stewart, *The Proton: Applications to Organic Chemistry*, Academic Press, Orlando, 1985, p 1.

More detailed information about acid/base extraction can be found in any organic practical book. The details of the Cannizarro reaction are from J. C. Gilbert and S. F. Martin, *Experimental Organic Chemistry*, Harcourt, Fort Worth, 2002. The reduction of amides to amines comes from B. S. Furniss, A. J. Hannaford, P. W. G. Smith,

and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, 5th edn, Longman, Harlow, 1989.

Details about the acylation of amines with anhydrides and acid chlorides are in L. M. Harwood, C. J. Moody, and J. M. Percy, *Experimental Organic Chemistry*, 2nd edn, Blackwell, Oxford, 1999, p 279.

There is more about the discovery of cimetidine in W. Sneader, *Drug Discovery: a History*, Wiley, Chichester, 2005.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 9

# 使用有机金属试剂构建 C–C 键

## 联系

### 基础

- Electronegativity and the polarization of bonds ch4
- Grignard reagents and organolithiums attack carbonyl groups ch6
- C–H deprotonated by very strong bases ch8

### 目标

- Organometallics: nucleophilic and often strongly basic
- Making organometallics from halo-compounds
- Making organometallics by deprotonating carbon atoms
- Using organometallics to make new C–C bonds from C=O groups

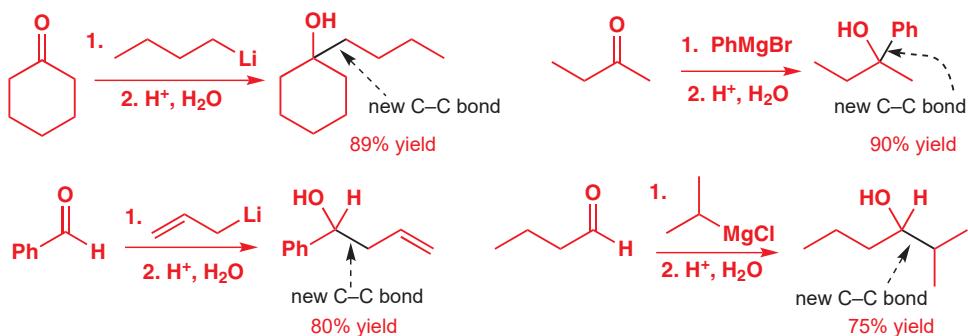
### 展望

- More about organometallics ch24 & ch40
- More ways to make C–C bonds from C=O groups ch25, ch26, & ch27
- Synthesis of molecules ch28

## Introduction

In Chapters 2–8 we covered basic chemical concepts concerning *structure* (Chapters 2–4 and 7) and *reactivity* (Chapters 5, 6, and 8). These concepts are the bare bones supporting all of organic chemistry, and now we shall start to put flesh on these bare bones. In Chapters 9–22 we shall tell you about the most important classes of organic reaction in more detail.

One of the things organic chemists do, for all sorts of reasons, is to make molecules, and making organic molecules means making C–C bonds. In this chapter we are going to look at one of the most important ways of making C–C bonds: using organometallics, such as organolithiums and Grignard reagents, in combination with carbonyl compounds. We will consider reactions such as these:

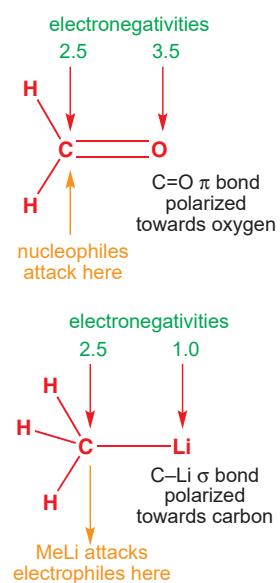


You met these types of reactions in Chapter 6: in this chapter we will be adding more detail with regard to the nature of the organometallic reagents and what sort of molecules can be made using the reactions. The organometallic reagents act as nucleophiles towards the

electrophilic carbonyl group, and this is the first thing we need to discuss: why are organometallics nucleophilic? We then move on to, firstly, how to make organometallics, then to the sorts of electrophiles they will react with, and finally to the sort of molecules we can make with them.

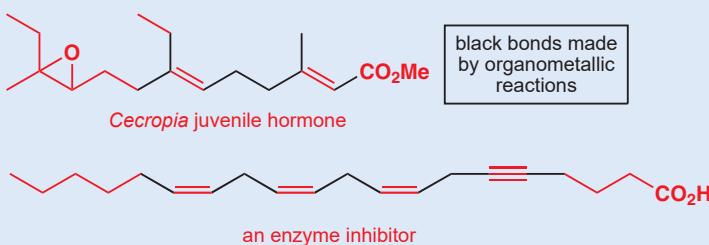
## Organometallic compounds contain a carbon–metal bond

The polarity of a covalent bond between two different elements is determined by electronegativity. The more electronegative an element is, the more it attracts the electron density in the bond. So the greater the *difference* between the electronegativities, the greater the difference between the attraction for the bonding electrons, and the more polarized the bond becomes. In the extreme case of complete polarization, the covalent bond ceases to exist and is replaced by electrostatic attraction between ions of opposite charge. We discussed this in Chapter 4 (p. 96), where we considered the extreme cases of bonding in NaCl.



### How important are organometallics for making C–C bonds?

As an example, let's take a molecule known as 'juvenile hormone'. It is a compound that prevents several species of insects from maturing and can be used as a means of controlling insect pests. Only very small amounts of the naturally occurring compound can be isolated from the insects, but it can instead be made in the laboratory from simple starting materials. At this stage you need not worry about how, but we can tell you that, in one synthesis, of the 16 C–C bonds in the final product, seven were made by reactions of organometallic reagents, many of them the sort of reactions we will describe in this chapter. This is not an isolated example. As further proof, take an important enzyme inhibitor, closely related to arachidonic acid which you met in Chapter 7. It has been made by a succession of C–C bond-forming reactions using organometallic reagents: eight of the 20 C–C bonds in the product were formed using organometallic reactions.



When we discussed (in Chapter 6) the electrophilic nature of carbonyl groups we saw that their reactivity is a direct consequence of the polarization of the carbon–oxygen bond towards the more electronegative oxygen, making the carbon a site for nucleophilic attack. In Chapter 6 you also met the two most important organometallic compounds—organolithiums and organomagnesium halides (known as Grignard reagents). In these organometallic reagents the key bond is polarized in the opposite direction—*towards* carbon—making carbon a nucleophilic centre. This is true for most organometallics because, as you can see from this edited version of the periodic table, metals (such as Li, Mg, Na, and Al) all have lower electronegativity than carbon.

Pauling electronegativities of selected elements

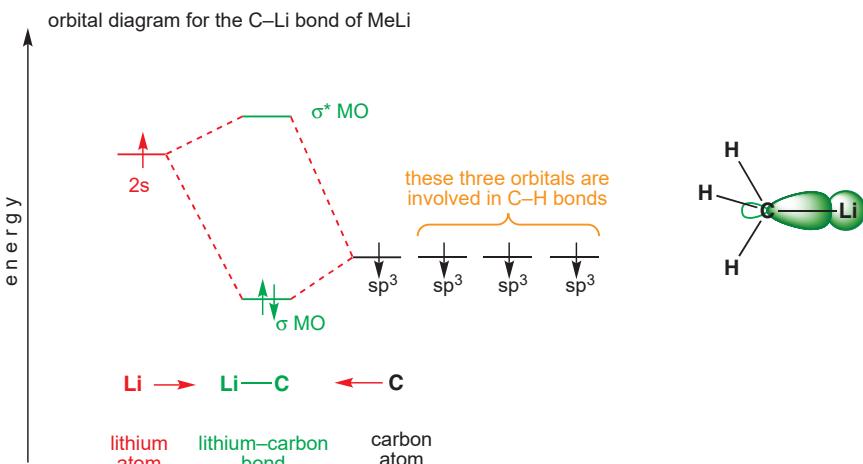
Li 1.0	
Na 0.9	Mg 1.3
B 2.0	C 2.5
Al 1.6	Si 1.9
N 3.0	P 2.2
O 3.5	S 2.6
F 4.0	Cl 3.2

Interactive display of polarity of organometallics

The molecular orbital energy level diagram—the kind you met in Chapter 4—represents the C–Li bond in methyl lithium in terms of the sum of the atomic orbitals of carbon and lithium. The more electronegative an atom is, the lower in energy are its atomic orbitals (p. 96). The filled C–Li  $\sigma$  orbital is closer in energy to the carbon's  $\text{sp}^3$  orbital than to the lithium's 2s orbital, so we can say that the carbon's  $\text{sp}^3$  orbital makes a greater contribution to the C–Li  $\sigma$  bond and that the C–Li bond has a larger coefficient on carbon. Reactions involving the filled

We explained this reasoning on p. 104.

$\sigma$  orbital will therefore take place at C rather than Li. The same arguments hold for the C–Mg bond of organo-magnesium or Grignard reagents, named after their inventor Victor Grignard.



■ Carbon atoms that carry a negative charge are known as **carbanions**.

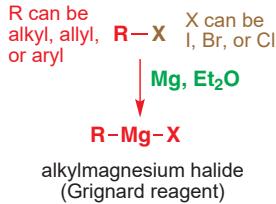
You have already met cyanide (p. 121), a carbanion that really does have a lone pair on carbon. Cyanide's lone pair is stabilized by being in a lower-energy sp orbital (rather than sp<sup>3</sup>) and by having the electronegative nitrogen atom triply bonded to the carbon.

We can also say that, because the carbon's sp<sup>3</sup> orbital makes a greater contribution to the C–Li  $\sigma$  bond, the  $\sigma$  bond is close in structure to a filled C sp<sup>3</sup> orbital—a lone pair on carbon. This useful idea can be carried too far: methyl lithium is not an ionic compound Me<sup>−</sup>Li<sup>+</sup>—although you may sometimes see MeLi or MeMgCl represented in mechanisms as Me<sup>−</sup>.

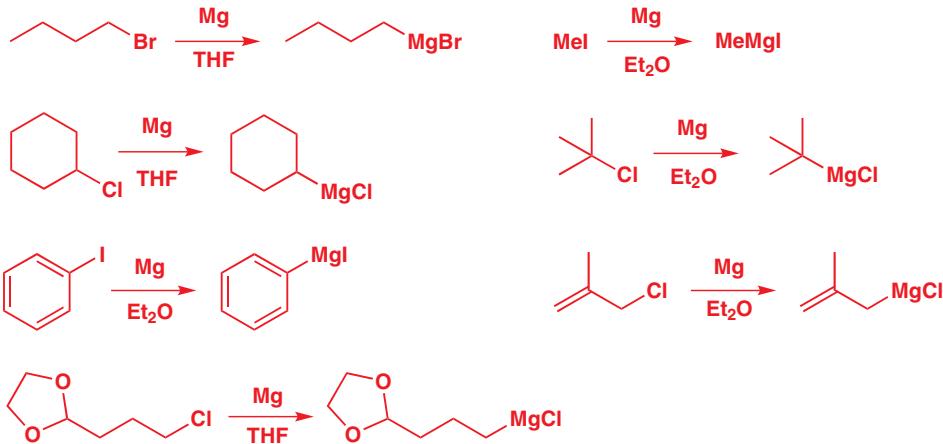
**The true structure of organolithiums and Grignard reagents** is rather more complicated! Even though these organometallic compounds are extremely reactive towards water and oxygen, and have to be handled under an atmosphere of nitrogen or argon, some have been studied by X-ray crystallography in the solid state and by NMR in solution. It turns out that they generally form complex aggregates with two, four, six, or more molecules bonded together, often with solvent molecules, one reason why apparently polar compounds such as BuLi dissolve in hydrocarbons. In this book we shall not be concerned with these details, and we shall represent organometallic compounds as simple monomeric structures.

## Making organometallics

### How to make Grignard reagents



Grignard reagents are made by reacting magnesium turnings with alkyl halides in ether solvents to form solutions of alkylmagnesium halide. Iodides, bromides, and chlorides can be used, as can both aryl and alkyl halides. Our examples include methyl, primary, secondary, and tertiary alkyl halides, aryl and allyl halides. They cannot contain any functional groups that would react with the Grignard reagent once it is formed. The final example has an acetal functional group as an example of one that does not react with the Grignard reagent. (See Chapter 23 for further discussion.)



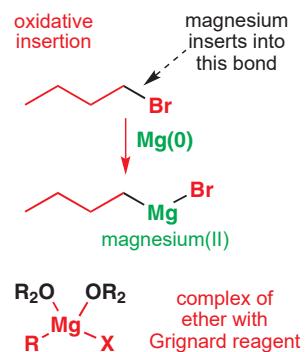
The solvents in these examples are all ethers, either diethyl ether  $\text{Et}_2\text{O}$  or THF. Other solvents that are sometimes used include the diethers dioxane and dimethoxyethane (DME).

common ether solvents



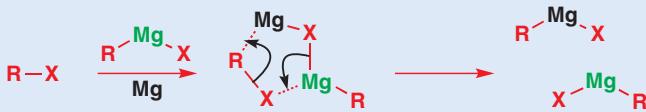
The reaction scheme is easy enough to draw, but what is the mechanism? Overall it involves an *insertion* of magnesium into the carbon–halogen bond. There is also a change in oxidation state of the magnesium, from  $\text{Mg}(0)$  to  $\text{Mg}(\text{II})$ . The reaction is therefore known as an oxidative insertion or oxidative addition, and is a general process for many metals such as Mg, Li (which we meet shortly), Cu, and Zn.  $\text{Mg}(\text{II})$  is much more stable than  $\text{Mg}(0)$  and this drives the reaction.

The mechanism of the reaction is not completely understood, and probably involves radical intermediates. But what is sure is that by the end of the reaction the magnesium has surrendered its lone pair of electrons and gained two  $\sigma$  bonds. The true product is a complex between the Grignard reagent and, probably, two molecules of the ether solvent, as  $\text{Mg}(\text{II})$  prefers a tetrahedral structure.



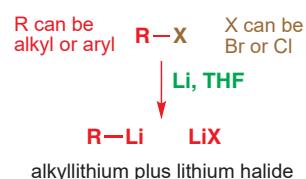
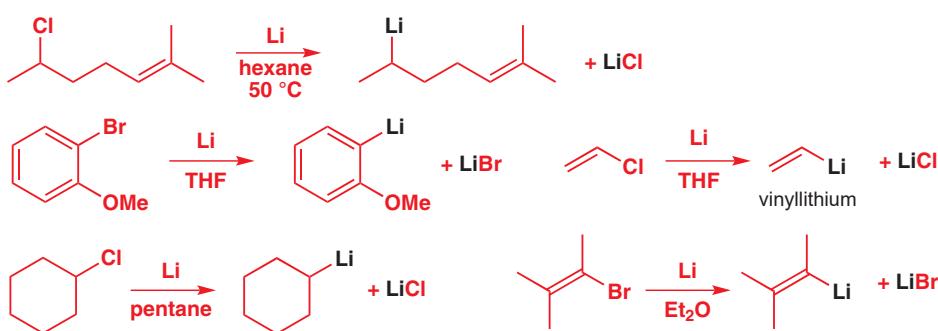
### More on making Grignard reagents

The reaction takes place not in solution but on the surface of the metal, and how easy it is to make a Grignard reagent can depend on the state of the surface—how finely divided the metal is, for example. Magnesium is usually covered by a thin coating of magnesium oxide, and Grignard formation generally requires ‘initiation’ to allow the metal to come into direct contact with the alkyl halide. Initiation usually means adding a small amount of iodine or 1,2-diiodoethane, or using ultrasound to dislodge the oxide layer. Once the Grignard starts to form, it catalyses further reactions of  $\text{Mg}(0)$ , perhaps by this mechanism:



### How to make organolithium reagents

Organolithium compounds may be made by a similar oxidative insertion reaction from lithium metal and alkyl halides. Each inserting reaction requires two atoms of lithium and generates one equivalent of lithium halide salt. As with Grignard formation, there is really very little limit on the types of organolithium that can be made this way.



You will notice secondary alkylolithiums, an aryllithium, and two vinylolithiums. The only other functional groups are alkenes and an ether. So far, that is quite like the formation of Grignard reagents. However, there are differences. Lithium goes from  $\text{Li}(0)$  to  $\text{Li}(\text{I})$  during the

Interactive mechanism for organolithium addition

reaction and there is no halide attached to the Li. Instead a second Li atom has to be used to make the Li halide. Again, Li(I) is very much more stable than Li(0) so the reaction is irreversible. Although ether solvents are often used, there is less need for extra coordination and hydrocarbon solvents such as pentane or hexane are also good.

### Commercially available organometallics

Some Grignard and organolithium reagents are commercially available. Most chemists (unless they were working on a very large scale) would not usually make the simpler organolithiums or Grignard reagents by these methods, but would buy them in bottles from chemical companies (who, of course, do use these methods). The table lists some of the most important commercially available organolithiums and Grignard reagents.

**methylolithium** (MeLi) in Et<sub>2</sub>O or DME

**methylmagnesium chloride, bromide, and iodide** (MeMgX) in Et<sub>2</sub>O, or THF

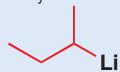
**n-butylolithium** (*n*-BuLi or just BuLi)

**ethylmagnesium bromide** (EtMgBr)



in cyclohexane or hexanes

**sec-butyllithium** (sec-BuLi or *s*-BuLi) in pentane or cyclohexane



**butylmagnesium chloride** (BuMgCl) in Et<sub>2</sub>O or THF

**tert-butyllithium** (*tert*-BuLi or *t*-BuLi) in pentane



**allylmagnesium chloride and bromide**



**phenyllithium** (PhLi) in (*n*-Bu)<sub>2</sub>O

**phenylmagnesium chloride and bromide** (PhMgCl or PhMgBr) in Et<sub>2</sub>O or THF

### Organometallics as bases

Organometallics need to be kept absolutely free of moisture—even moisture in the air will destroy them. The reason is that they react very rapidly and highly exothermically with water to produce alkanes. Anything that can protonate them will do the same thing. The organometallic reagent is a strong base, and is protonated to form its conjugate acid—methane or benzene in these cases. The p*K*<sub>a</sub> of methane (Chapter 8) is somewhere around 50: it isn't an acid at all and essentially nothing will remove a proton from methane.



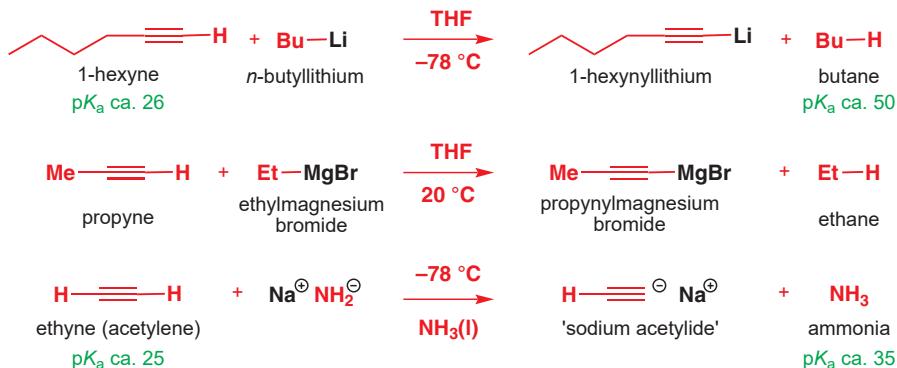
The equilibria lie vastly to the right: methane and Li<sup>+</sup> are much more stable than MeLi while benzene and Mg<sup>2+</sup> are much more stable than PhMgBr. Some of the most important uses of organolithiums—butyllithium, in particular—are as bases and, because they are so strong, they will deprotonate almost anything. That makes them very useful as reagents for making *other* organolithiums.



### Making organometallics by deprotonating alkynes

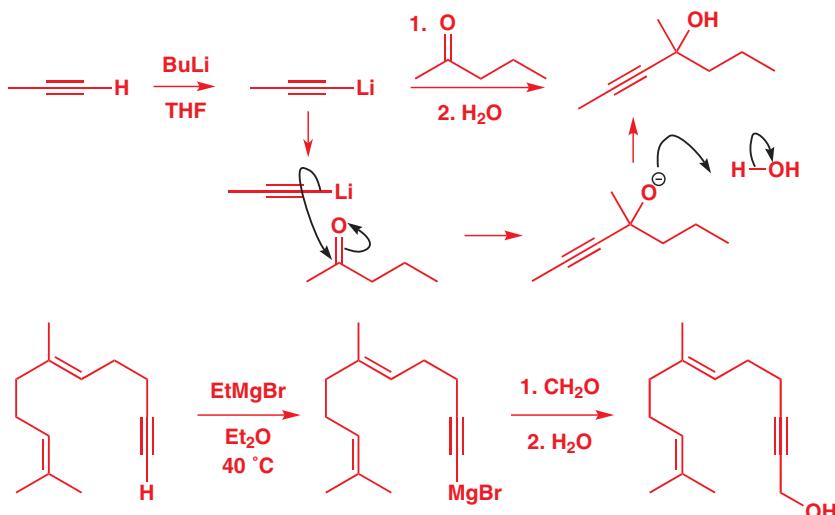
In Chapter 8 (p. 175) we talked about how hybridization affects acidity. Alkynes, with their C–H bonds formed from sp orbitals, are the most acidic of hydrocarbons, with p*K*<sub>a</sub>s of about 25.

They can be deprotonated by more basic organometallics such as butyllithium or ethylmagnesium bromide. Alkynes are sufficiently acidic to be deprotonated even by nitrogen bases and you saw on p. 171 that a common way of deprotonating alkynes is to use  $\text{NaNH}_2$  (sodium amide), obtained by reacting sodium with liquid ammonia. An example of each is shown here. Propyne and acetylene are gases, and can be bubbled through a solution of the base.



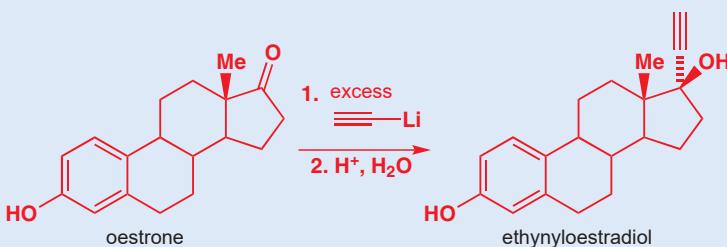
We have chosen to represent the alkynyl lithium and alkynyl magnesium halides as organometallics and the alkynyl sodium as an ionic salt. Both probably have some covalent character but lithium is less electropositive than sodium so alkynyl lithiums are more covalent and usually used in non-polar solvents while the sodium derivatives are more ionic and usually used in polar solvents.

The metal derivatives of alkynes can be added to carbonyl electrophiles, as in the following examples. The first (we have reminded you of the mechanism for this) is the initial step of an important synthesis of the antibiotic erythronolide A, and the second is the penultimate step of a synthesis of the widespread natural product farnesol.



### Ethyloestradiol

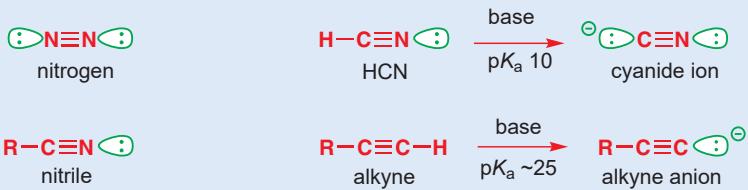
The ovulation-inhibiting component of almost all oral contraceptive pills is a compound known as ethynodiol, and this compound too is made by an alkynyllithium addition to the female sex hormone oestrone. A range of similar synthetic analogues of hormones containing an ethynyl unit are used in contraceptives and in treatments for disorders of the hormonal system.



### Triple bonds: stability and acidity

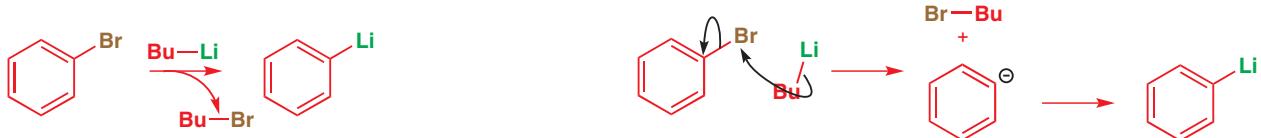
You have now met all the more important compounds with triple bonds. They all have electrons in low-energy sp hybrid orbitals (shown in green on the diagrams below), a feature which gives them stability or even unreactivity. Remember, an sp orbital has 50% s character, so electrons in this orbital are on average closer to the nucleus, and therefore more stable, than electrons in an sp<sup>2</sup> or sp<sup>3</sup> orbital.

Nitrogen, N<sub>2</sub>, has sp orbitals at both ends and is almost inert. It is neither basic nor nucleophilic and a major achievement of life is the ‘fixing’ (trapping in reductive chemical reactions) of nitrogen by bacteria such as those in the roots of leguminous plants (peas and beans). HCN has an sp orbital on nitrogen and a C–H σ bond at the other end. The nitrogen’s sp lone pair is not at all basic, but HCN is quite acidic with a pK<sub>a</sub> of 10 because the negative charge in the conjugate base (CN<sup>−</sup>) is in an sp orbital. Nitriles have similar bonds and they are non-nucleophilic and non-basic. Finally, we have just met alkynes, which are among the most acidic of hydrocarbons, again because of the stability of an anion with its charge in an sp orbital.



### Halogen–metal exchange

Deprotonation is not the only way to use one simple organometallic reagent to generate another more useful one. Organolithiums can also remove halogen atoms from alkyl and aryl halides in a reaction known as halogen–metal exchange.

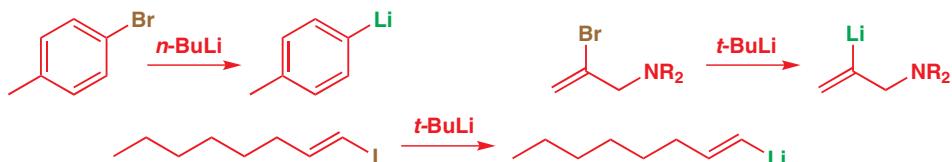


The bromine and the lithium simply swap places. As with many of these organometallic processes, the mechanism is not altogether clear, but can be represented as a nucleophilic attack on bromine by the butyllithium. But why does the reaction work? The product of our ‘mechanism’ is not PhLi and BuBr but a phenyl anion and a lithium cation. These could obviously combine to give PhLi and BuBr. But is this a reasonable interpretation and why does the reaction go that way and not the other? The key, again, is pK<sub>a</sub>. We can think of the organolithiums as a complex between Li<sup>+</sup> and a carbanion.



The reason for this is again that the anion lies in an sp<sup>2</sup> orbital rather than an sp<sup>3</sup> orbital. See Chapter 8, p. 175.

The lithium cation is the same in all cases: only the carbanion varies. So the stability of the complex depends on the stability of the carbanion ligand. Benzene, (pK<sub>a</sub> about 43) is more acidic than butane (pK<sub>a</sub> about 50) so the phenyl complex is more stable than the butyl complex and the reaction is a way to make PhLi from available BuLi. Vinylolithiums (the lithium must be bonded directly to the alkene) can also be made this way and a R<sub>2</sub>N– substituent is acceptable. Bromides or iodides react faster than chlorides.



Halogen–metal exchange tolls the knell of one appealing way to make carbon–carbon bonds. It may already have occurred to you that we might make a Grignard or organolithium reagent and combine it with another alkyl halide to make a new carbon–carbon σ bond.

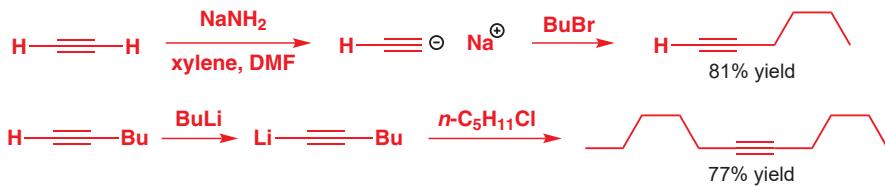


This reaction does not work because of transmetallation. The two alkyl bromides and their Grignard reagents will be in equilibrium with each other so that, even if the coupling were successful, three coupled products will be formed.



You will see later that transition metals are needed for this sort of reaction. The only successful reactions of this kind are couplings between metal derivatives of alkynes and alkyl halides. These do not exchange the metal as the alkynyl metal is much more stable than the alkyl metal.

A good example is the synthesis of a substituted alkyne starting from acetylene (ethyne) itself. One alkylation uses  $\text{NaNH}_2$  as the base to make sodium acetylide and the other uses  $\text{BuLi}$  to make a lithium acetylide.

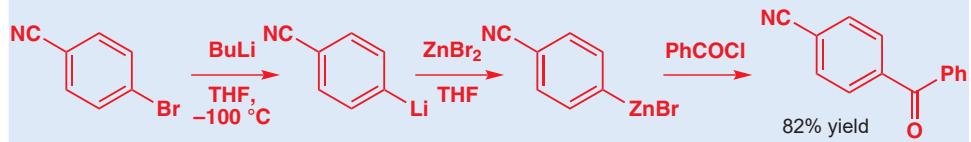


### Transmetallation

Organolithiums can be converted to other types of organometallic reagents by transmetallation—simply treating with the salt of a less electropositive metal. The more electropositive Mg or Li goes into solution as an ionic salt, while the less electropositive metal such as Zn takes over the alkyl group.



But why bother? Well, the high reactivity—and in particular the basicity—of Grignard reagents and organolithiums sometimes causes unwanted side reactions. Their combination with very strong electrophiles like acid chlorides usually results in a violent uncontrolled reaction. If a much less reactive organozinc compound is used instead, the reaction is more under control. These organozinc compounds can be made from either Grignard reagents or organolithium compounds. E. Negishi, a pioneer of organozinc chemistry, got the Nobel Prize for Chemistry in 2010 with R. F. Heck and A. Suzuki for their work on organometallic compounds.



## Using organometallics to make organic molecules

Now that you have met all of the most important ways of making organometallics (summarized here as a reminder), we shall move on to consider how to use them to make molecules:

what sorts of electrophiles do they react with and what sorts of products can we expect to get from their reactions? Having told you how you can make other organometallics, we shall really be concerned for the rest of this chapter only with Grignard reagents and organolithiums. In nearly all of the cases we shall talk about, the two classes of organometallics can be used interchangeably.

● **Ways of making organometallics**

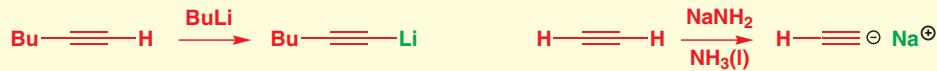
- Oxidative insertion of Mg into alkyl halides



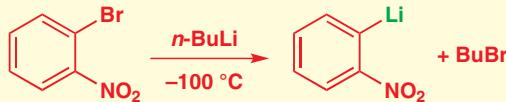
- Oxidative insertion of Li into alkyl halides



- Deprotonation of alkynes



- Halogen–metal exchange

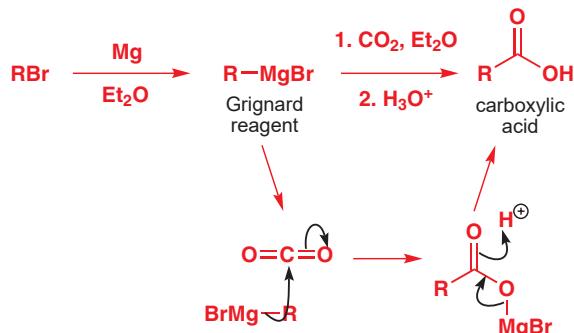


- Transmetallation



### Making carboxylic acids from organometallics and carbon dioxide

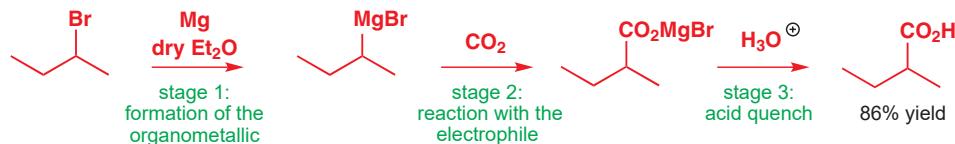
Carbon dioxide reacts with organolithiums and Grignard reagents to give carboxylate salts. Protonating the salt with acid gives a carboxylic acid with one more carbon atom than the starting organometallic. The reaction is usually done by adding solid CO<sub>2</sub> to a solution of the organolithium in THF or ether, but it can also be done using a stream of dry CO<sub>2</sub> gas.



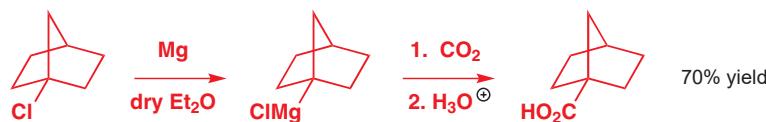
The example below shows the three stages of the reaction: (1) forming the organometallic, (2) reaction with the electrophile (CO<sub>2</sub>), and (3) the acidic work-up or quench, which protonates the product and destroys any unreacted organometallic. The three stages of

the reaction have to be monitored carefully to make sure that each is finished before the next is begun. In particular it is absolutely essential that there is no water present during either of the first two stages—water must be added only at the end of the reaction, *after* the organometallic has all been consumed by reaction with the electrophile. You may occasionally see schemes written out without the quenching step included, but it is nonetheless always needed.

#### carboxylic acids from organometallics

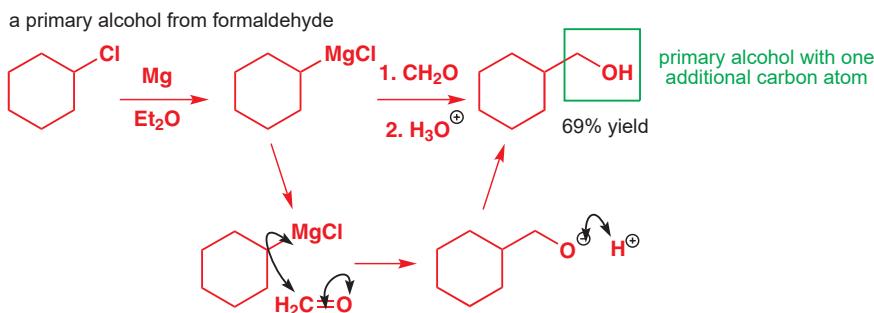


This next example shows that even very hindered chlorides can be used successfully. The significance of this will be clearer when you reach Chapter 15.

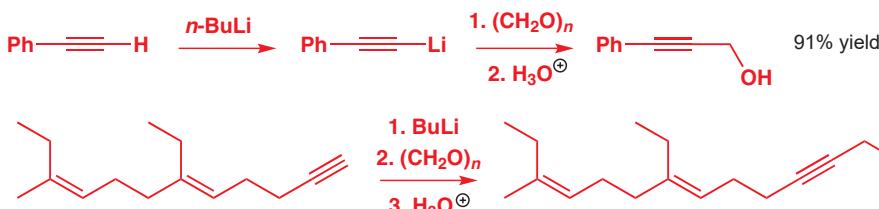


#### Making primary alcohols from organometallics and formaldehyde

You met formaldehyde, the simplest aldehyde, in Chapter 6, where we discussed the difficulties of using it in anhydrous reactions: it is either hydrated or a polymer paraformaldehyde,  $(\text{CH}_2\text{O})_n$ , and in order to get pure, dry formaldehyde it is necessary to heat ('crack') the polymer to decompose it. But formaldehyde is a remarkably useful reagent for making primary alcohols, in other words alcohols that have just one carbon substituent on the hydroxy-bearing C atom. Just as carbon dioxide adds one carbon and makes an acid, formaldehyde adds one carbon and makes an alcohol.



In the next two examples, formaldehyde makes a primary alcohol from two deprotonated alkynes. The second reaction here (for which we have shown organolithium formation, reaction, and quench simply as a series of three consecutive reagents) forms one of the last steps of the synthesis of *Cecropia* juvenile hormone, whose structure you met right at the beginning of the chapter.

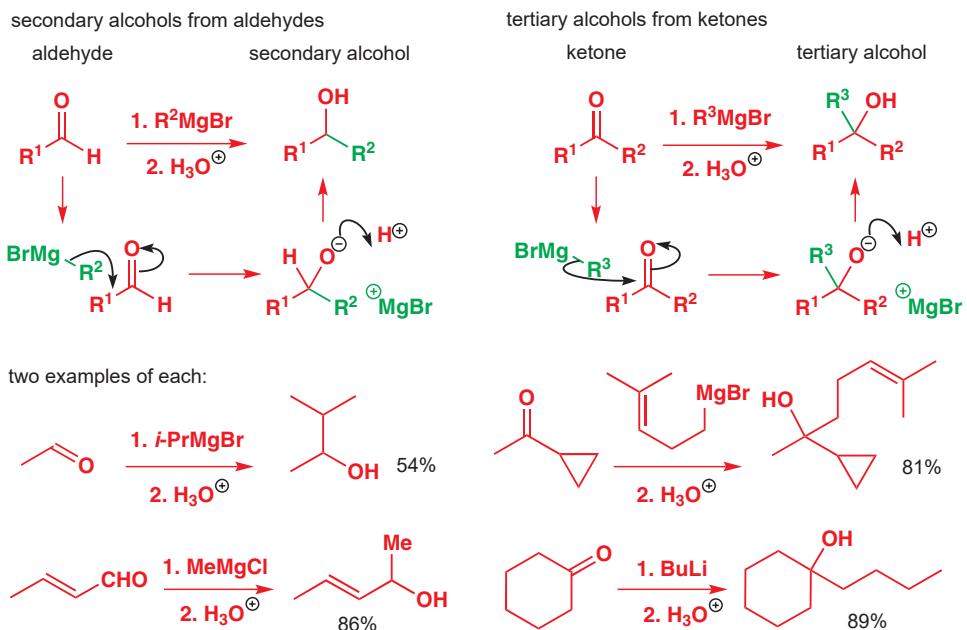


● Something to bear in mind with all organometallic additions to carbonyl compounds is that the addition takes the oxidation level down one (oxidation levels were described in Chapter 2, p. 33). In other words, if you start with an aldehyde, you end up with an alcohol. More specifically,

- additions to  $\text{CO}_2$  give carboxylic acids
- additions to formaldehyde ( $\text{CH}_2\text{O}$ ) give primary alcohols
- additions to other aldehydes ( $\text{RCHO}$ ) give secondary alcohols
- additions to ketones give tertiary alcohols

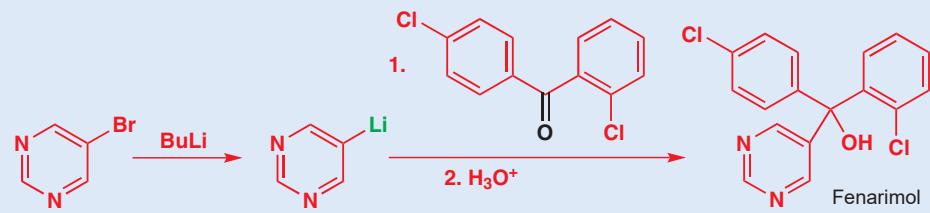
### Secondary and tertiary alcohols: which organometallic, which aldehyde, which ketone?

Aldehydes and ketones react with organometallic reagents to form secondary and tertiary alcohols, respectively, and some examples are shown with the general schemes here.



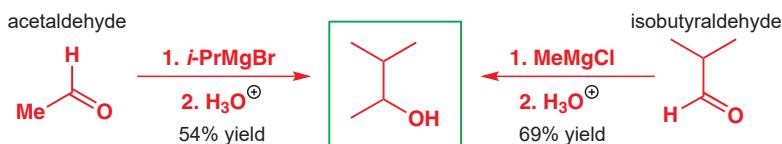
### Fenarimol

Fenarimol is a fungicide that works by inhibiting the fungus's biosynthesis of important steroid molecules. It is made by reaction of a diarylketone with an organolithium derived by halogen–metal exchange.



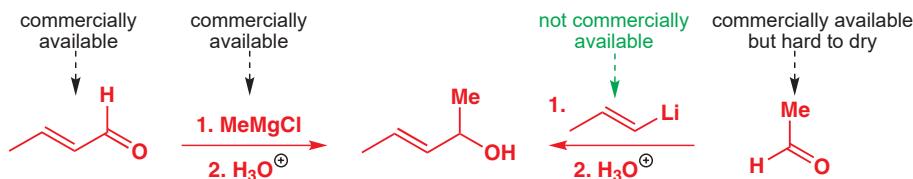
To make any secondary alcohol, however, there may be a choice of two possible routes, depending on which part of the molecule you choose to make the organometallic and which part you choose to make the aldehyde. For example, the first example here shows the synthesis of a secondary alcohol from isopropylmagnesium chloride and acetaldehyde. But it is

equally possible to make this same secondary alcohol from isobutyraldehyde and methyl-lithium or a methylmagnesium halide.



Indeed, back in 1912, when this alcohol was first described in detail, the chemists who made it chose to start with acetaldehyde, while in 1983, when it was needed as a starting material for a synthesis, it was made from isobutyraldehyde. Which way is better? The 1983 chemists probably chose the isobutyraldehyde route because it gave a better yield. But, if you were making a secondary alcohol for the first time, you might just have to try both in the laboratory and see which one gave a better yield.

Or you might be more concerned about which uses the cheaper, or more readily available, starting materials—this was probably also a factor in the choice of methylmagnesium chloride and the unsaturated aldehyde in the second example. Both can be bought commercially, while the alternative route to this secondary alcohol would require a vinyl lithium or vinylmagnesium bromide reagent that would have to be made from a vinyl halide, which is itself not commercially available, along with difficult-to-dry acetaldehyde.

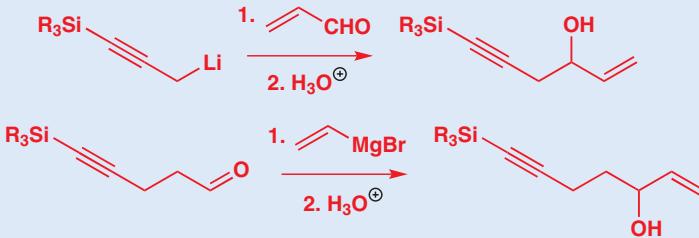


There is another choice for secondary alcohols: the reduction of a ketone. The ketone reacts with sodium borohydride to give a secondary alcohol. An obvious case where this would be a good route is the synthesis of a cyclic alcohol. This bicyclic ketone gives the secondary alcohol in good yield, and in the second example a diketone has both its carbonyl groups reduced.



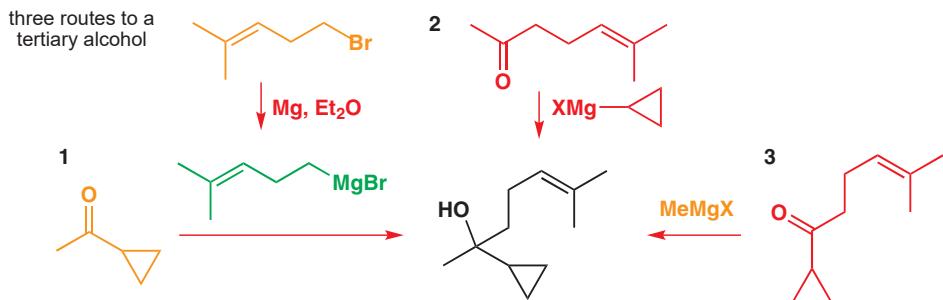
## Flexibility in the synthesis of alcohols

As an illustration of the flexibility available in making secondary alcohols, one synthesis of bongkrekic acid, a highly toxic compound that inhibits transport across certain membranes in the cell, requires both of these (very similar) alcohols. The chemists making the compound at Harvard University chose to make each alcohol from quite different starting materials: an unsaturated aldehyde and an alkyne-containing organolithium in the first instance, and an alkyne-containing aldehyde and vinyl magnesium bromide in the second.



With tertiary alcohols, there is even more choice. The example below is a step in a synthesis of the natural product, nerolidol. But the chemists in Paris who made this tertiary alcohol

could in principle have chosen any of three routes. Note that we have dropped the aqueous quench step from these schemes to avoid cluttering them.

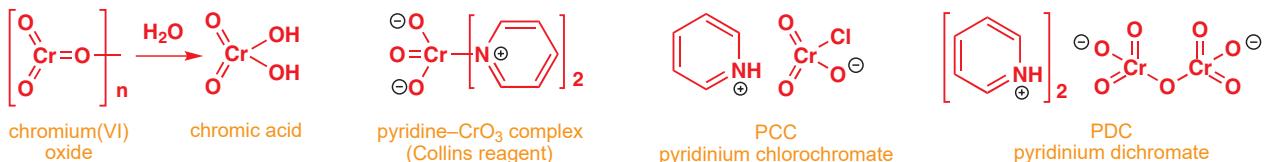


Only the reagents in orange are commercially available, but, as it happens, the green Grignard reagent can be made from an alkyl bromide, which is itself commercially available, making route 1 on the left the most reasonable.

Now, do not be dismayed! We are not expecting you to remember a chemical catalogue and to know which compounds you can buy and which you can't. All we want you to appreciate at this stage is that there are usually two or three ways of making any given secondary or tertiary alcohol, and you should be able to suggest alternative combinations of aldehyde or ketone and Grignard or organolithium reagent that will give the same product. You are not expected to be able to assess the relative merits of the different possible routes to a compound. That is a topic we leave for a much later chapter on retrosynthetic analysis, Chapter 28.

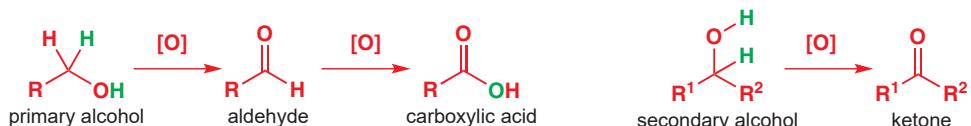
## Oxidation of alcohols

So far the metals we have used have had one oxidation state other than zero: Li(I), Mg(II), and Zn(II). If we want to oxidize organic compounds we need metals that have at least two higher oxidation states and that means transition metals. The most important by far is chromium, with Cr(III) and Cr(VI) as the useful oxidation states. Orange Cr(VI) compounds are good oxidizing agents: they remove hydrogen from organic compounds and are themselves reduced to green Cr(III). There are many Cr(VI) reagents used in organic chemistry, some of the more important ones are related to the polymeric oxide  $\text{CrO}_3$ . This is the anhydride of chromic acid and water breaks up the polymer to give a solution of chromic acid. Pyridine also breaks up the polymer to give a complex. This (Collins' reagent) was used to oxidize organic compounds but it is rather unstable and pyridinium dichromate (PDC) and pyridinium chlorochromate (PCC) are usually now preferred, especially as they are soluble in organic solvents such as  $\text{CH}_2\text{Cl}_2$ .

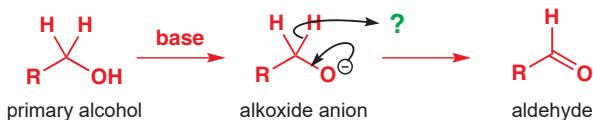


Oxidation by these reagents of the various primary and secondary alcohols we have been making in this chapter takes us to a higher oxidation level. Oxidation of primary alcohols gives aldehydes and then carboxylic acids, while oxidation of secondary alcohols gives ketones. Note that you can't oxidize tertiary alcohols (without breaking a C–C bond).

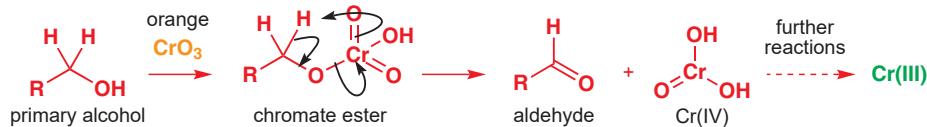
■ The symbol [O] means an unspecified oxidizing agent.



You will notice that the oxidation steps involve the removal of two hydrogen atoms and/or the addition of one oxygen atom. In Chapter 6 you saw that reduction meant the addition of hydrogen (and can also mean the removal of oxygen). Hiding behind these observations is the more fundamental idea that reduction requires the addition of electrons while oxidation requires the removal of electrons. If we used basic reagents, we could remove the OH proton from a primary alcohol, but to get the aldehyde we should have to remove a C–H proton as well *with a pair of electrons*. We should have to expel a hydride ion  $H^-$  and this doesn't happen. So we need some reagent that can remove a hydrogen atom *and a pair of electrons*. That defines an oxidizing agent.

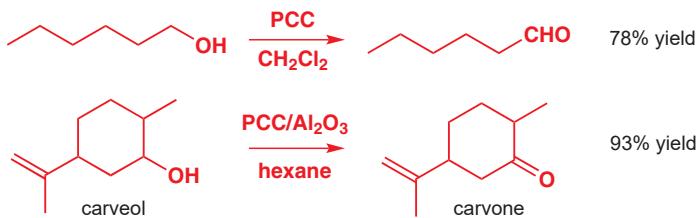


Here  $\text{Cr(VI)}$  can remove electrons to make  $\text{Cr(III)}$ . It does so by a cyclic mechanism on a  $\text{Cr(VI)}$  ester. One hydrogen atom is removed (from the OH group) to make the ester and the second is removed (from carbon) in the cyclic mechanism. Notice how the arrows stop on the Cr atom and start again on the  $\text{Cr=O}$  bond, so two electrons are added to the chromium. This actually makes  $\text{Cr(IV)}$ , an unstable oxidation state, but this gives green  $\text{Cr(III)}$  by further reactions.

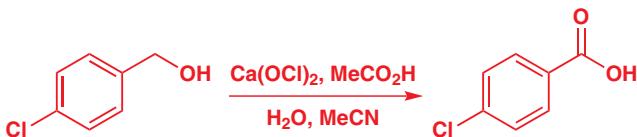


Interactive mechanism for chromium (VI) oxidation of alcohols

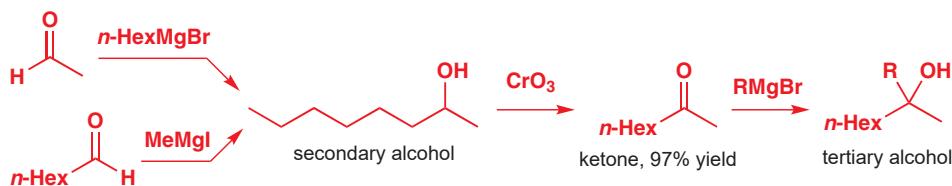
Two examples of the use of PCC in these oxidations come from Vogel. Hexanol is oxidized to hexanal in dichloromethane solution and commercial carveol (an impure natural product) to pure carvone with PCC supported on alumina in hexane solution. In both cases the pure aldehyde or ketone was isolated by distillation.



But a word of warning: stronger oxidizing agents like calcium hypochlorite or sodium hypochlorite (bleach) may oxidize primary alcohols all the way to carboxylic acids, especially in water. This is the case with *p*-chloro benzyl alcohol and the solid acid is easily isolated by the type of acid/base extraction we met in the previous chapter.



You will find further discussion of oxidizing agents in later chapters of the book. We have introduced them here so that you can see how primary and secondary alcohols, made by addition of organometallic reagents, can be oxidized to aldehydes or ketones so that the process can be repeated. A secondary alcohol, which could be made in two ways, can be oxidized with the pyridine– $\text{CrO}_3$  complex to the ketone and reacted with any Grignard or organolithium compound to give a range of tertiary alcohols.



## Looking forward

In this chapter we have covered interconversions between ketones, aldehydes, and alcohols by forming C–C bonds using organometallics. We looked at oxidation and reduction as ways of complementing these methods—you should now be able to suggest at least one way of making any primary, secondary, or tertiary alcohol from simple precursors. In the next two chapters we will broaden our horizons beyond aldehydes and ketones to look at the reactivity of other carbonyl compounds—carboxylic acids and their derivatives such as esters and amides—and other nucleophiles. But the idea that we study organic reactions not only for their own sake but also so we can use them to make things should stay with you. We will come back to how to design ways of making molecules in Chapter 28. Many of these methods will employ the organometallics you have just met. We will then devote Chapter 40 to a broader range of more complex organometallic methods.

## 延伸阅读

For more on the detailed structures of Grignard reagents, see P. G. Williard in *Comprehensive Organic Synthesis*, vol. 1, 1999, p. 1. The alkylation of alkynes is described by P. J. Garratt in *Comprehensive Organic Synthesis*, vol. 1, 3rd edn, 1999, p. 271. The examples come from T. F. Rutledge, *J. Org. Chem.*, 1959, **24**, 840, D. N. Brattesoni and C. H. Heathcock, *Synth. Commun.* 1973, **3**, 245, R. Giovannini and P. Knochel, *J. Am. Chem. Soc.*, 1998, **120**, 11186, C. E. Tucker, T. N. Majid, and P. Knochel, *J. Am. Chem. Soc.*, 1992, **114**, 3983. For a rather advanced review of organozinc compounds, see P. Knochel, J. J. Almena Perea, and P. Jones, *Tetrahedron*, 1998, **54**, 8275.

Discovery of pyridinium chlorochromate (PCC): G. Piancatelli, A. Scettri, and M. D'Auria, *Synthesis*, 1982, 245; H. S. Kasmai, S. G. Mischke, and T. J. Blake, *J. Org. Chem.*, 1995, **60**, 2267 and PDC: E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, 2647. Details of oxidation experiments: B. S. Furniss, A. J. Hannaford, P. W. G. Smith, and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, 5th edn, Longman, Harlow, 1989, pp. 590 and 610; J. C. Gilbert and S. F. Martin, *Experimental Organic Chemistry*, Harcourt, Fort Worth, 2002, p. 507.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

## 联系

### 基础

Drawing mechanisms ch5

Nucleophilic attack on carbonyl groups  
ch6 & ch9

- Acidity and  $pK_a$  ch8

Grignard and RLi addition to  $C=O$   
groups ch9

### 目标

- Nucleophilic attack followed by loss of leaving group
- What makes a good nucleophile
- What makes a good leaving group
- There is always a tetrahedral intermediate
- How to make acid derivatives
- Reactivity of acid derivatives
- How to make ketones from acids
- How to reduce acids to alcohols

### 展望

- Loss of carbonyl oxygen ch11
- Kinetics and mechanism ch12
- Reactions of enols ch20, ch25, & ch26
- Chemoselectivity ch23

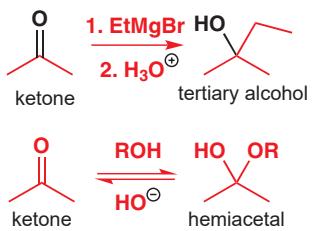
You are already familiar with reactions of compounds containing carbonyl groups. Aldehydes and ketones react with nucleophiles at the carbon atom of their carbonyl group to give products containing hydroxyl groups. Because the carbonyl group is such a good electrophile, it reacts with a wide range of different nucleophiles: you have met reactions of aldehydes and ketones with (in Chapter 6) cyanide, water, and alcohols, and (in Chapter 9) organometallic reagents (organolithiums and organomagnesiums, or Grignard reagents).

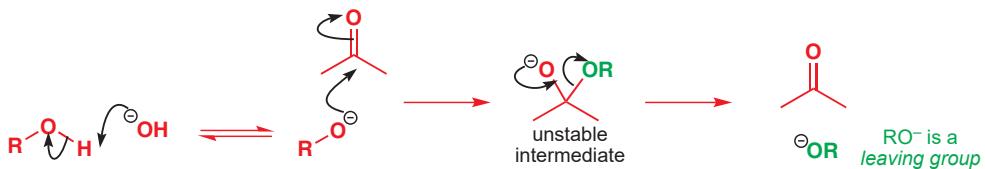
In this chapter and Chapter 11 we shall look at some more reactions of the carbonyl group—and revisit some of the ones we touched on in Chapter 6. It is a tribute to the importance of this functional group for organic chemistry that we have devoted four chapters of this book to its reactions. Just like the reactions in Chapters 6 and 9, the reactions in Chapters 10 and 11 all involve attack of a nucleophile on a carbonyl group. The difference is that this step is followed by other mechanistic steps, which means that the overall reactions are not just *additions* but also *substitutions*.

## The product of nucleophilic addition to a carbonyl group is not always a stable compound

Addition of a Grignard reagent to an aldehyde or ketone gives a stable alkoxide, which can be protonated with acid to produce an alcohol (you met this reaction in Chapter 9). The same is not true for addition of an alcohol to a carbonyl group in the presence of base—in Chapter 6 we drew a reversible, equilibrium arrow for this transformation and said that the product, a hemiacetal, is formed to a significant extent only if it is cyclic.

The reason for this instability is that  $RO^-$  is easily expelled from the molecule. We call groups that can be expelled from molecules, usually taking with them a negative charge, **leaving groups**. We'll look at leaving groups in more detail later in this chapter and again in Chapter 15.



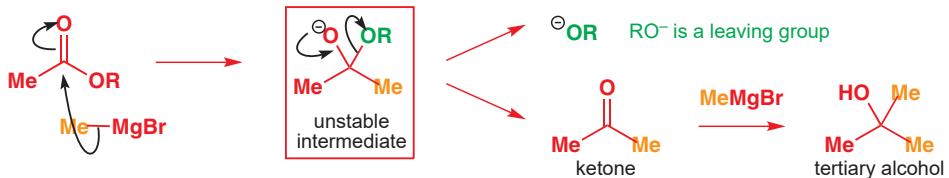


### ● Leaving groups

Leaving groups are anions such as Cl<sup>-</sup>, RO<sup>-</sup>, and RCO<sub>2</sub><sup>-</sup> that can be expelled from molecules taking their negative charge with them.

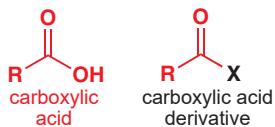
So, if the nucleophile is also a leaving group, there is a chance that it will be lost again and that the carbonyl group will reform—in other words, the reaction will be reversible. The energy released in forming the C=O bond (bond strength 720 kJ mol<sup>-1</sup>) makes up for the loss of two C–O single bonds (about 350 kJ mol<sup>-1</sup> each), one of the reasons for the instability of the hemiacetal product in this case.

The same thing can happen if the starting carbonyl compound contains a potential leaving group. The unstable negatively charged intermediate in the red box below is formed when a Grignard reagent is added to an ester.



Again, it collapses with loss of RO<sup>-</sup> as a leaving group. This time, though, we have not gone back to starting materials: instead we have made a new compound (a ketone) by a **substitution reaction**—the OR group of the starting material has been substituted by the Me group of the product. In fact the ketone product can react with the Grignard reagent a second time to give a tertiary alcohol. Later in this chapter we'll discuss why the reaction doesn't stop at the ketone.

## Carboxylic acid derivatives



Most of the starting materials for, and products of, these substitutions will be carboxylic acid derivatives, with the general formula RCOX. You met the most important members of this class in Chapter 2: here they are again as a reminder.

Carboxylic acid derivatives

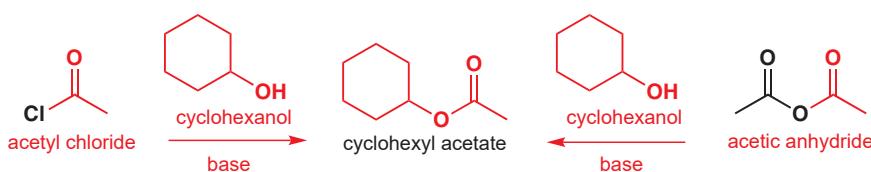
Carboxylic acid	Derivative of RCO <sub>2</sub> H
	acid chloride or acyl chloride*
	ester
	acid anhydride
	amide

The reactions of alcohols with acid chlorides and with acid anhydrides are the most important ways of making esters, but not the only ways. We shall see later how carboxylic acids can be made to react directly with alcohols.

\*We shall use these two terms interchangeably.

### Acid chlorides and acid anhydrides react with alcohols to make esters

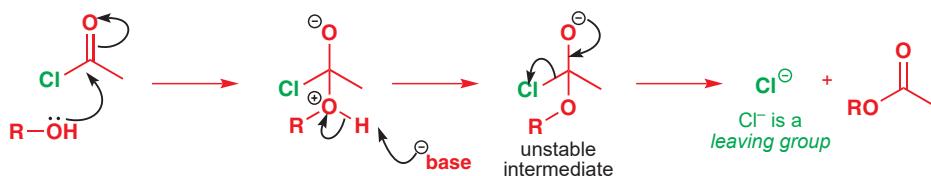
Acetyl chloride will react with an alcohol in the presence of a base to give an acetate ester and we get the same product if we use acetic anhydride.



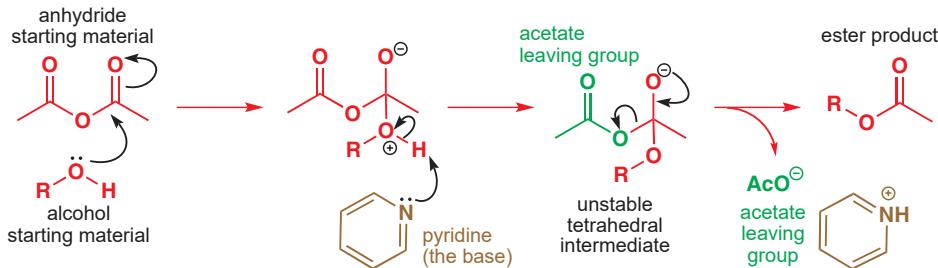
Remember the symbol for acetyl?  $\text{Ac}=\text{CH}_3\text{CO}$ . You can represent the acetate of an alcohol  $\text{ROH}$  as  $\text{ROAc}$  but not as  $\text{RAc}$  as this would be a ketone.

In each case, a substitution (of the black part of the molecule,  $\text{Cl}^-$  or  $\text{AcO}^-$ , by  $\text{OH}^-$ ) has taken place—but how? It is important that you learn not only the *fact* that acyl chlorides and acid anhydrides react with alcohols but also the *mechanism* of the reaction. In this chapter you will meet a lot of reactions, but relatively few mechanisms—once you understand one, you should find that the rest follow on quite logically.

The first step of the reaction is, as you might expect, addition of the nucleophilic alcohol to the electrophilic carbonyl group—we'll take the acyl chloride first. The base is important because it removes the proton from the alcohol once it attacks the carbonyl group. A base commonly used for this is pyridine. If the electrophile had been an aldehyde or a ketone, we would have got an unstable hemiacetal, which would collapse back to starting materials by eliminating the alcohol. With an acyl chloride, the alkoxide intermediate we get is also unstable. It collapses again by an elimination reaction, this time losing chloride ion, to form the ester. Chloride is the *leaving group* here—it leaves with its negative charge.



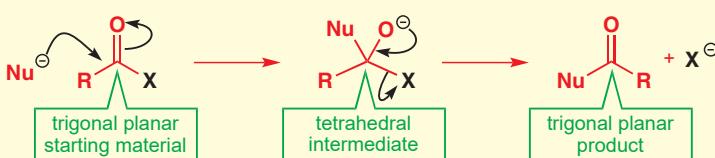
With this reaction as a model, you should be able to work out the mechanism of ester formation from acetic anhydride and an alcohol. Try to write it down without looking at the acyl chloride mechanism above, and certainly not at the answer below. Here it is, with pyridine as the base. Again, addition of the nucleophile gives an unstable intermediate, which undergoes an elimination reaction, this time losing a carboxylate anion to give an ester.



We call the unstable intermediate formed in these reactions the **tetrahedral intermediate** because the trigonal ( $\text{sp}^2$ ) carbon atom of the carbonyl group has become a tetrahedral ( $\text{sp}^3$ ) carbon atom.

### ● Tetrahedral intermediates

Substitutions at trigonal carbonyl groups go through a tetrahedral intermediate and then on to a trigonal product.



### More details of this reaction

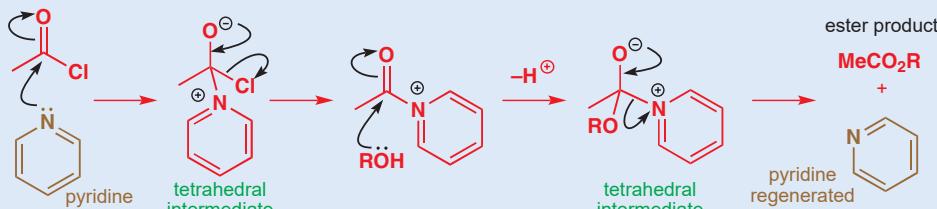
Acylation with acyl chlorides in the presence of pyridine has more subtleties than first meet the eye. If you are reading this chapter for the first time, you might skip this box, as it is not essential to the general flow of what we are saying. There are three more points to notice.

Pyridine is consumed during both of these reactions, since it ends up protonated. One whole equivalent of pyridine is therefore necessary and, in fact, the reactions are often carried out with pyridine as solvent.

The observant among you may also have noticed that the (weak—pyridine) base catalyst in this reaction works very slightly differently from the (strong—hydroxide) base catalyst in the hemiacetal-forming reaction on p. 197: pyridine removes the proton *after* the nucleophile has added; hydroxide removes the proton *before* the nucleophile has added. This is deliberate, and will be discussed further in Chapters 12 and 40. The basicities of pyridine ( $pK_a$  for protonation 5.5) and hydroxide ( $pK_a$  of water 15.7) were discussed in Chapter 8.

Pyridine is, in fact, more nucleophilic than the alcohol, and it attacks the acyl chloride rapidly, forming a highly electrophilic (because of the positive charge) intermediate. It is then this intermediate that subsequently reacts with the alcohol to give the ester. Because pyridine is acting as a nucleophile to speed up the reaction, yet is unchanged by the reaction, it is called a **nucleophilic catalyst**.

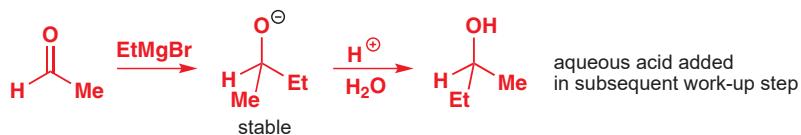
nucleophilic catalysis in ester formation



Interactive mechanism for pyridine nucleophilic catalysis

### Why are the tetrahedral intermediates unstable?

The alkoxide formed by addition of a Grignard reagent to an aldehyde or ketone is stable, lasting long enough to be protonated on work-up in acid to give an alcohol as product.



Tetrahedral intermediates are similarly formed by addition of a nucleophile, say ethanol in base, to the carbonyl group of acetyl chloride, but these tetrahedral intermediates are unstable. Why are they *unstable*? The answer is to do with leaving group ability. Once the nucleophile has added to the carbonyl compound, the stability of the product (or tetrahedral intermediate) depends on how good the groups attached to the new tetrahedral carbon atom are at leaving with the negative charge. In order for the tetrahedral intermediate to collapse (and therefore be just an intermediate and not the final product) one of the groups has to be able to leave and carry off the negative charge from the alkoxide anion formed in the addition.



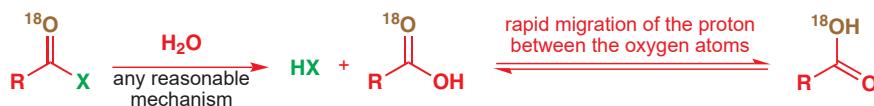
The most stable anion will be the best leaving group. There were three choices for the leaving group:  $\text{Cl}^-$ ,  $\text{EtO}^-$ , or  $\text{Me}^-$ . We can make  $\text{MeLi}$  but not  $\text{Me}^-$  because it is very unstable so  $\text{Me}^-$  must be a very bad leaving group.  $\text{EtO}^-$  is not so bad—alkoxide salts are stable, but they are still strong, reactive bases. But  $\text{Cl}^-$  is the best leaving group:  $\text{Cl}^-$  ions are perfectly stable and quite unreactive, and happily carry off the negative charge from the oxygen atom.

You probably eat several grams of  $\text{Cl}^-$  every day but you would be unwise to eat  $\text{EtO}^-$  or  $\text{MeLi}$ . So neither of these reactions occurs:



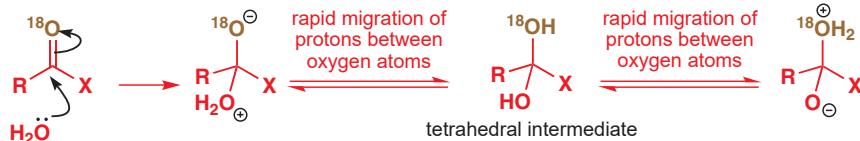
### How do we know that the tetrahedral intermediate exists?

We don't expect you to be satisfied with the bland statement that tetrahedral intermediates are formed in these reactions: of course, you wonder how we know that this is true. The first evidence for tetrahedral intermediates in the substitution reactions of carboxylic acid derivatives was provided by Bender in 1951. He made carboxylic acid derivatives  $\text{RCOX}$  that had been 'labelled' with an isotope of oxygen,  $^{18}\text{O}$ . This is a non-radioactive isotope that is detected by mass spectrometry. He then reacted these derivatives with water to make labelled carboxylic acids. By any reasonable mechanism, the products would have one  $^{18}\text{O}$  atom from the labelled starting material. Because the proton on a carboxylic acid migrates rapidly from one oxygen to another, both oxygens are labelled equally.

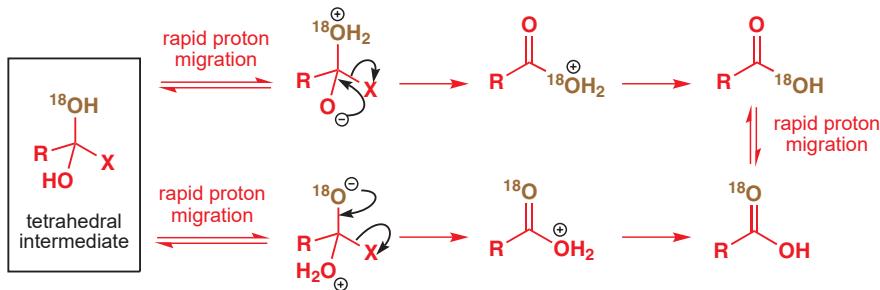


In Bender's original work, X was an alkoxy group (i.e.  $\text{RCOX}$  was an ester).

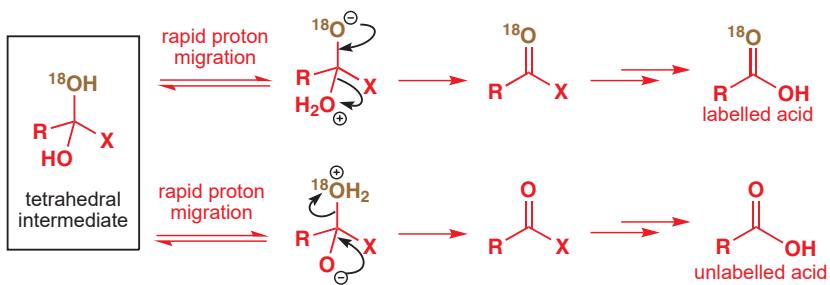
He then reacted these derivatives with insufficient water for complete consumption of the starting material. At the end of the reaction, he found that the proportion of labelled molecules in the *remaining starting material* had decreased significantly: in other words, it was no longer completely labelled with  $^{18}\text{O}$ ; some contained 'normal'  $^{16}\text{O}$ . The formation of the tetrahedral intermediate would be as before but rapid proton transfer would also mean that the two oxygen atoms would be the same. Now you may see the next step in the argument.



This result cannot be explained by direct substitution of X by  $\text{H}_2\text{O}$ , but is consistent with the existence of an intermediate in which the unlabelled  $^{16}\text{O}$  and labelled  $^{18}\text{O}$  can 'change places'. This intermediate is the *tetrahedral intermediate* for this reaction. Either isomer can lose X and in each case labelled carboxylic acid is formed.



But either tetrahedral intermediate could lose water instead. In one case (top line below) the original starting material is regenerated complete with label. But in the second case, labelled water is lost and *unlabelled starting material is formed*. This result would be difficult to explain without a tetrahedral intermediate with a lifetime long enough to allow for proton exchange. This 'addition–elimination' mechanism is now universally accepted.



### pK<sub>a</sub> is a useful guide to leaving group ability

It's useful to be able to compare leaving group ability quantitatively. This is impossible to do exactly, but a good guide is the pK<sub>a</sub> of the conjugate acid (Chapter 8). If X<sup>-</sup> is the leaving group, the lower the pK<sub>a</sub> of HX, the better X<sup>-</sup> is as a leaving group. If we go back to the example of ester formation from acyl chloride plus alcohol, there's a choice of Me<sup>-</sup>, EtO<sup>-</sup>, and Cl<sup>-</sup>. HCl is a stronger acid than EtOH, which is a much stronger acid than methane. So Cl<sup>-</sup> is the best leaving group and EtO<sup>-</sup> the next best. These observations apply only to reactions at the carbonyl group.

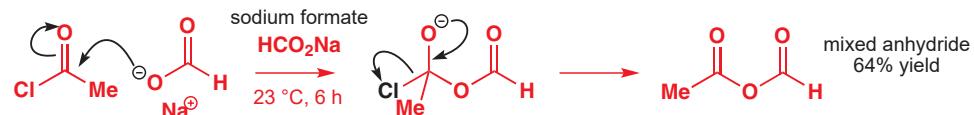
#### ● Leaving group ability

The lower the pK<sub>a</sub> of HX, the better the leaving group of X<sup>-</sup> in carbonyl substitution reactions.

The most important substituents in carbonyl reactions are alkyl or aryl groups (R), amino groups in amides (NH<sub>2</sub>), alkoxy groups in esters (RO<sup>-</sup>), carboxylate groups (RCO<sub>2</sub><sup>-</sup>) in anhydrides, and chloride (Cl<sup>-</sup>) in acyl chlorides. The order of leaving group ability is then:

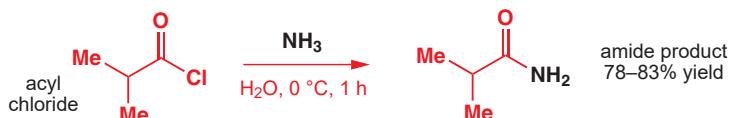
carboxylic acid derivative	leaving group, X <sup>-</sup>	conjugate acid, HX	pK <sub>a</sub> of HX	leaving group?
acyl chloride	Cl <sup>-</sup>	HCl	<0	excellent
anhydride	RCO <sub>2</sub> <sup>-</sup>	RCO <sub>2</sub> H	about 5	good
ester	RO <sup>-</sup>	ROH	about 15	poor
amide	NH <sub>2</sub> <sup>-</sup>	NH <sub>3</sub>	about 25	very poor
alkyl or aryl derivative	R <sup>-</sup>	RH	>40	not a leaving group

We can use pK<sub>a</sub> to predict what happens if we react an acyl chloride with a carboxylate salt. We expect the carboxylate salt (here, sodium formate or sodium methanoate, HCO<sub>2</sub>Na) to act as the nucleophile to form a tetrahedral intermediate, which could collapse in any one of three ways. We can straightaway rule out loss of Me<sup>-</sup> and we might guess that Cl<sup>-</sup> is a better leaving group than HCO<sub>2</sub><sup>-</sup> as HCl is a much stronger acid than a carboxylic acid, and we'd be right. Sodium formate reacts with acetyl chloride to give a mixed anhydride.

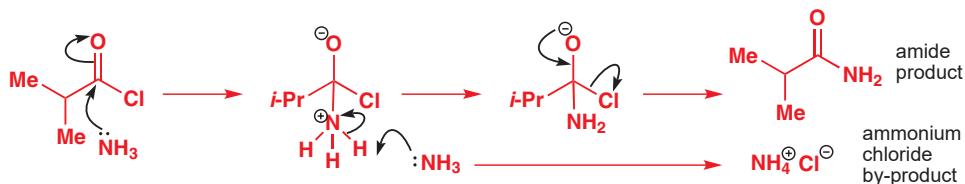


### Amines react with acyl chlorides to give amides

Using the principles we've outlined above, you should be able to see how these compounds can be interconverted by substitution reactions with appropriate nucleophiles. We've seen that acid chlorides react with carboxylic acids to give acid anhydrides, and with alcohols to give esters. They also react with amines (such as ammonia) to give amides.

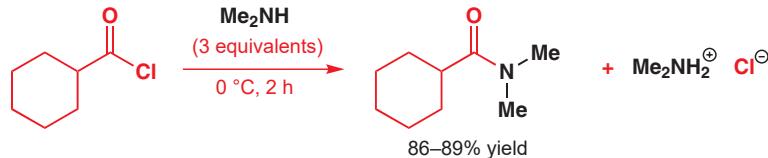


The mechanism is very similar to the mechanism of ester formation. Notice the second molecule of ammonia, which removes a proton, and the loss of chloride ion—the leaving group—to form the amide. Ammonium chloride is formed as a by-product in the reaction.



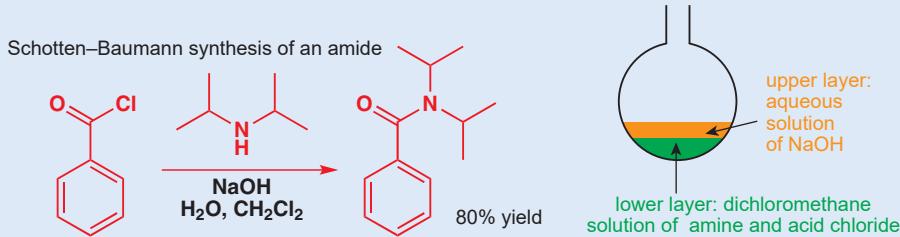
## Interactive mechanism for amide formation

Here is another example, using a secondary amine, dimethylamine. Try writing down the mechanism now without looking at the one above. Again, two equivalents of dimethylamine are necessary, although the chemists who published this reaction added three for good measure.



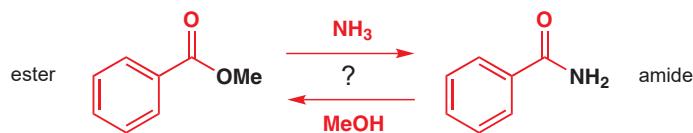
## Schotten–Baumann synthesis of an amide

As these mechanisms show, the formation of amides from acid chlorides and amines is accompanied by production of one equivalent of HCl, which needs to be neutralized by a second equivalent of amine. An alternative method for making amides is to carry out the reaction in the presence of another base, such as NaOH, which then does the job of neutralizing the HCl. The trouble is, OH<sup>-</sup> also attacks acyl chlorides to give carboxylic acids. Schotten and Baumann, in the late nineteenth century, published a way round this problem by carrying out these reactions in two-phase systems of immiscible water and dichloromethane. The organic amine (not necessarily ammonia) and the acyl chloride remain in the (lower) dichloromethane layer, while the base (NaOH) remains in the (upper) aqueous layer. Dichloromethane and chloroform are two common organic solvents that are heavier (more dense) than water. The acyl chloride reacts only with the amine, but the HCl produced can dissolve in, and be neutralized by, the aqueous solution of NaOH.



## **Using base strength to predict the outcome of substitution reactions of carboxylic acid derivatives**

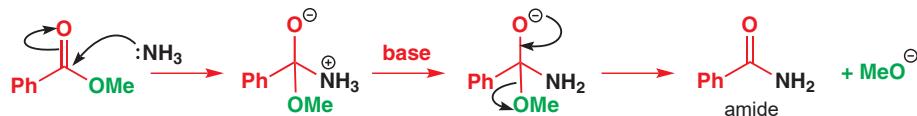
You saw that acid anhydrides react with alcohols to give esters: they will also react with amines to give amides. But would you expect esters to react with amines to give amides, or amides to react with alcohols to give esters? Both appear reasonable.



In fact only the top reaction works: amides can be formed from esters but esters cannot be formed from amides. The key question is: which group will leave from the common tetrahedral intermediate? The answer is  $\text{MeO}^-$  and not  $\text{NH}_2^-$ . You should have worked this out from the stability of the anions. Alkoxides are reasonably strong bases ( $pK_a$  of ROH about 15) so they are not good leaving groups. But  $\text{NH}_2^-$  is a very unstable anion ( $pK_a$  of  $\text{NH}_3$  about 25) and is a very bad leaving group.

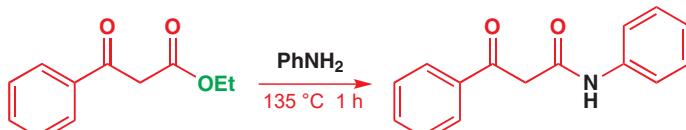
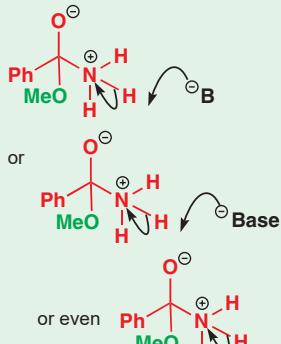


So  $\text{MeO}^-$  leaves and the amide is formed. The base used to deprotonate the first formed intermediate may be either the  $\text{MeO}^-$  produced in the reaction or, to start with, another molecule of  $\text{NH}_3$ .



Here is a slightly unusual example in that there is a ketone present in the molecule as well. Later in the book we shall consider how to work out whether another functional group might interfere with the reaction we want to do.

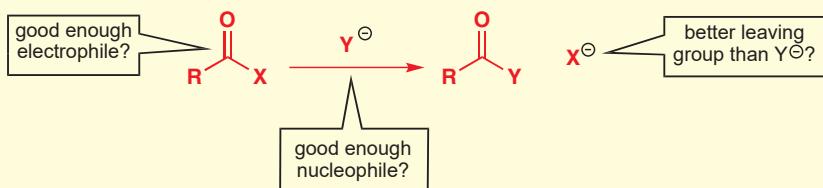
■ You will meet many more mechanisms like this, in which an unspecified base removes a proton from an intermediate. As long as you can satisfy yourself that there is a base available to perform the task, it is quite acceptable to write any of these shorthand mechanisms.



### Factors other than leaving group ability can be important

In fact, the tetrahedral intermediate would simply never form from an amide and an alcohol; the amide is too bad an electrophile and the alcohol not a good enough nucleophile. We've looked at leaving group ability: next we'll consider the strength of the nucleophile Y and then the strength of the electrophile RCOX.

#### ● Conditions for reaction



If this reaction is to go:

- 1  $\text{X}^-$  must be a better leaving group than  $\text{Y}^-$  (otherwise the reverse reaction would take place).
- 2  $\text{Y}^-$  must be a strong enough nucleophile to attack  $\text{RCOX}$ .
- 3  $\text{RCOX}$  must be a good enough electrophile to react with  $\text{Y}^-$ .

## Strength of nucleophile and leaving group ability are related and $pK_a$ is a guide to both

We have seen how  $pK_a$  gives us a guide to leaving group ability: it is also a good guide to how strong a nucleophile will be. These two properties are the reverse of each other: good nucleophiles are bad leaving groups. A stable anion is a good leaving group but a poor nucleophile. Anions of weak acids ( $\text{HA}$  has high  $pK_a$ ) are bad leaving groups but good nucleophiles towards the carbonyl group.

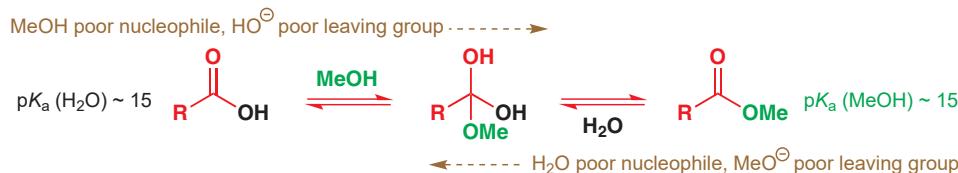
► We will come back to this concept again in Chapter 15, where you will see that this principle does not apply to substitution at saturated carbon atoms.

### ● Guide to nucleophilicity

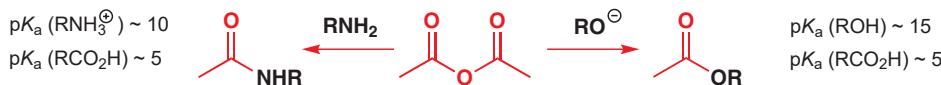
*In general, the higher the  $pK_a$  of  $\text{AH}$  the better  $\text{A}^-$  is as a nucleophile.*

But just a moment—we've overlooked an important point. We have sometimes used anions as nucleophiles (for example when we made acid anhydrides from acid chlorides plus carboxylate salts, we used an anionic nucleophile  $\text{RCO}_2^-$ ) but on other occasions we have used neutral nucleophiles (for example when we made amides from acid chlorides plus amines, we used a neutral nucleophile  $\text{NH}_3$ ). Anions are better nucleophiles for carbonyl groups than are neutral compounds so we can choose our nucleophilic reagent accordingly.

For proper comparisons, we should use the  $pK_a$  of  $\text{NH}_4^+$  (about 10) if we are using neutral ammonia, but the  $pK_a$  of  $\text{RCO}_2\text{H}$  (about 5) if we're using the carboxylate anion. Ammonia is a good nucleophile and we don't usually need its anion but carboxylic acids are very weak nucleophiles and we often use their anions. You will see later in this chapter that we can alter this with acid catalysts. So this reaction works badly in either direction. We don't make or hydrolyse esters this way.

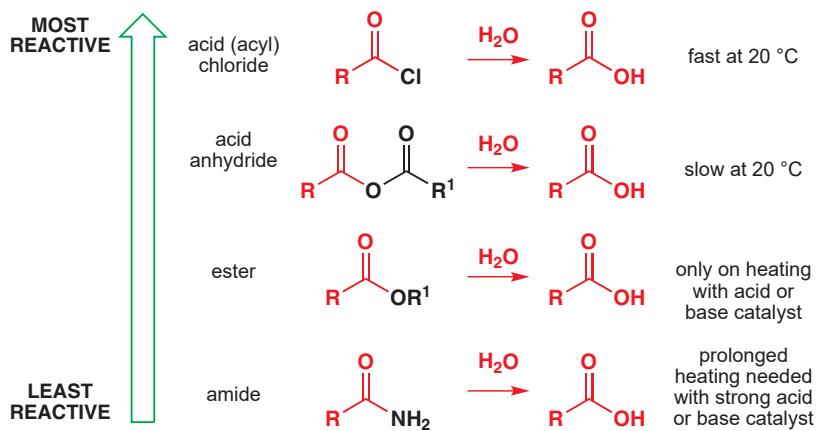


While amines react with acetic anhydride quite rapidly at room temperature (reaction complete in a few hours), alcohols react extremely slowly in the absence of a base. On the other hand, an alkoxide anion reacts with acetic anhydride extremely rapidly—the reactions are often complete within seconds at 0 °C. We don't have to deprotonate an alcohol completely to increase its reactivity: just a catalytic quantity of a weak base can do this job. All the  $pK_a$ s you need are in Chapter 8.



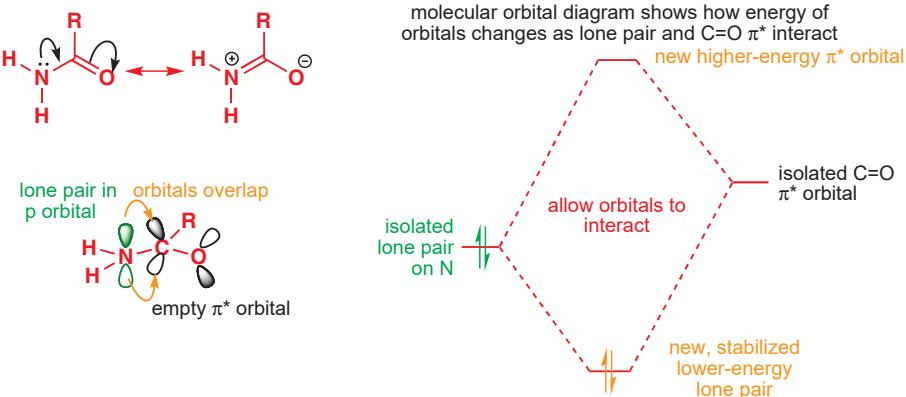
## Not all carboxylic acid derivatives are equally reactive

We can list the common carboxylic acid derivatives in a ‘hierarchy’ of reactivity, with the most reactive at the top and the least reactive at the bottom. The nucleophile is the same in each case (water), as is the product, the carboxylic acid, but the electrophiles vary from very reactive to unreactive. The conditions needed for successful reaction show just how large is the variation on reactivity. Acid chlorides react violently with water. Amides need refluxing with 10% NaOH or concentrated HCl in a sealed tube at 100 °C overnight. We've seen that this hierarchy is partly due to how good the leaving group is (the ones at the top are best). But it also depends on the reactivity of the acid derivatives. Why is there such a large difference?

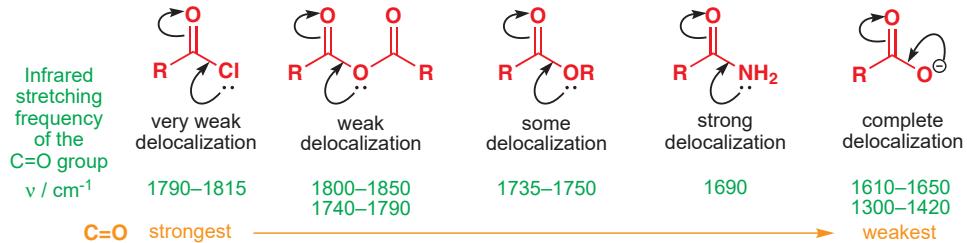


### Delocalization and the electrophilicity of carbonyl compounds

Amides are the least reactive towards nucleophiles because they exhibit the greatest degree of delocalization. You met this concept in Chapter 7 and we shall return to it many times more. In an amide, the lone pair on the nitrogen atom can be stabilized by overlap with the  $\pi^*$  orbital of the carbonyl group—this overlap is best when the lone pair occupies a p orbital (in an amine, it would occupy an  $sp^3$  orbital).



The molecular orbital diagram shows how this interaction both lowers the energy of the bonding orbital (the delocalized nitrogen lone pair), making it neither basic nor nucleophilic, and raises the energy of the  $\pi^*$  orbital, making it less ready to react with nucleophiles. Esters are similar, but because the oxygen lone pairs are lower in energy, the effect is less pronounced. The degree of delocalization depends on the electron-donating power of the substituent and increases along the series of compounds below from almost no delocalization from Cl to complete delocalization in the carboxylate anion, where the negative charge is equally shared between the two oxygen atoms.



The greater the degree of delocalization, the weaker the C=O bond becomes. This is most clearly evident in the stretching frequency of the carbonyl group in the IR spectra of

carboxylic acid derivatives—remember that the stretching frequency depends on the force constant of the bond, itself a measure of the bond's strength. The carboxylate anion is included because it represents the limit of the series, with complete delocalization of the negative charge over the two oxygen atoms. There are two frequencies for the anhydride and the carboxylate anion because of symmetric and antisymmetric stretching of identical bonds.

Amides react as electrophiles only with powerful nucleophiles such as  $\text{HO}^-$ . Acid chlorides, on the other hand, react with even quite weak nucleophiles: neutral  $\text{ROH}$ , for example. They are more reactive because the electron-withdrawing effect of the chlorine atom increases the electrophilicity of the carbonyl carbon atom.

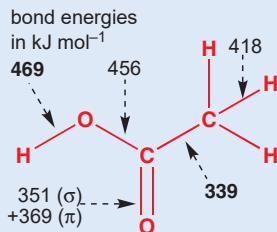
► Infrared spectroscopy was introduced in Chapter 3.

### Bond strengths and reactivity

You may think that a weaker  $\text{C}=\text{O}$  bond should be more reactive. This is not so because the partial positive charge on carbon is also lessened by delocalization and because the molecule as a whole is stabilized by the delocalization. Bond strength is not always a good guide to reactivity!

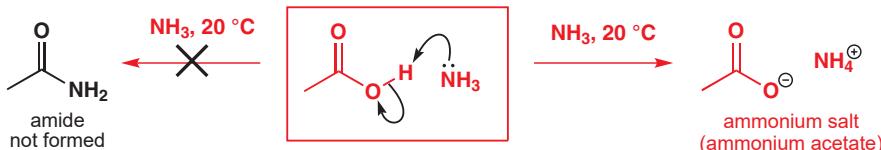
For example, in acetic acid the bond strengths are surprising. The strongest bond is the  $\text{O}-\text{H}$  bond and the weakest is the  $\text{C}-\text{C}$  bond. Yet very few reactions of acetic acid involve breaking the  $\text{C}-\text{C}$  bond, and its characteristic reactivity, as an acid, involves breaking  $\text{O}-\text{H}$ , the strongest bond of them all!

The reason is that polarization of bonds and solvation of ions play an enormously important role in determining the reactivity of molecules. In Chapter 37 you will see that radicals are relatively unaffected by solvation and that their reactions follow bond strengths much more closely.



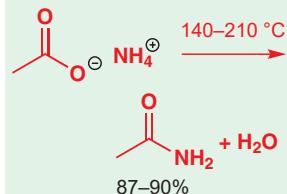
### Carboxylic acids do not undergo substitution reactions under basic conditions

Substitution reactions of  $\text{RCO}_2\text{H}$  require a leaving group  $\text{OH}^-$ . The  $\text{pK}_a$  of water is about 15, so acids should be about as electrophilic as esters. Esters react well with ammonia to give amides. However, if we try to react carboxylic acids with amines to give amides no substitution occurs: an ammonium salt is formed because the amines themselves are basic and remove the acidic proton from the acid.



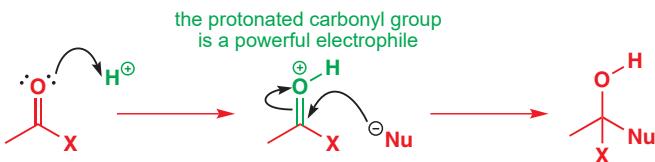
Once the carboxylic acid is deprotonated, substitutions are prevented because (almost) no nucleophile will attack the carboxylate anion. Under neutral conditions, alcohols are just not reactive enough to add to the carboxylic acid but, with *acid* catalysis, esters can be formed from alcohols and carboxylic acids.

■ In fact, amides *can* be made from carboxylic acids plus amines, but only if the ammonium salt is heated strongly to dehydrate it. This is not usually a good way of making amides!

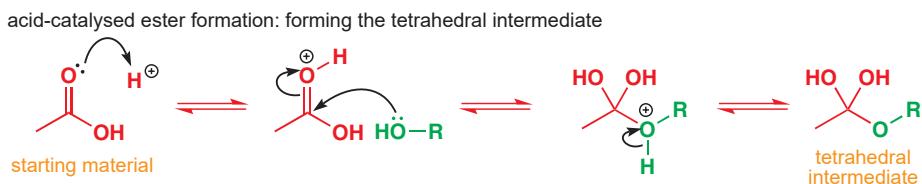


### Acid catalysts increase the reactivity of a carbonyl group

We saw in Chapter 6 that the lone pairs of a carbonyl group may be protonated by acid. Only strong acids are powerful enough to protonate carbonyl groups: the  $\text{pK}_a$  of protonated acetone is  $-7$  so, for example, even 1M HCl (pH 0) would protonate only 1 in  $10^7$  molecules of acetone. However, even proportions as low as this are sufficient to increase the rate of substitution reactions at carbonyl groups enormously because those carbonyl groups that are protonated become extremely powerful electrophiles.



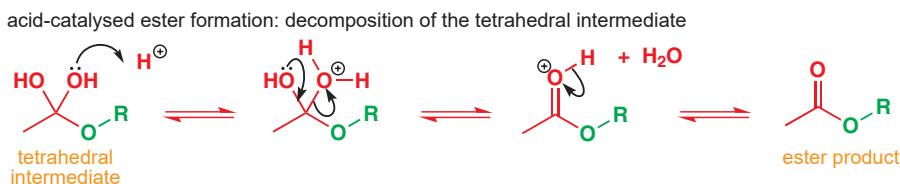
It is for this reason that alcohols will react with carboxylic acids under acid catalysis. The acid (usually HCl or  $\text{H}_2\text{SO}_4$ ) reversibly protonates a small percentage of the carboxylic acid molecules, and the protonated carboxylic acids are extremely susceptible to attack by even a weak nucleophile such as an alcohol. This is the first half of the reaction:



### Acid catalysts can make bad leaving groups into good ones

- Average bond strength C=O 720 kJ mol<sup>-1</sup>.
- Average bond strength C–O 350 kJ mol<sup>-1</sup>.

This tetrahedral intermediate is unstable because the energy to be gained by re-forming a C=O bond is greater than that used in breaking two C–O bonds. As it stands, none of the leaving groups ( $\text{R}^-$ ,  $\text{HO}^-$ , or  $\text{RO}^-$ ) is very good. However, help is again at hand in the acid catalyst. It can protonate any of the oxygen atoms reversibly. Again, only a very small proportion of molecules are protonated at any one time but, once the oxygen atom of, say, one of the OH groups is protonated, it becomes a much better leaving group (water instead of  $\text{HO}^-$ ). Loss of ROH from the tetrahedral intermediate is also possible: this leads back to starting materials—hence the equilibrium arrow in the scheme above. Loss of  $\text{H}_2\text{O}$  is more fruitful, and takes the reaction forwards to the ester product.

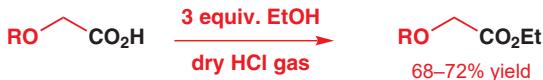


#### • Acid catalysts catalyse substitution reactions of carboxylic acids.

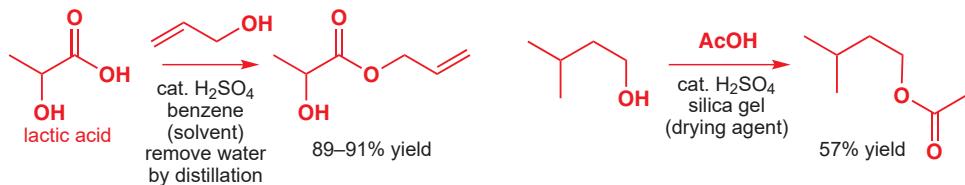
- They make the carbonyl group more electrophilic by protonation at *carbonyl* oxygen.
- They make the leaving group better by protonation there too.

### Ester formation is reversible: how to control an equilibrium

Loss of water from the tetrahedral intermediate is reversible too: just as ROH will attack a protonated carboxylic acid,  $\text{H}_2\text{O}$  will attack a protonated ester. In fact, every step in the sequence from carboxylic acid to ester is an equilibrium, and the overall equilibrium constant is about 1. In order for this reaction to be useful, it is therefore necessary to ensure that the equilibrium is pushed towards the ester side by using an excess of alcohol or carboxylic acid (usually the reactions are done in a solution of the alcohol or the carboxylic acid). In this reaction, for example, no water is added and an excess of alcohol is used. Using less than three equivalents of ethanol gave lower yields of ester.



Alternatively, the reaction can be done in the presence of a dehydrating agent (concentrated  $\text{H}_2\text{SO}_4$ , for example, or silica gel) or the water can be distilled out of the mixture as it forms.



### ● Making esters from alcohols

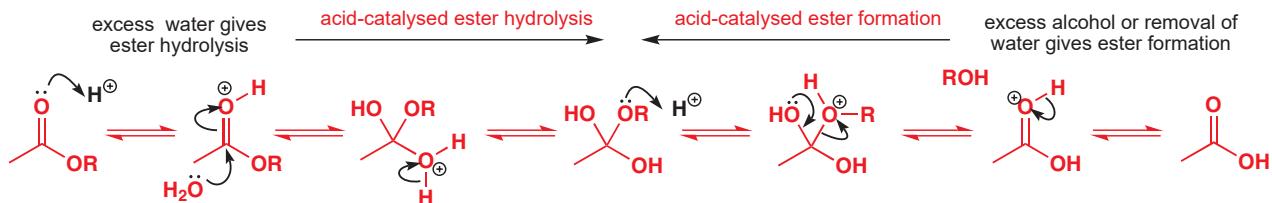
You have now met three ways of making esters from alcohols:

- with acyl chlorides
- with acid anhydrides
- with carboxylic acids.

Try to appreciate that different methods will be appropriate at different times. If you want to make a few milligrams of a complex ester, you are much more likely to work with a reactive acyl chloride or anhydride, using pyridine as a weakly basic catalyst, than to try to distil out a minute quantity of water from a reaction mixture containing a strong acid that may destroy the starting material. On the other hand, if you are a chemist making simple esters (such as those in Chapter 2, p. 31) for the flavouring industry on a scale of many tons, you might prefer the cheaper option of carboxylic acid and a strong acid (e.g.  $\text{H}_2\text{SO}_4$ ) in alcohol solution.

### Acid-catalysed ester hydrolysis and transesterification

By starting with an ester, an excess of water, and an acid catalyst we can persuade the reverse reaction to occur: formation of the carboxylic acid plus alcohol with consumption of water. Such a reaction is known as a hydrolysis reaction because water is used to break up the ester into carboxylic acid plus alcohol (*lysis*=breaking).

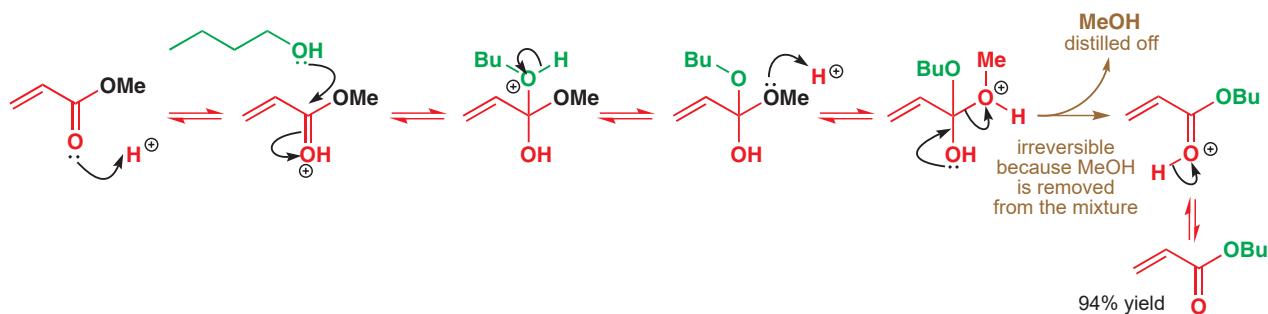


Acid-catalysed ester formation and hydrolysis are the exact reverse of one another: the only way we can control the reaction is by altering concentrations of reagents to drive the reaction the way we want it to go. The same principles can be used to convert an ester of one alcohol into an ester of another, a process known as transesterification. It is possible, for example, to force this equilibrium to the right by distilling methanol (which has a lower boiling point than the other components of the reaction) out of the mixture.

Interactive mechanism for acid-catalysed ester formation

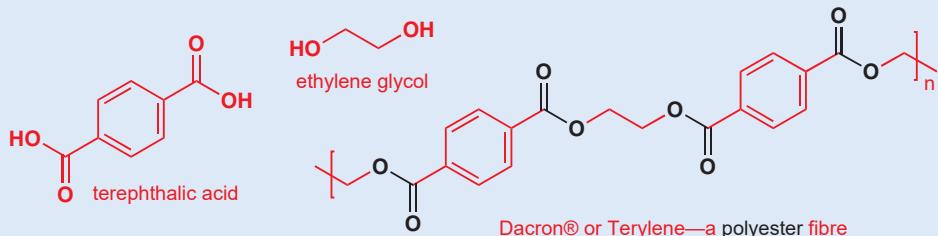


The mechanism for this transesterification simply consists of adding one alcohol (here  $\text{BuOH}$ ) and eliminating the other (here  $\text{MeOH}$ ), both processes being acid-catalysed. Notice how easy it is now to confirm that the reaction is *catalytic* in  $\text{H}^+$ .

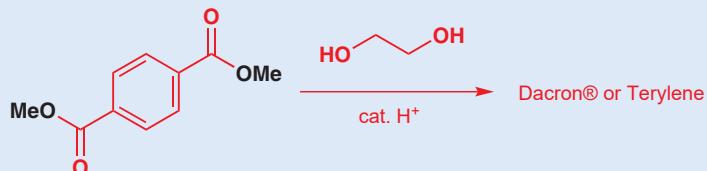


### Polyester fibre manufacture

A transesterification reaction is used to make the polyester fibres that are used for textile production. Terylene, or Dacron, for example, is a polyester of the dicarboxylic acid terephthalic acid and the diol ethylene glycol.



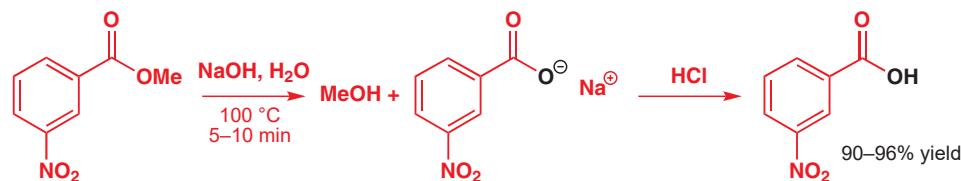
Terylene is actually made by ester exchange: dimethyl terephthalate is heated with ethylene glycol and an acid catalyst, distilling off the methanol as it is formed.



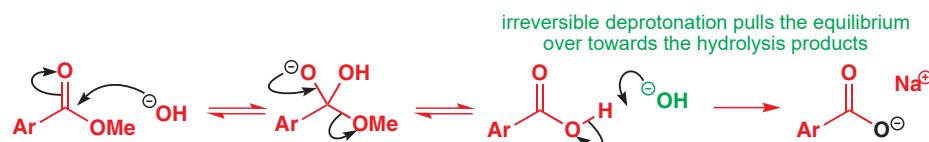
Interactive structure of polyester fibres

### Base-catalysed hydrolysis of esters is irreversible

You can't make esters from carboxylic acids and alcohols under basic conditions because the base deprotonates the carboxylic acid (see p. 207). However, you can reverse that reaction and hydrolyse an ester to a carboxylic acid (more accurately, a carboxylate salt) and an alcohol.



This time the ester is, of course, not protonated first as it would be in acid, but the unprotonated ester is a good enough electrophile because OH<sup>-</sup>, and not water, is the nucleophile. The tetrahedral intermediate can collapse either way, giving back ester or going forward to acid plus alcohol.



The backward reaction is impossible because the basic conditions straightaway deprotonate the acid to make a carboxylate salt (which, incidentally, consumes the base, making at least one equivalent of base necessary in the reaction). Carboxylate salts do not usually react with nucleophiles, even those a good deal stronger than alcohols.

## How do we know this is the mechanism?

Ester hydrolysis is such an important reaction that chemists have spent a lot of time and effort finding out exactly how it works. Many of the experiments that tell us about the mechanism involve oxygen-18 labelling. The starting material is an ester enriched in the heavy oxygen isotope  $^{18}\text{O}$ . By knowing where the heavy oxygen atoms start off, and following (by mass spectrometry—Chapter 3) where they end up, the mechanism can be established.

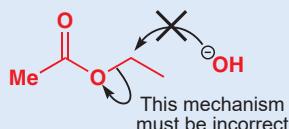
1. An  $^{18}\text{O}$  label in the 'ether' oxygen of the ester ends up in the alcohol product.



2. Hydrolysis with  $^{18}\text{OH}_2$ , gives  $^{18}\text{O}$ -labelled carboxylic acid, but no  $^{18}\text{O}$ -labelled alcohol.



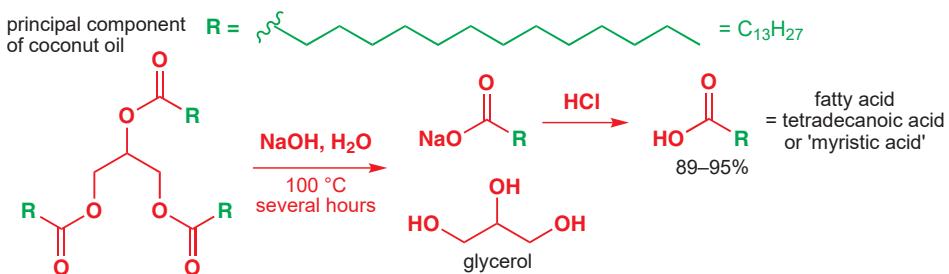
These experiments tell us that a displacement (substitution) has occurred at the carbonyl carbon atom, and rule out the alternative displacement at saturated carbon.



One further labelling experiment showed that a tetrahedral intermediate must be formed: an ester labelled with  $^{18}\text{O}$  in its carbonyl oxygen atom passes some of its  $^{18}\text{O}$  label to the water. We discussed this on p. 201.

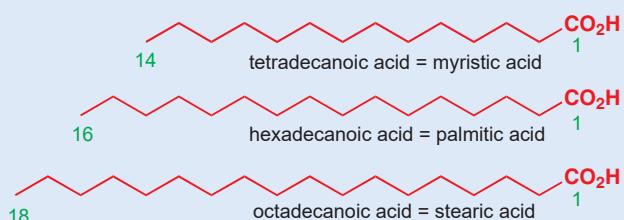
There is more on the mechanism of ester hydrolysis in Chapter 12.

The saturated fatty acid tetradecanoic acid (also known as myristic acid) is manufactured commercially from coconut oil by hydrolysis in base. You may be surprised to learn that coconut oil contains more saturated fat than butter, lard, or beef dripping: much of it is the trimyristate ester of glycerol. Hydrolysis with aqueous sodium hydroxide, followed by reprotonation of the sodium carboxylate salt with acid, gives myristic acid. Notice how much longer it takes to hydrolyse this branched ester than it did to hydrolyse a methyl ester (p. 210).



### Saponification

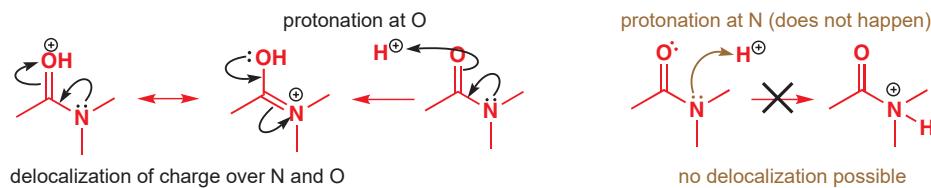
The alkaline hydrolysis of esters to give carboxylate salts is known as saponification because it is the process used to make soap. Traditionally, beef tallow (the tristearate ester of glycerol—stearic acid is octadecanoic acid,  $C_{17}H_{35}CO_2H$ ) was hydrolysed with sodium hydroxide to give sodium stearate,  $C_{17}H_{35}CO_2Na$ , the principal component of soap. Finer soaps are made from palm oil and contain a higher proportion of sodium palmitate,  $C_{15}H_{31}CO_2Na$ . Hydrolysis with KOH gives potassium carboxylates, which are used in liquid soaps. Soaps like these owe their detergent properties to the combination of polar (carboxylate group) and non-polar (long alkyl chain) properties.



### Amides can be hydrolysed under acidic or basic conditions too

In order to hydrolyse amides, the least reactive of the carboxylic acid derivatives, we have a choice: we can persuade the amine leaving group to leave by protonating it, or we can use brute force and forcibly eject it with concentrated hydroxide solution.

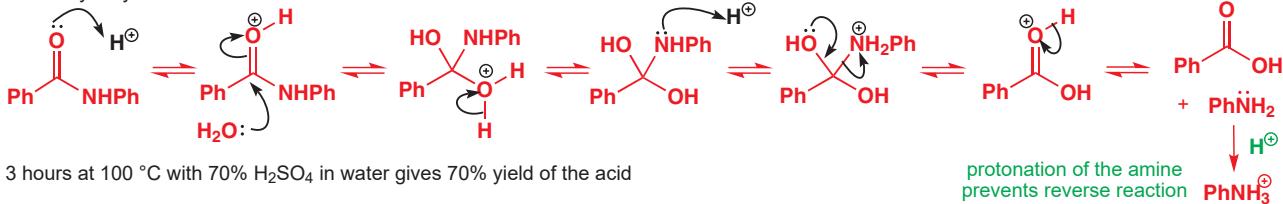
Amides are very unreactive as electrophiles, but they are also rather more basic than most carboxylic acid derivatives: a typical protonated amide has a  $pK_a$  of  $-1$ ; most other carbonyl compounds are much less basic. You might therefore imagine that the protonation of an amide would take place on nitrogen—after all, *amine* nitrogen atoms are readily protonated. And, indeed, the reason for the basicity of amides is the nitrogen atom's delocalized lone pair, making the carbonyl group unusually electron rich. But amides are always protonated on the oxygen atom of the carbonyl group, never the nitrogen, because protonation at nitrogen would disrupt the delocalized system that makes amides so stable. Protonation at oxygen gives a delocalized cation (Chapter 8).



■ Notice that this means that one equivalent of acid is used up in this reaction—the acid is not solely a catalyst.

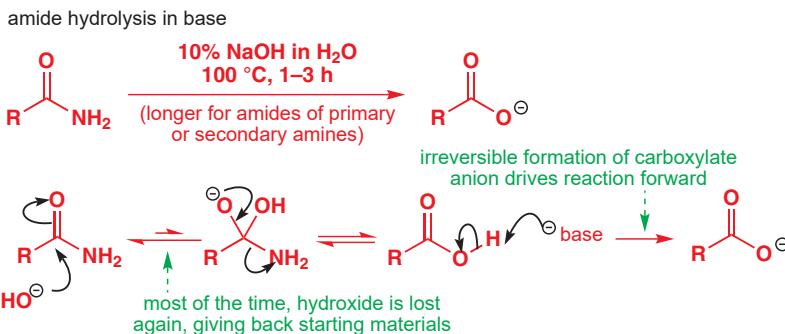
Protonation of the carbonyl group by acid makes the carbonyl group electrophilic enough for attack by water, giving a neutral tetrahedral intermediate. The amine nitrogen atom in the tetrahedral intermediate is much more basic than the oxygen atoms, so now *it* gets protonated, and the  $RNH_2$  group becomes really quite a good leaving group. Once it has left, it will immediately be protonated again, and therefore become completely non-nucleophilic. The conditions are very vigorous—70% sulfuric acid for 3 hours at  $100^\circ C$ .

amide hydrolysis in acid

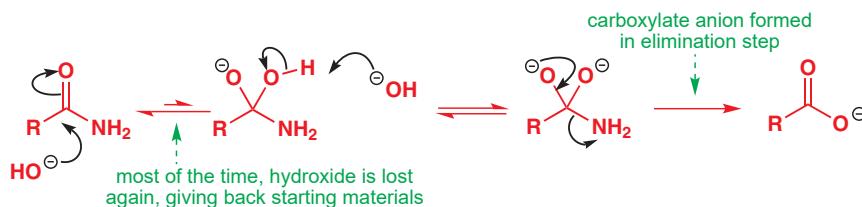


3 hours at  $100^\circ C$  with 70%  $H_2SO_4$  in water gives 70% yield of the acid

Hydrolysis of amides in base requires similarly vigorous conditions. Hot solutions of hydroxide are sufficiently powerful nucleophiles to attack an amide carbonyl group, although even when the tetrahedral intermediate has formed  $\text{NH}_2^-$  ( $\text{p}K_a$  of the ammonium ion 35) has only a slight chance of leaving when  $\text{HO}^-$  ( $\text{p}K_a$  of water 15) is an alternative. Nonetheless, at high temperatures amides are slowly hydrolysed by concentrated base since one product is the carboxylate salt and this does not react with nucleophiles. The 'base' for the irreversible step might be hydroxide or  $\text{NH}_2^-$ .

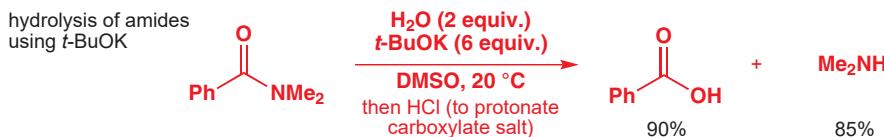


Secondary and tertiary amides hydrolyse much more slowly under these conditions. With all these amides a second mechanism kicks in if the hydroxide concentration is large enough. More hydroxide deprotonates the tetrahedral anion to give a dianion that must lose  $\text{NH}_2^-$  as the only alternative is  $\text{O}^{2-}$ . This leaving group deprotonates water so the second molecule of hydroxide ion is simply a catalyst.



■ You've not seen the option of  $\text{O}^{2-}$  as a leaving group before but this is what you would need if you want to break the bond to  $\text{O}^-$ . Asking  $\text{O}^{2-}$  to be a leaving group is like asking  $\text{HO}^-$  to be an acid.

A similar mechanism is successful with only a little water and plenty of strong base. Then even tertiary amides can be hydrolysed at room temperature. Potassium *tert*-butoxide is a strong enough base ( $\text{p}K_a$  of *t*-BuOH about 18) to deprotonate the tetrahedral intermediate.



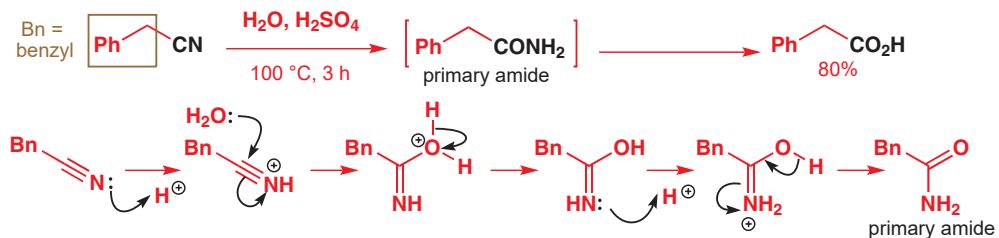
### Hydrolysing nitriles: how to make the almond extract, mandelic acid

Closely related to the amides are nitriles. You can view them as primary amides that have lost one molecule of water and, indeed, they can be made by dehydrating primary amides.

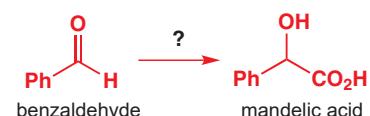
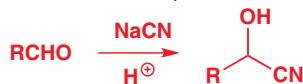


They can be hydrolysed just like amides too. Addition of water to the protonated nitrile gives a primary amide, and hydrolysis of this amide gives carboxylic acid plus ammonia.

- Don't be put off by the number of steps in this mechanism—look carefully and you will see that most of them are simple proton transfers. The only step that isn't a proton transfer is the addition of water.

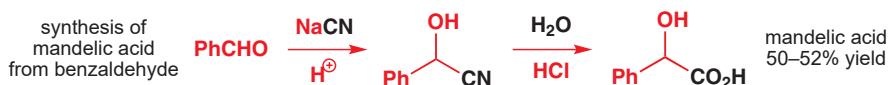


You met a way of making nitriles—from HCN (or NaCN + HCl) plus aldehydes—in Chapter 6: the hydroxynitrile products are known as **cyanohydrins**. With this in mind, you should be able to suggest a way of making mandelic acid, an extract of almonds, from benzaldehyde.



This is how some chemists did it.

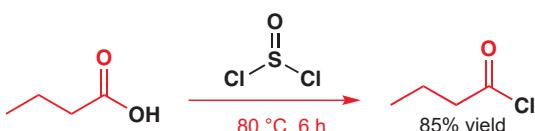
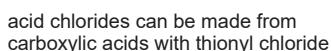
■ You have just designed your first total synthesis of a natural product. We return to designing syntheses much later in this book, in Chapter 28.



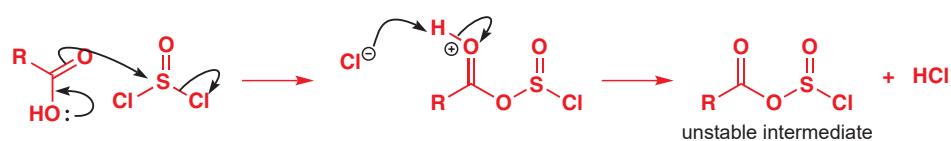
**Acid chlorides can be made from carboxylic acids using  $\text{SOCl}_2$  or  $\text{PCl}_5$**

We have looked at a whole series of interconversions between carboxylic acid derivatives and, after this next section, we shall summarize what you need to understand. We said that it is always easy to move down the series of acid derivatives we listed early in the chapter, and so far that is all we have done. But some reactions of carboxylic acids also enable us to move upwards in the series. What we need is a reagent that changes the bad leaving group  $\text{HO}^-$  into a good leaving group. Strong acid does this by protonating the  $\text{OH}^-$ , allowing it to leave as  $\text{H}_2\text{O}$ . In this section we look at two more reagents,  $\text{SOCl}_2$  and  $\text{PCl}_5$ , which convert the OH group of a carboxylic acid and also turn it into a good leaving group. Thionyl chloride,  $\text{SOCl}_2$ , reacts with carboxylic acids to make acyl chlorides.

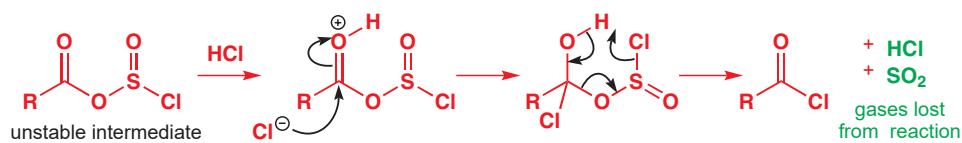
■ Note that it is the more nucleophilic carbonyl oxygen which actually attacks S. If you follow the fate of the two oxygens right through the mechanism you will see which fact it is the oxygen that starts off in the C=O group which is replaced by Cl. You may also be surprised to see the way we substituted at S=O without forming a 'tetrahedral intermediate'. Well, this trivalent sulfur atom is already tetrahedral (it still has one lone pair), and substitution can go by a direct substitution at sulfur.



This volatile liquid with a choking smell is electrophilic at the sulfur atom (as you might expect with two chlorine atoms and an oxygen atom attached) and is attacked by carboxylic acids to give an unstable, and highly electrophilic, intermediate.

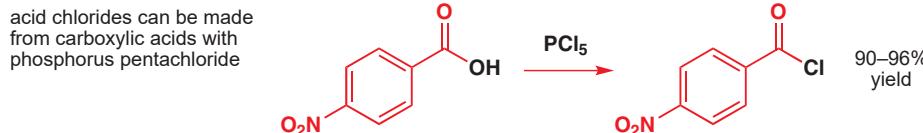


Reprotonation of the unstable intermediate (by the HCl just produced, i.e. reversal of the last step above) gives an electrophile powerful enough to react even with the weak nucleophile  $\text{Cl}^-$  (HCl is a strong acid, so  $\text{Cl}^-$  is a poor nucleophile). The tetrahedral intermediate collapses to the acyl chloride, sulfur dioxide, and hydrogen chloride. This step is irreversible because  $\text{SO}_2$  and HCl are gases that are lost from the reaction mixture.



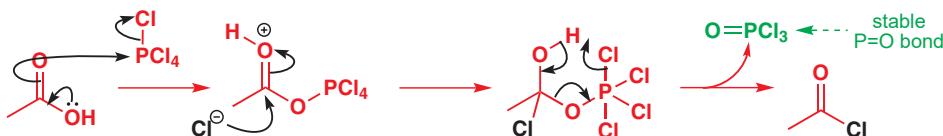
Interactive mechanism for acid chloride formation with  $\text{SOCl}_2$

Although  $\text{HCl}$  is involved in this reaction, it cannot be used as the sole reagent for making acid chlorides. It is necessary to have a sulfur or phosphorus compound to remove the oxygen. An alternative reagent for converting  $\text{RCOOH}$  into  $\text{RCOCl}$  is phosphorus pentachloride,  $\text{PCl}_5$ . The mechanism is similar—try writing it out before looking at the scheme below.



The mechanism is closely related to the previous one, except that the formation of a very stable  $\text{P}=\text{O}$  bond is the vital factor rather than the loss of two gaseous reagents.

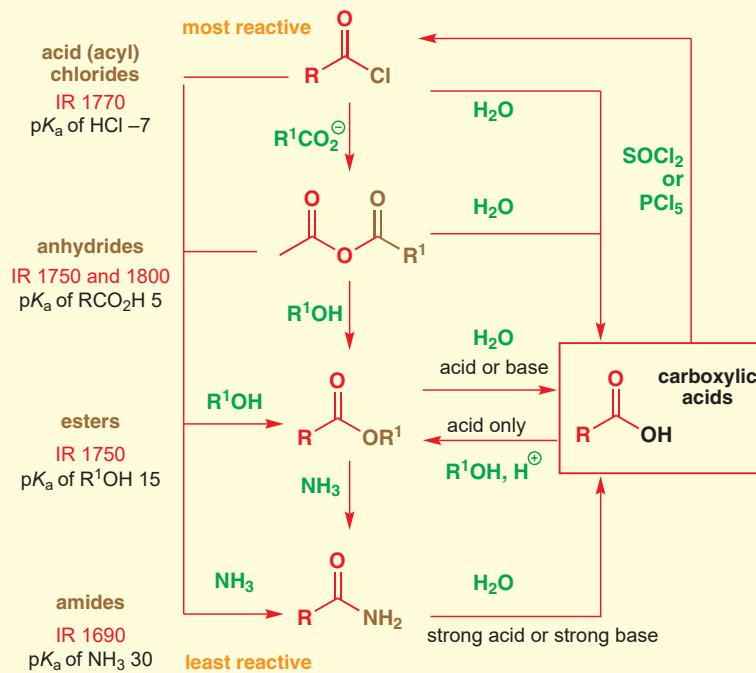
Interactive mechanism for acid chloride formation with  $\text{PCl}_5$



These conversions of acids into acid chlorides complete all the methods we need to convert acids into any acid derivatives. You can convert acids directly to esters and now to acid chlorides, the most reactive of acid derivatives, and can make any other derivative from them. The chart below adds reaction conditions, relevant  $\text{pK}_a$ s, and infrared stretching frequencies to the reactivity order we met earlier.

We will explore the link between infrared stretching frequency and reactivity in Chapter 18.

### ● Interconversion of carboxylic acid derivatives



All these acid derivatives can, of course, be hydrolysed to the acid itself with water alone or with various levels of acid or base catalysis depending on the reactivity of the derivative.

To climb the reactivity order therefore, the simplest method is to hydrolyse to the acid and convert the acid into the acid chloride. You are now at the top of the reactivity order and can go down to whatever level you require.

## Making other compounds by substitution reactions of acid derivatives

- Five 'oxidation levels'—(1) hydrocarbon, (2) alcohol, (3) aldehyde and ketone, (4) carboxylic acid, and (5)  $\text{CO}_2$ —were defined in Chapter 2.

We've talked at length about the interconversions of acid derivatives, explaining the mechanism of attack of nucleophiles such as  $\text{ROH}$ ,  $\text{H}_2\text{O}$ , and  $\text{NH}_3$  on acyl chlorides, acid anhydrides, esters, acids, and amines, with or without acid or base present. We shall now go on to talk about substitution reactions of acid derivatives that take us out of this closed company of compounds and allow us to make compounds containing functional groups at other oxidation levels, such as ketones and alcohols.

## Making ketones from esters: the problem

Substitution of the OR group of an ester by an R group would give us a ketone. You might therefore think that reaction of an ester with an organolithium or Grignard reagent would be a good way of making ketones. However, if we try the reaction, something else happens, as you saw at the start of this chapter.



Two molecules of Grignard have been incorporated and we get an alcohol! If we look at the mechanism we can understand why this should be so. First, as you would expect, the nucleophilic Grignard reagent attacks the carbonyl group to give a tetrahedral intermediate. The only reasonable leaving group is  $\text{RO}^-$ , so it leaves to give us the ketone we set out to make.

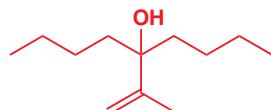


Now, the next molecule of Grignard reagent has a choice. It can react with either the ester starting material or the newly formed ketone. Ketones are more electrophilic than esters so the Grignard reagent prefers to react with the ketone in the manner you saw in Chapter 9. A stable alkoxide anion is formed, which gives the tertiary alcohol on acid work-up.

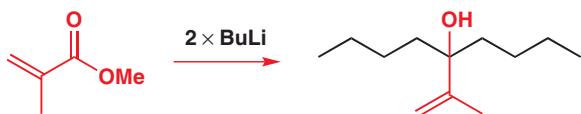


### Making alcohols instead of ketones

In other words, the problem here lies in the fact that the ketone product is more reactive than the ester starting material. We shall meet more examples of this general problem later (in Chapter 23, for example): in the next section we shall look at ways of overcoming it. Meanwhile, why not see it as a useful reaction? This compound, for example, was needed by some chemists in the course of research into explosives.



It is a tertiary alcohol with the hydroxyl group flanked by two identical R (= butyl) groups. The chemists who wanted to make the compound knew that an ester would react twice with the same organolithium reagent, so they made it from this unsaturated ester (known as methyl methacrylate) and butyllithium.



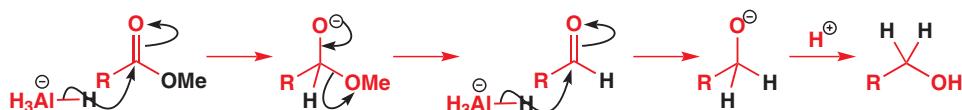
### ● Tertiary alcohol synthesis

Tertiary alcohols with two identical  $\text{R}^2$  groups can be made from ester  $\text{R}^1\text{CO}_2\text{R}$  plus two equivalents of organolithium  $\text{R}^2\text{Li}$  or Grignard reagent  $\text{R}^2\text{MgBr}$ .



This reaction works in reduction too if we use lithium aluminium hydride,  $\text{LiAlH}_4$ . This is a powerful reducing agent that readily attacks the carbonyl group of an ester. Again, collapse of the tetrahedral intermediate gives a compound, this time an aldehyde, which is more reactive than the ester starting material, so a second reaction takes place and the ester is converted (reduced) into an alcohol. Sodium borohydride, often used for the reduction of ketones, does not usually reduce esters.

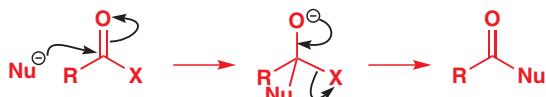
reduction of esters by  $\text{LiAlH}_4$



This is an extremely important reaction, and one of the best ways of making alcohols from esters. Stopping the reaction at the aldehyde stage is more difficult: we shall discuss this in Chapter 23.

### A bit of shorthand

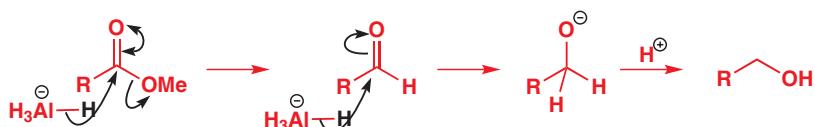
Before we go any further, we should introduce to you a little bit of chemical shorthand that makes writing many mechanisms easier. As you now appreciate, all substitution reactions at a carbonyl group go via a tetrahedral intermediate.



A convenient way to save writing a step is to show the formation and collapse of the tetrahedral intermediate in the same structure, by using a double-headed arrow, as in the diagrams below. Now, this is a useful shorthand, but it is not a substitute for understanding the true mechanism. Certainly, you must never ever write the reaction as a single step not involving the carbonyl group.



Here's the 'shorthand' at work in the  $\text{LiAlH}_4$  reduction you have just met.



## Making ketones from esters: the solution

We diagnosed the problem with our intended reaction as one of reactivity: the product ketone is more reactive than the starting ester. To get round this problem we need to do one of two things:

1. make the starting material more reactive *or*
2. make the product less reactive.

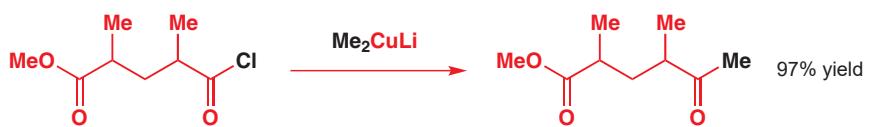
### Making the starting materials more reactive

A more reactive starting material would be an acyl chloride: how about reacting one of these with a Grignard reagent? This approach can work—for example this reaction is successful.



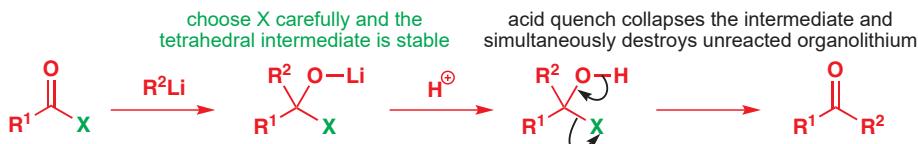
Often, better results are obtained by transmetallating (see Chapter 9) the Grignard reagent, or the organolithium, with copper salts. Organocupper reagents are too unreactive to add to the product ketones, but they react well with the acyl chloride. Consider this reaction, for example: the product was needed for a synthesis of the antibiotic septamycin.

■ Notice how this reaction illustrates the difference in reactivity between an acyl chloride functional group and an ester functional group.

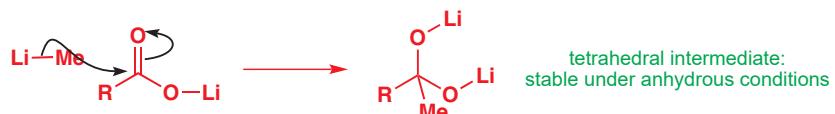


### Making the products less reactive

This alternative solution is often better. With the right starting material, the tetrahedral intermediate can become stable enough not to collapse to a ketone during the reaction; it therefore remains completely unreactive towards nucleophiles. The ketone is formed only when the reaction is finally quenched with acid but the nucleophile is also destroyed by the acid and none is left for further addition.

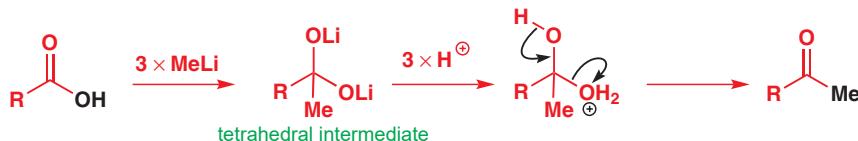


We can illustrate this concept with a reaction of an unlikely looking electrophile, a lithium carboxylate. Towards the beginning of the chapter we said that carboxylic acids were bad electrophiles and that carboxylate salts were even worse. Well, that is true, but with a sufficiently powerful nucleophile (an organolithium) it is just possible to get addition to the carbonyl group of a lithium carboxylate.

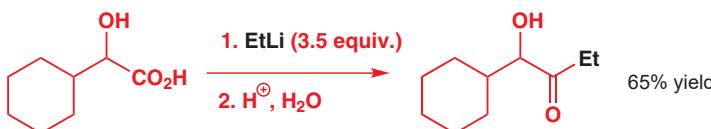


We could say that the affinity of lithium for oxygen means that the Li–O bond has considerable covalent character, making the  $\text{CO}_2\text{Li}$  less of a true anion. And the intermediate after addition of  $\text{MeLi}$  is probably best represented as a covalent compound too. Anyway, the

product of this addition is a dianion of the sort that we met during one of the mechanisms of base-catalysed amide hydrolysis. But in this case there is no possible leaving group, so there the dianion sits. Only at the end of the reaction, when water is added, are the oxygen atoms protonated to give a hydrated ketone, which collapses immediately (remember Chapter 6) to give the ketone that we wanted. The water quench also destroys any remaining organolithium, so the ketone is safe from further attack.

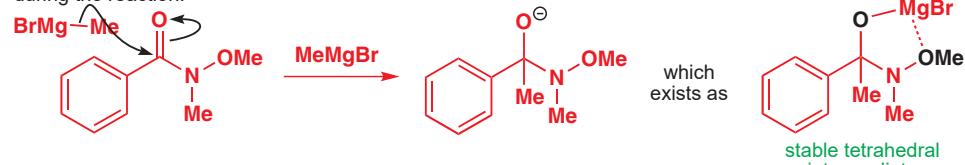


This method has been used to make some ketones that are important starting materials for making cyclic natural products known as macrolides.



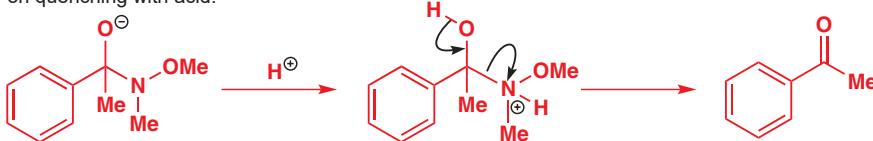
Another good set of starting materials that lead to non-collapsible tetrahedral intermediates is known as the **Weinreb amides**, after their inventor, S. M. Weinreb. Addition of organolithium or organomagnesium reagents to *N*-methoxy-*N*-methyl amides gives the tetrahedral intermediate shown, stabilized by *chelation* of the magnesium atom by the two oxygen atoms. Chelation means the coordination of more than one electron-donating atom in a molecule to a single metal atom.

during the reaction:



This intermediate collapses to give a ketone only when acid is added at the end of the reaction.

on quenching with acid:



The mechanism looks complicated but the reaction is easy to do:

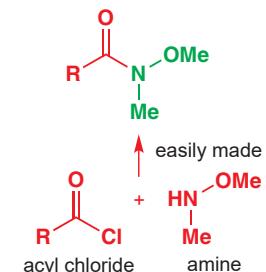


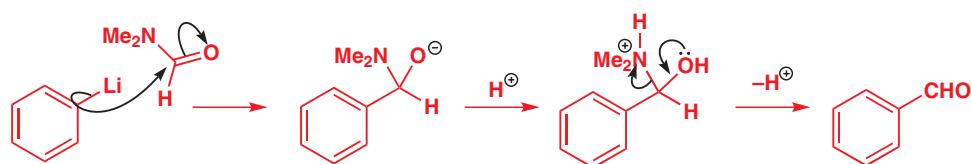
This strategy even works for making aldehydes, if the starting material is dimethylformamide (DMF,  $\text{Me}_2\text{NCHO}$ ). This is an extremely useful way of adding electrophilic CHO groups to organometallic nucleophiles. Once again, the tetrahedral intermediate is stable until acid is added at the end of the reaction and the protonated tetrahedral intermediate collapses.

■ Notice that three equivalents of organolithium are needed in this reaction: one to deprotonate the acid, one to deprotonate the hydroxyl group, and one to react with the lithium carboxylate. These chemists added a further 0.5 for good measure.

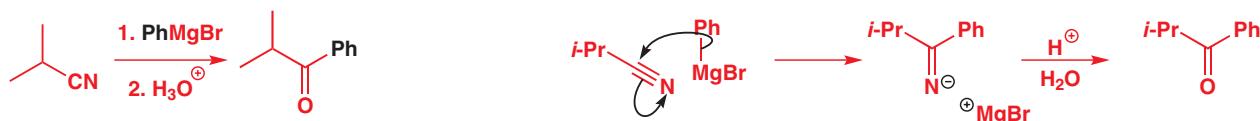
■ The word chelation derives from *chele*, the Greek for 'claw'.

a Weinreb amide (an *N*-methoxy-*N*-methyl amide)



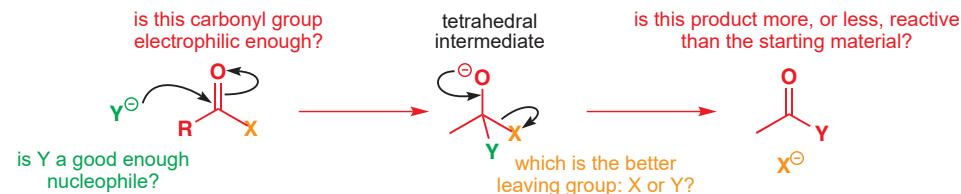


A final alternative is to use a nitrile instead of an ester. The intermediate is the anion of an imine (see Chapter 12 for more about imines), which is not electrophilic at all—in fact, it's quite nucleophilic, but there are no electrophiles for it to react with until the reaction is quenched with acid. It gets protonated and hydrolyses (we'll discuss this in the next chapter) to the ketone.



### To summarize...

To finish, we should just remind you of what to think about when you consider a nucleophilic substitution at a carbonyl group.



### And to conclude...

In this chapter you have been introduced to some important reactions—you can consider them to be a series of facts if you wish, but it is better to see them as the logical outcome of a few simple mechanistic steps. Relate what you have seen to what you gathered from Chapters 6 and 9, when we first started looking at carbonyl groups. All we did in this chapter was to build some subsequent transformations on to the simplest organic reaction, addition to a carbonyl group. You should have noticed that the reactions of all acid derivatives are related and are very easily explained by writing out proper mechanisms, taking into account the presence of acid or base. In the next two chapters we shall see more of these acid- and base-catalysed reactions of carbonyl groups. Try to view them as closely related to the ones in this chapter—the same principles apply to their mechanisms.

## 延伸阅读

Section 2, 'Nucleophilic substitution to the carbonyl group' in S. Warren, *Chemistry of the Carbonyl Group*, Wiley, Chichester, 1974.

The dehydration of amides to give nitriles is described in *Vogel*, p. 716.

## Check your understanding

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To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 11

## 伴随羰基氧失去的羰基亲核取代

### 联系

#### 基础

- Nucleophilic attack on carbonyl groups ch6
- Acidity and  $pK_a$  ch8
- Nucleophilic substitution at carbonyl groups ch10

#### 目标

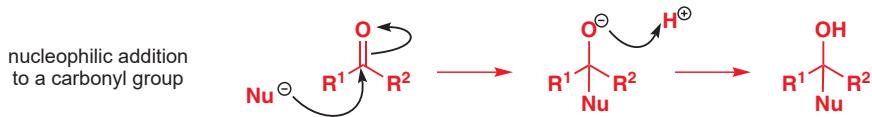
- Replacement of carbonyl oxygen
- Acetal formation
- Imine formation
- Stable and unstable imines
- The Strecker and Wittig reactions

#### 展望

- Rate and pH ch12
- Protecting groups ch23
- Acylation of enolates ch26
- Synthesis of alkenes ch27

### Introduction

Nucleophiles add to carbonyl groups to give compounds in which the trigonal carbon atom of the carbonyl group has become tetrahedral.

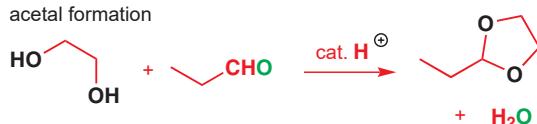
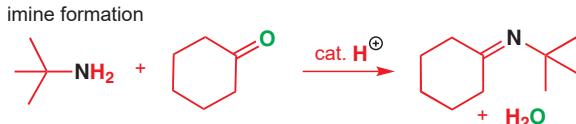


In Chapter 10 you saw that these compounds are not always stable: if the starting material contains a leaving group, the addition product is a **tetrahedral intermediate**, which collapses with loss of the leaving group to give back the carbonyl group, with overall substitution of the leaving group by the nucleophile.



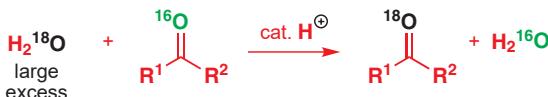
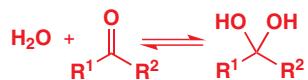
■ Acetals had walk-on parts in Chapters 2 and 6; in this chapter they are one of the stars. They are simply compounds with two oxygen atoms bound to the same saturated carbon atom. This example is cyclic, but others are not, for example  $\text{CH}_2(\text{OMe})_2$ .

In this chapter you will meet substitution reactions of a different type. Instead of losing a leaving group, the carbonyl group loses its oxygen atom. Here are two important examples: the carbonyl oxygen atom has been replaced by a nitrogen atom during imine formation and by two atoms of oxygen during acetal formation. Notice too the acid catalyst—we shall see shortly why it is required. These are examples of *nucleophilic substitution at the carbonyl group with loss of carbonyl oxygen*.



You have, in fact, already met some less important reactions in which the carbonyl oxygen atom can be lost, but you probably didn't notice at the time. The equilibrium between an aldehyde or ketone and its hydrate (p. 134) is one such reaction.

When the hydrate reverts to starting materials, either of its two oxygen atoms must leave: one came from the water and one from the carbonyl group, so 50% of the time the oxygen atom that belonged to the carbonyl group will be lost. Usually, this is of no consequence, but it can be useful. For example, in 1968 some chemists studying the reactions that take place inside mass spectrometers needed to label the carbonyl oxygen atom of a ketone with the isotope  $^{18}\text{O}$ .



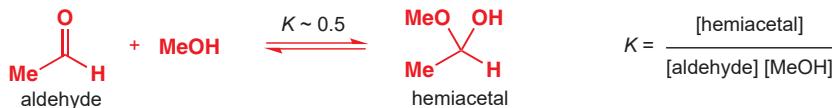
By stirring the 'normal'  $^{16}\text{O}$  compound with a large excess of isotopically labelled water for a few hours in the presence of a drop of acid they were able to make the required labelled compound. Without the acid catalyst, the exchange is very slow. Acid catalysis speeds the reaction up by making the carbonyl group more electrophilic so that equilibrium is reached more quickly.

## Aldehydes can react with alcohols to form hemiacetals

When acetaldehyde is dissolved in methanol, a reaction takes place: we know this because the IR spectrum of the mixture shows that a new compound has been formed. Most dramatically, the carbonyl frequency is no longer there. However, isolating the product is impossible: it decomposes back to acetaldehyde and methanol.



The product is in fact a hemiacetal. Like hydrates, most hemiacetals are unstable with respect to their parent aldehydes and alcohols, for example the equilibrium constant for reaction of acetaldehyde with simple alcohols is about 0.5.



► You met the mechanism for this reversible reaction in Chapter 6.

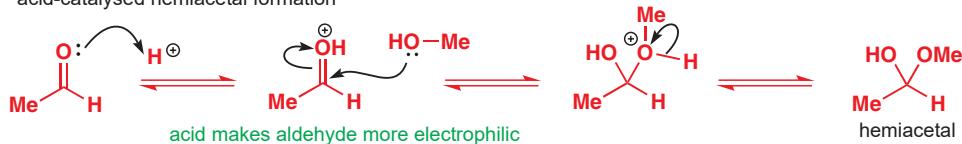
So by making [MeOH] very large (using it as the solvent, for example) we can turn most of the aldehyde into the hemiacetal. However, if we try to purify the hemiacetal by removing the methanol, more hemiacetal keeps decomposing to maintain the equilibrium constant. That is why we can never isolate such hemiacetals in a pure form.

### Acid or base catalysts increase the rate of equilibration of hemiacetals with their aldehyde and alcohol parents

Acyclic hemiacetals form relatively slowly from an aldehyde or ketone plus an alcohol, but their rate of formation is greatly increased either by acid or by base. As you would expect from Chapters 6 and 10, acid catalysts work by increasing the electrophilicity of the carbonyl group.

■ The exceptions are cyclic hemiacetals, as you saw in Chapter 6, in which the nucleophilic OH group is in the same molecule as the electrophilic carbonyl. We will explain how *entropy* accounts for this in Chapter 12.

acid-catalysed hemiacetal formation



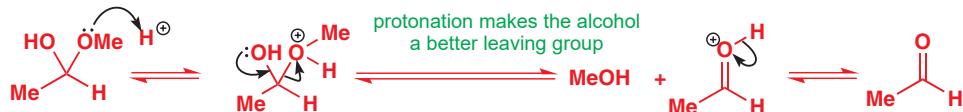
Base catalysts, on the other hand, work by increasing the nucleophilicity of the alcohol by removing the OH proton before it attacks the C=O group. In both cases the energy of the starting materials is raised: in the acid-catalysed reaction the aldehyde is destabilized by protonation and in the base-catalysed reaction the alcohol is destabilized by deprotonation.

base-catalysed hemiacetal formation

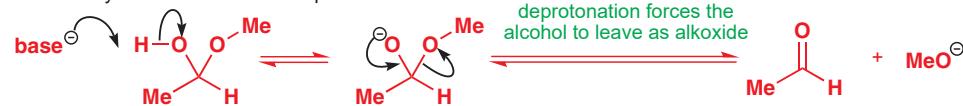


You can see why hemiacetals are unstable: they are essentially tetrahedral intermediates containing a leaving group and, just as acid or base catalyses the formation of hemiacetals, acid or base also catalyses their decomposition back to starting aldehyde or ketone and alcohol. That's why the title of this section indicated that acid or base catalysts increase the rate of equilibration of hemiacetals with their aldehyde and alcohol components—catalysts never change the position of that equilibrium!

acid-catalysed hemiacetal decomposition

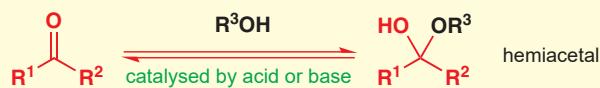


base-catalysed hemiacetal decomposition



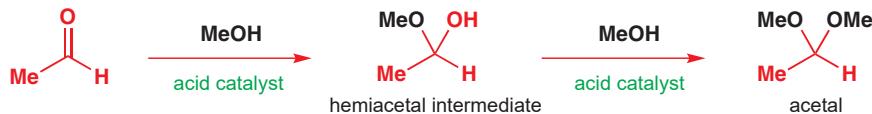
● To summarize

Hemiacetal formation and decomposition are catalysed by acid or base.



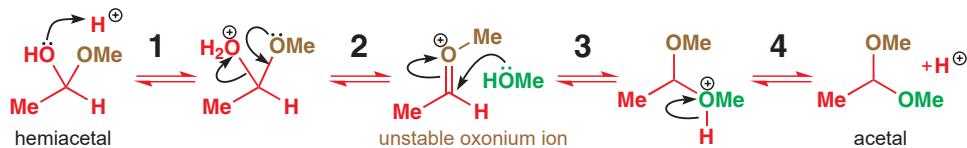
## Acetals are formed from aldehydes or ketones plus alcohols in the presence of acid

We said that a solution of acetaldehyde in methanol contains a new compound: a hemiacetal. We've also said that the rate of formation of hemiacetals is increased by adding an acid (or a base) catalyst to the alcohol plus aldehyde mixture. But, if we add catalytic acid to our acetaldehyde-methanol mixture, we find not only that the rate of reaction of the acetaldehyde with the methanol increases, but also that a different product is formed. This product is an acetal; the hemiacetal is half-way there.



In the presence of acid (but not base!) hemiacetals can undergo an elimination reaction (different from the one that just gives back aldehyde plus alcohol), losing the oxygen atom that once belonged to the parent aldehyde's carbonyl group.

acid-catalysed acetal formation from hemiacetal



The stages are:

1. Protonation of the hydroxyl group of the hemiacetal.
2. Loss of water by elimination. This elimination leads to an unstable and highly reactive oxonium ion.
3. Addition of methanol to the oxonium ion (breaking the  $\pi$  bond and not the  $\sigma$  bond, of course).
4. Loss of a proton to give the acetal.

### Oxonium ions

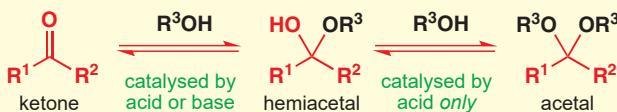
Oxonium ions have three bonds to a positively charged oxygen atom. All three bonds can be  $\sigma$  bonds, as in  $\text{H}_3\text{O}^+$  or Meerwein's salt, trimethyloxonium fluoroborate, a stable (though reactive) alkylating agent, or one bond can be a  $\pi$  bond as in the acetal intermediate. The term 'oxonium ion' describes either of these structures. They are like alkylated ethers or  $O$ -alkylated carbonyl compounds.



Just as protonated carbonyl groups are much more electrophilic than unprotonated ones, these oxonium ions are powerful electrophiles. They can react rapidly with a second molecule of alcohol to form the new, stable compounds known as acetals. An oxonium ion was also an intermediate in the formation of hemiacetals in acid solution. Before reading any further, it would be worthwhile to write out the whole mechanism of acetal formation from aldehyde or ketone plus alcohol through the hemiacetal to the acetal, preferably without looking at the fragments of mechanism above or the answer overleaf.

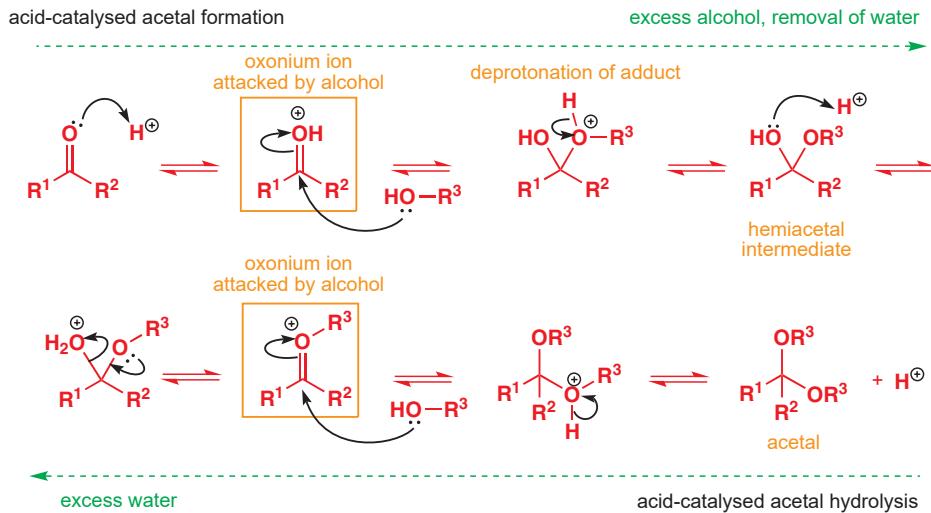
### Formation of acetals and hemiacetals

Hemiacetal formation is catalysed by acid or base, but acetal formation is possible only with an acid catalyst because an OH group must be made into a good leaving group.



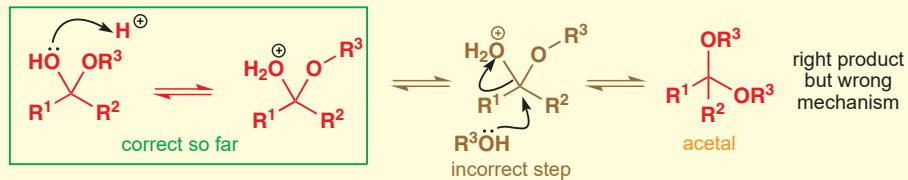
The mechanism is the most complex you have met and it will help you to recall it if you see it in two halves, each very similar to the other. The reaction starts with a protonation on carbonyl oxygen and addition of an alcohol to the  $\text{C}=\text{O}$   $\pi$  bond. When you get to the temporary haven of the hemiacetal, you start again with protonation of that same oxygen then lose the OH group by breaking what was the  $\text{C}=\text{O}$   $\sigma$  bond to form an oxonium ion. Each half goes through an oxonium ion and the alcohol adds to each oxonium ion. The last step in the formation of both the acetal and the hemiacetal is the loss of a proton from the recently added alcohol. From your complete mechanism you should also be able to verify that acetal formation is indeed catalytic in acid.

 Interactive mechanism for acetal formation



● Remember the oxonium ion!

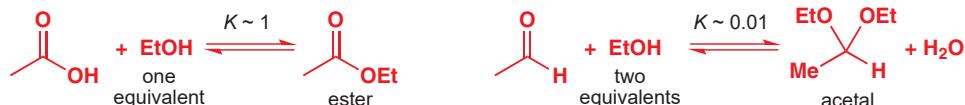
When you wrote out your mechanism for acetal formation, we hope you didn't miss out the oxonium ion! It's easy to do so, but the mechanism most definitely does not go via a direct displacement of water by alcohol.



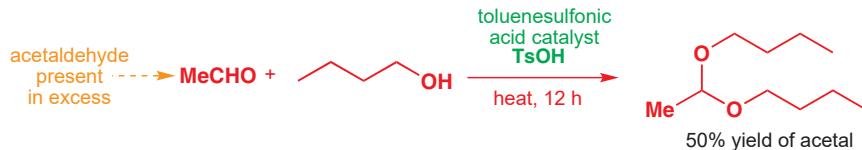
If you wonder how we know this, consult a specialized book on organic reaction mechanisms. After you have read Chapter 15 in this book, you will be able to spot that this substitution step goes via an  $S_N1$  and not an  $S_N2$  mechanism.

### Making acetals

Just as with the ester formation and hydrolysis reactions we discussed in Chapter 10, every step in the formation of an acetal is reversible. To make acetals, therefore, we must use an excess of alcohol or remove the water from the reaction mixture as it forms, by distillation for example.



In fact, acetal formation is even more difficult than ester formation: while the equilibrium constant for acid-catalysed formation of ester from carboxylic acid plus alcohol is usually about 1, for acetal formation from an aldehyde and ethanol (shown above), the equilibrium constant is  $K = 0.0125$ . For ketones, the value is even lower: in fact, it is often very difficult to make the acetals of ketones (sometimes called ketals) unless they are cyclic (we consider cyclic acetals later in the chapter). However, there are several techniques that can be used to prevent the water produced in the reaction from hydrolysing the product.

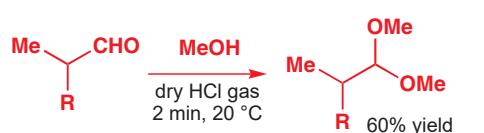


### para-Toluenesulfonic acid

para-Toluenesulfonic acid is commonly used to catalyse reactions of this sort. It is a stable solid, yet is as strong an acid as sulfuric acid. It is widely available and cheap because it is produced as a by-product in the synthesis of saccharin (for more details, see Chapter 21).



With the more reactive aldehyde, it was sufficient just to have an excess of one of the reagents (acetaldehyde) to drive the reaction to completion. Dry HCl gas can work too. With a less reactive ketone, molecular sieves (zeolite) were used to remove water from the reaction as it proceeded.



Molecular sieves are minerals that have very small cavities that can absorb only even smaller molecules. The ones used in acetal formation selectively absorb water. They are supplied as tiny cylinders of whitish material.

### Acetals hydrolyse only in the presence of acid

Just as acetal formation requires acid catalysis, acetals can be hydrolysed only by using an acid catalyst. With aqueous acid, the hydrolysis of acyclic acetals is very easy. Our examples are the two acetals we made earlier.



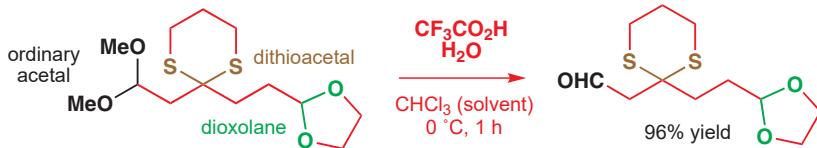
#### • Acetal hydrolysis

Acetals can be hydrolysed in acid but are stable to base.

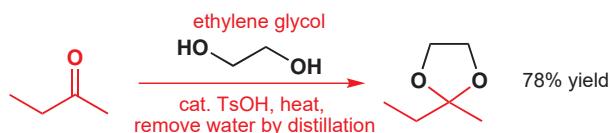
We won't go through the mechanism again—you've already seen it as the reverse of acetal formation, but the fact that acetals are stable to base is really a very important point, which we will use on the next page and capitalize on further in Chapter 23.

### Cyclic acetals are more stable than acyclic acetals

Of course you want us to prove it. Well, in this example the starting material has three acetals: an ordinary acetal formed from methanol (in black), a five-membered cyclic acetal, and a dithioacetal. Only the black acetal hydrolyses under these mild conditions.



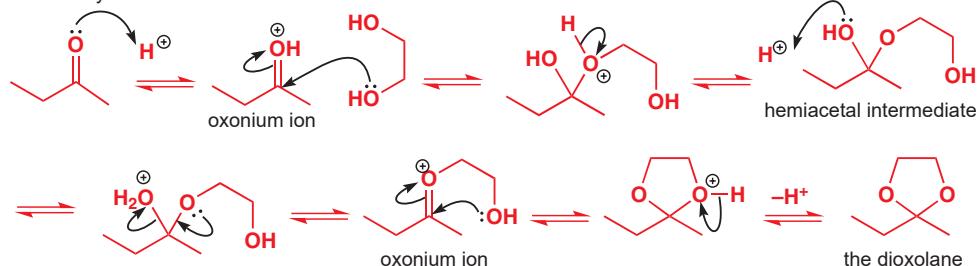
The acetals you have met so far were formed by reaction of two molecules of alcohol with one of carbonyl compound. Cyclic acetals, formed by reaction of a single molecule of a diol, a compound containing two hydroxyl groups, are also important. When the diol is ethylene glycol (as in this example) the five-membered cyclic acetal is known as a **dioxolane**.



■ We hope you didn't make the mistake of missing out the oxonium ion steps!

Before looking at the answer below, try to write a mechanism for this reaction. If you need it, use the mechanism we gave for the formation of acyclic acetals.

#### acid-catalysed dioxolane formation



- Cyclic acetals like this are more resistant to hydrolysis than acyclic ones, and easier to make—they form quite readily even from ketones. One explanation for this is that whenever the second oxonium ion in this mechanism forms, the hydroxyl group is always held close by, ready to snap shut and give back the dioxolane; water gets less of a chance to attack it and hydrolyse the acetal. We will discuss in *entropic* terms why cyclic acetals and hemiacetals are more stable in Chapter 12.

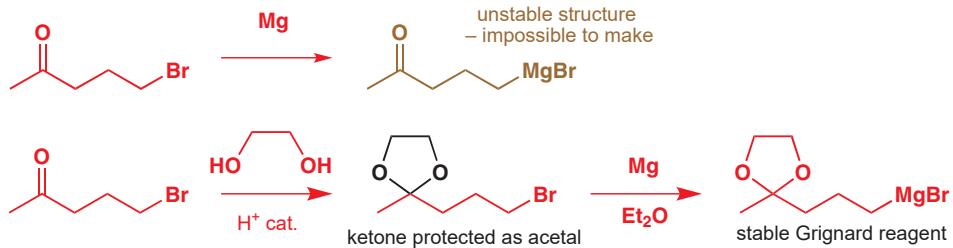
Water is still generated, and needs to be got rid of: in the example above you can see that water was distilled out of the reaction mixture. This is possible with these diols because they have a boiling point above that of water (the boiling point of ethylene glycol is 197 °C). You can't distil water from a reaction mixture containing methanol or ethanol because the alcohols distil too! One very useful piece of equipment for removing water from reaction mixtures containing only reagents that boil at higher temperatures than water is called a Dean Stark head.

## Dean Stark head

When a mixture of toluene and water boils, the vapour produced is a constant ratio mixture of toluene vapour and water vapour known as an **azeotrope**. If this mixture is condensed, the liquid toluene and water, being immiscible, separate out into two layers with the water below. By using a Dean Stark apparatus, or Dean Stark head, the toluene layer can be returned to the reaction mixture while the water is removed. Reactions requiring removal of water by distillation are therefore often carried out in refluxing toluene or benzene under a Dean Stark head.

## Modifying reactivity using acetals

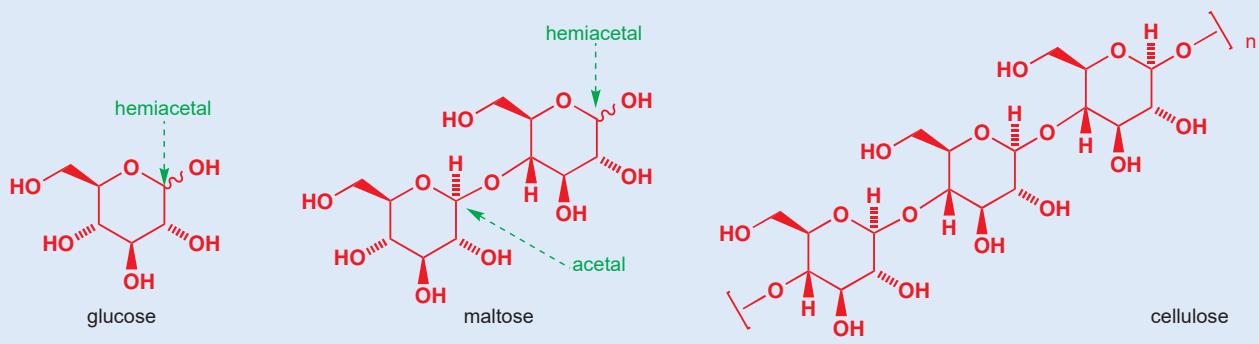
Why are acetals so important? Well, they're important to both nature and chemists because many carbohydrates are acetals or hemiacetals (see the box below). One important use that chemists have put them to is as *protecting groups*. One synthesis of the steroid class of compounds (about which more later) requires a Grignard reagent with an impossible structure. This compound cannot exist as the Grignard functional group would attack the ketone: it would react with itself. Instead, the protected Grignard reagent is used, made from the same bromoketone, but with an acetal-forming step.



Acetals, as we stressed, are stable to base and to basic nucleophiles such as Grignard reagents, so we no longer have a reactivity problem. Once the Grignard reagent has reacted with an electrophile, the ketone can be recovered by hydrolysing the acetal in dilute acid. The acetal is functioning here as a protecting group because it protects the ketone from attack by the Grignard reagent. Protecting groups are extremely important in organic synthesis and we will return to them in Chapter 23.

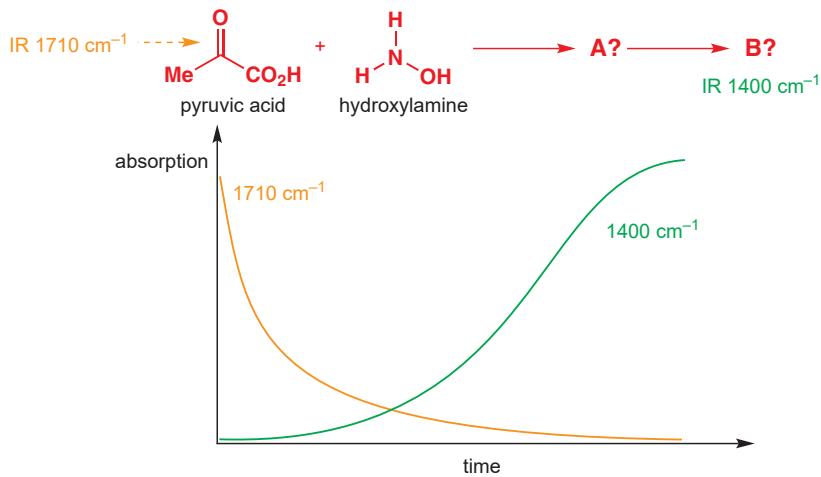
### Acetals in nature

We showed you glucose as on p.137 an example of a stable, cyclic hemiacetal. Glucose can, in fact, react with itself to form an acetal known as maltose. Maltose is a disaccharide (made of two sugar units) produced by the enzymatic hydrolysis of starch or cellulose, which are themselves polyacetals made up of a string of glucose units.

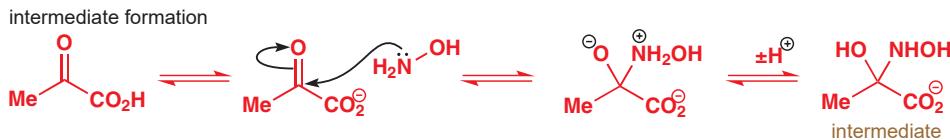


### Amines react with carbonyl compounds

The ketone carbonyl group of pyruvic acid (or 2-oxopropanoic acid) has a stretching frequency of a typical ketone,  $1710\text{ cm}^{-1}$ . When hydroxylamine is added to a solution of pyruvic acid, this stretching frequency slowly disappears. Later, a new IR absorption appears at  $1400\text{ cm}^{-1}$ . What happens?

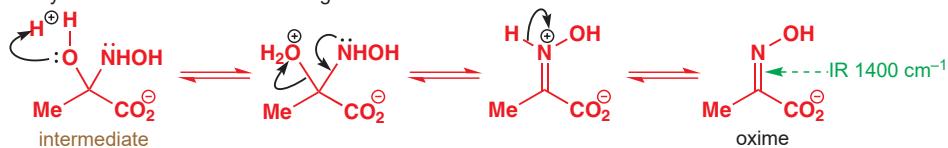


You can probably apply something of what you know from Chapters 6 and 10 about the reactivity of carbonyl compounds towards nucleophiles to work out what is happening in this reaction between a carbonyl compound and an amine. The hydroxylamine first adds to the ketone to form an unstable intermediate similar to a hemiacetal.

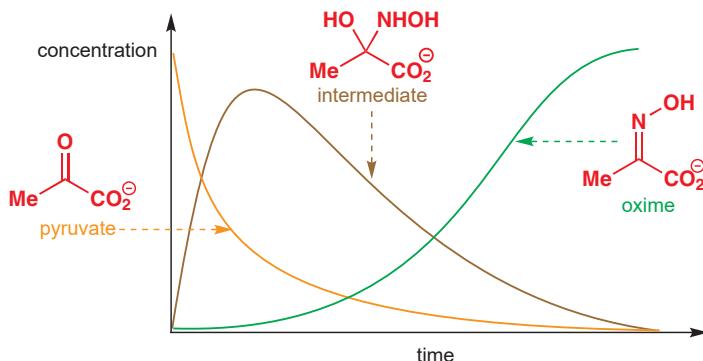


Notice that it is the more nucleophilic nitrogen atom, and not the oxygen atom, of hydroxylamine that adds to the carbonyl group. Like hemiacetals, these intermediates are unstable and can decompose by loss of water. The product is known as an oxime and it is this compound, with its  $\text{C}=\text{N}$  double bond, that is responsible for the IR absorption at  $1400\text{ cm}^{-1}$ .

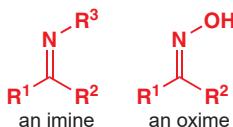
dehydration of the intermediate to give oxime



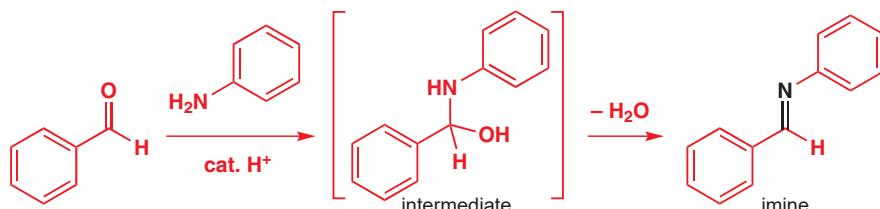
We know that the oxime is formed *via* an intermediate because the  $1400\text{ cm}^{-1}$  absorption hardly appears until after the  $1710\text{ cm}^{-1}$  absorption has almost completely gone. There must really be another curve to show the formation and decay of the intermediate. The only difference is that the intermediate has no double bond to give an IR absorbance in this region of the spectrum. We come back to oximes later in the chapter.



## Imines are the nitrogen analogues of carbonyl compounds

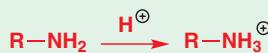


In fact, the oxime formed from a ketone and hydroxylamine is just a special example of an imine. All imines have a C=N double bond and are formed when any primary amine reacts with an aldehyde or a ketone under appropriate conditions, for example aniline and benzaldehyde.



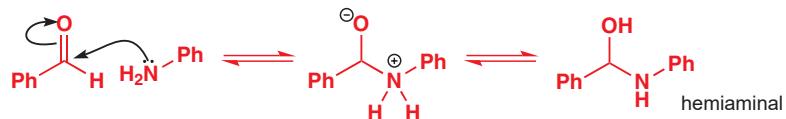
You shouldn't need us to tell you the mechanism of this reaction: even without looking at the mechanism we gave for the formation of the oxime it should come as no surprise to you by now. But as the reaction is very important in chemistry and biology, we'll discuss it in some depth. First, the amine attacks the aldehyde and the intermediate known as a hemiacetal is formed. Amines are good nucleophiles for carbonyl groups, and aldehydes and ketones are electrophilic. There is no need for any catalysis in this step. Indeed, addition of acid would slow the reaction down as the nucleophilic amine would be removed as a salt.

■ Acid would protonate the amine and remove it from the equilibrium and so slow this step down. Acid is not needed for the first step.



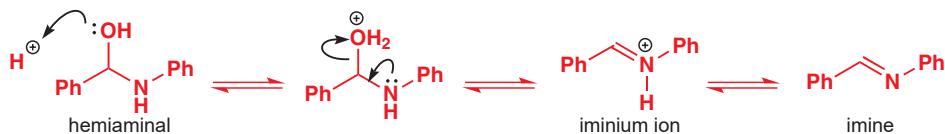
acid would remove the nucleophilic amine

First step in imine formation:  
the amine attacks the carbonyl group to form the hemiaminal intermediate:



Dehydration of the hemiaminal gives the imine. Now there is some need for catalysis: acid must be added so that the OH group can become a good leaving group. This step resembles the conversion of hemiacetals to acetals. The difference is that the iminium ion can lose a proton and become a neutral imine.

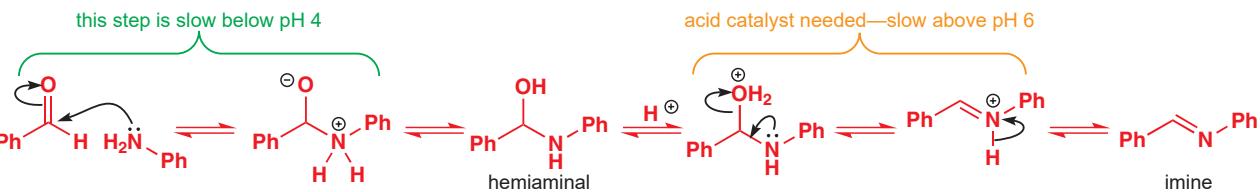
Second step in imine formation: acid-catalysed dehydration of the hemiaminal intermediate:



Interactive mechanism for imine formation

● Imine formation requires acid catalysis.

So acid is needed for the second step but hinders the first step. Clearly some compromise is needed. Without an acid catalyst, the reaction is very slow, although in some cases it may still take place. Imine formation is in fact fastest at about pH 4–6: at lower pH, too much amine is protonated and the rate of the first step is slow; above this pH the proton concentration is too low to allow protonation of the OH leaving group in the dehydration step. Imine formation is like a biological reaction: it is fastest near neutrality.



### Imines are usually unstable and are easily hydrolysed

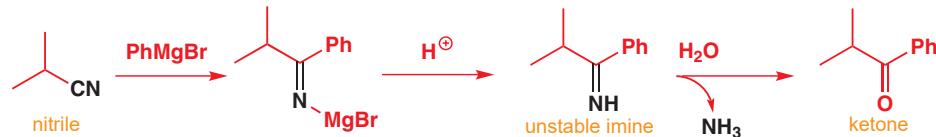
Like acetals, imines are unstable with respect to their parent carbonyl compound and amine, and must be formed by a method that allows removal of water from the reaction mixture.



Imines are formed from aldehydes or ketones with most primary amines. In general, they are stable enough to be isolated only if either the C or N of the imine double bond bears an aromatic substituent. Imines formed from ammonia are unstable, but can be detected in solution.  $\text{CH}_2=\text{NH}$ , for example, decomposes at temperatures above  $-80^\circ\text{C}$ , but  $\text{PhCH}=\text{NH}$  is detectable by UV spectroscopy in a mixture of benzaldehyde and ammonia in methanol.

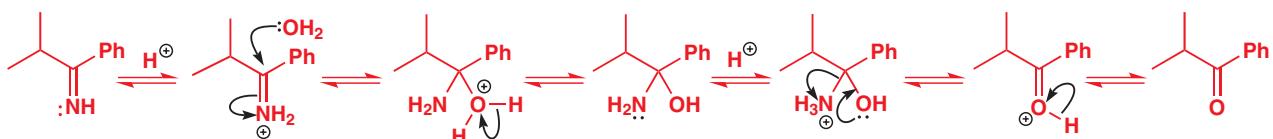


Imines are readily hydrolysed to the carbonyl compound and amine by aqueous acid—in fact, except for the particularly stable special cases we discuss below, most can be hydrolysed by water without acid or base catalysis. You have, in fact, already met an imine hydrolysis: at the end of Chapter 10 we talked about the addition of Grignard reagents to nitriles. The product is an imine that hydrolyses in acid solution to ketone plus ammonia.



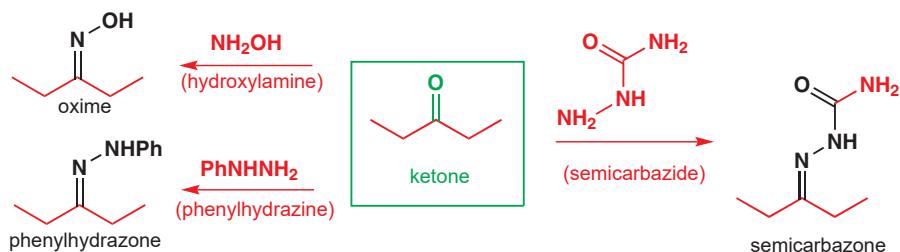
The mechanism of the hydrolysis is the reverse of imine formation, going through the same hemiaminal intermediate and the same iminium and oxonium ions. All these steps are reversible and this should remind you that the relative stability of the starting material and product is as important in imine formation and hydrolysis as it is in acetal formation and hydrolysis.

Because it is made from an unsymmetrical ketone this imine can exist as a mixture of *E* and *Z* isomers, just like an alkene. When it is formed by this method the ratio obtained is 8:1 *E*:*Z*. Unlike the geometrical isomers of alkenes, however, those of an imine usually interconvert quite rapidly at room temperature. The geometrical isomers of oximes on the other hand are stable and can even be separated.



### Some imines are stable

Imines in which the nitrogen atom carries an electronegative group are usually stable: examples include oximes, hydrazones, and semicarbazones.



Interactive mechanism for hydrazone formation

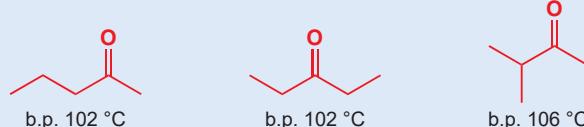
These compounds are more stable than imines because the electronegative substituent can participate in delocalization of the imine double bond. Delocalization decreases the small positive charge on the carbon atom of the imine double bond and raises the energy of the LUMO, making it less susceptible to nucleophilic attack. Oximes, hydrazones, and semicarbazones require acid or base catalysis to be hydrolysed.



### Historical note

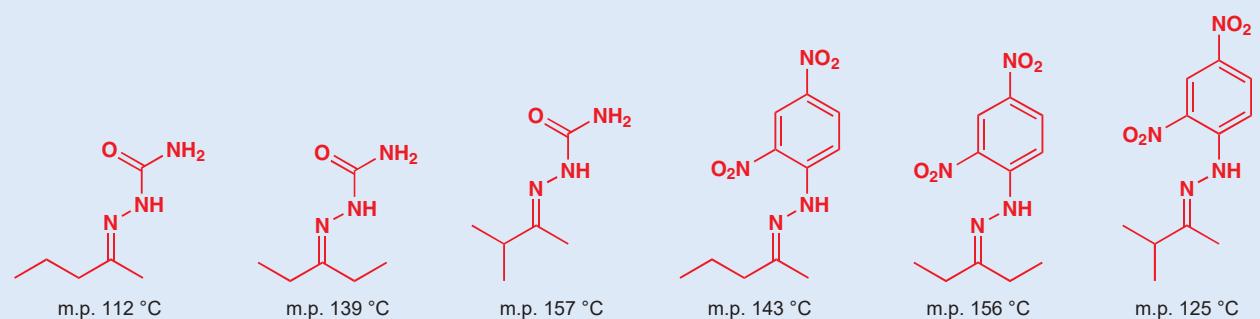
Because the hydrazone and semicarbazone derivatives of carbonyl compounds are often stable, crystalline solids, they used to be used to confirm the supposed identity of aldehydes and ketones. For example, the boiling points of these

three isomeric five-carbon ketones are all similar and before the days of NMR spectroscopy it would have been hard to distinguish between them.



Their semicarbazones and 2,4-dinitrophenylhydrazones, on the other hand, all differ in their melting points. By making these derivatives of the ketones, identification was made much easier. Of course, all of this has been totally super-

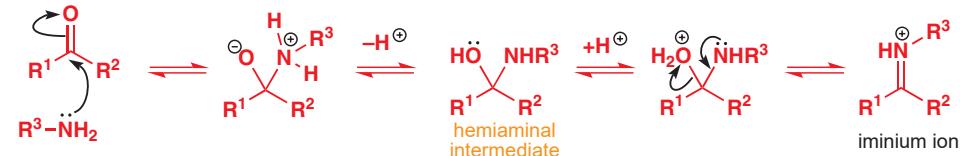
seeded by NMR! However, these crystalline derivatives are still useful in the purification of volatile aldehydes and ketones, and in solving structures by X-ray crystallography.



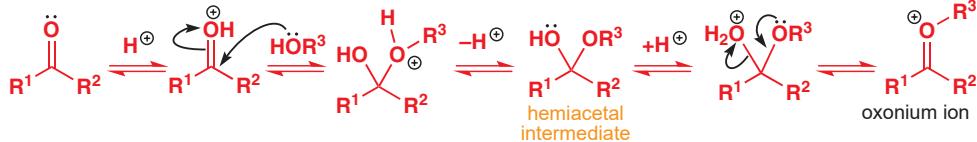
### Iminium ions and oxonium ions

Let's return to the mechanism of imine formation, and compare it for a moment with that of acetal formation. The only difference to begin with is that there is no need for acid catalysis for the addition of the amine but there is need for acid catalysis in the addition of the alcohol, a much weaker nucleophile.

acid-catalysed imine formation

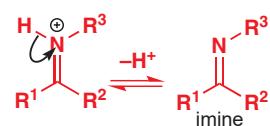


acid-catalysed acetal formation

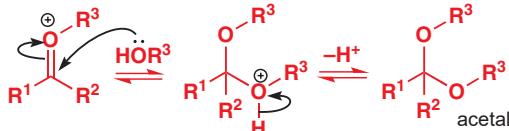


Up to this point, the two mechanisms follow a very similar path, with clear analogy between the hemiaminal and hemiacetal intermediates, and between the iminium and oxonium ions. Here, though, they diverge, because the iminium ion carries a proton, which the oxonium ion doesn't have. The iminium ion therefore acts as an acid, losing a proton to become the imine. The oxonium ion, on the other hand, acts as an electrophile, adding another molecule of alcohol to become the acetal.

iminium ion



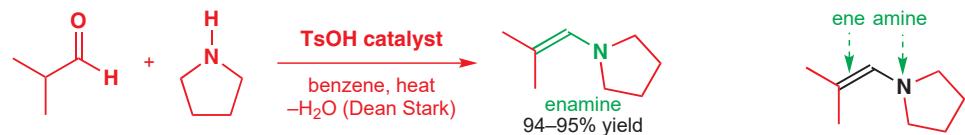
oxonium ion



As you might guess, however, iminium ions can be persuaded to act as electrophiles, just like oxonium ions, provided a suitable nucleophile is present. We will spend the next few pages considering reactions in which an iminium ion acts as an electrophile. First, though, we will look at a reaction in which the iminium ion cannot lose an N–H proton because it has none.

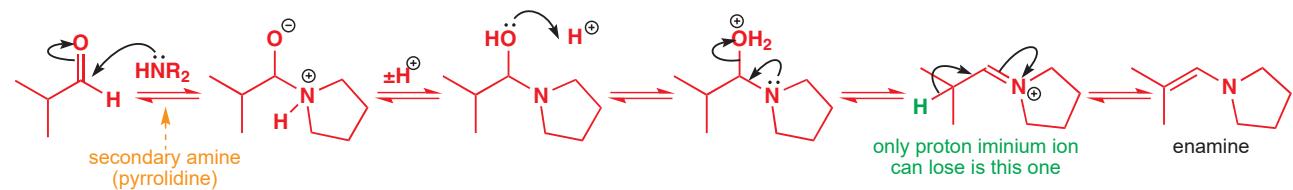
### Secondary amines react with carbonyl compounds to form enamines

Pyrrolidine, a secondary amine, reacts with isobutyraldehyde, under the sort of conditions you would use to make an imine, to give an enamine. The name enamine combines 'ene' (C=C double bond) and 'amine'.



The mechanism consists of the same steps as those that take place when imines form from primary amines, up to formation of the iminium ion. This iminium ion has no N–H proton to lose, so it loses one of the C–H protons next to the C=N to give the enamine. Enamines, like imines, are unstable to aqueous acid.

Interactive mechanism for enamine formation

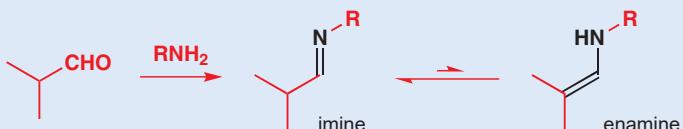


● **Imines and enamines**

- Imines are formed from aldehydes or ketones with primary amines.
- Enamines are formed from aldehydes or ketones with secondary amines.

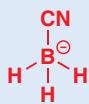
Both require acid catalysis and removal of water.

Enamines of primary amines, or even of ammonia, also exist, but only in equilibrium with an imine isomer. The interconversion between imine and enamine is the nitrogen analogue of **enolization**, which is discussed in detail in Chapter 20.



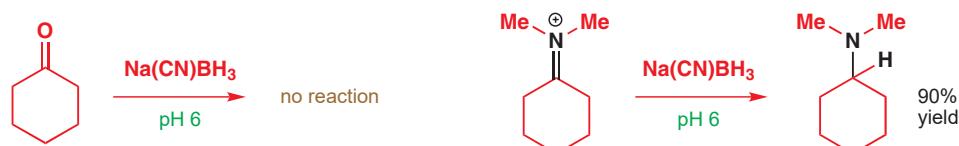
**Iminium ions can react as electrophilic intermediates**

We made the point above that the difference in reactivity between an iminium ion and an oxonium ion is that an iminium ion can lose H<sup>+</sup> and form an imine or an enamine, while an oxonium ion reacts as an electrophile. Iminium ions can, however, react as electrophiles provided suitable nucleophiles are present. In fact, they are very good electrophiles, and are significantly more reactive than carbonyl compounds. For example, iminium ions are reduced rapidly by the mild reducing agent sodium cyanoborohydride, Na(CN)BH<sub>3</sub>, while carbonyl compounds are not. An alternative to Na(CN)BH<sub>3</sub> is NaBH(OAc)<sub>3</sub> (sodium triacetoxyborohydride)—somewhat safer because strong acid can release deadly HCN from Na(CN)BH<sub>3</sub>.



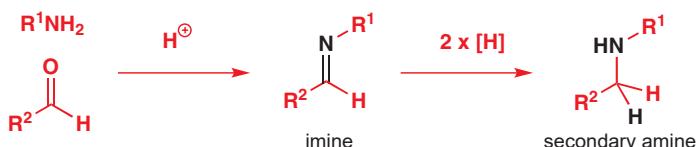
Sodium cyanoborohydride contains the cyanoborohydride anion, whose structure has tetrahedral boron.

It is a ‘toned down’ version of sodium borohydride—the electron-withdrawing cyano group decreases the ease with which hydride is transferred.

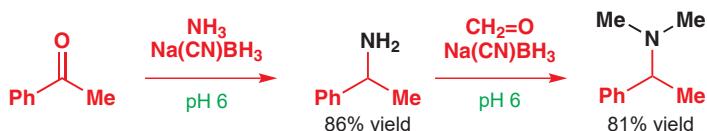


**Amines from imines: reductive amination**

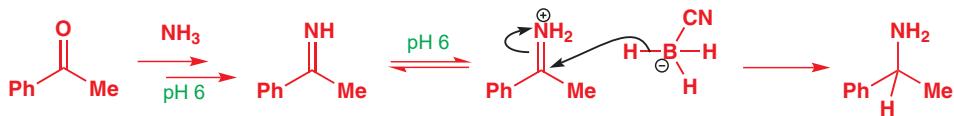
A useful way of making amines is by reduction of imines (or iminium ions). This overall process, from carbonyl compound to amine, is called **reductive amination**. This is, in fact, one of the few successful ways, and the best way, of making secondary amines. This should be your first choice in amine synthesis.



This can be done in two steps, provided the intermediate is stable, but, because the instability of many imines makes them hard to isolate, the most convenient way of doing it is to form and reduce the imine in a single reaction. The selective reduction of iminium ions (but not carbonyl compounds) by sodium cyanoborohydride makes this possible. When Na(CN)BH<sub>3</sub> is added to a typical imine-formation reaction it reacts with the iminium ion but not with the starting carbonyl compound nor with the imine. Here is an example of an amine synthesis using reductive amination.

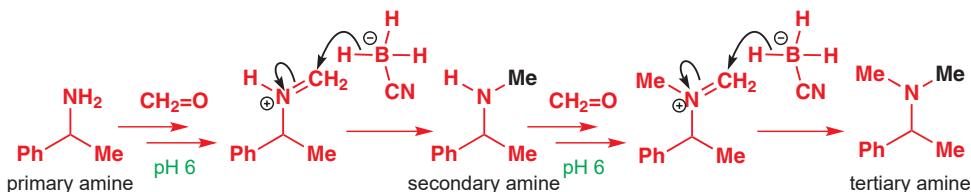


In the first step, the ketone and ammonia are in equilibrium with their imine, which, at pH 6, is partly protonated as an iminium ion. The iminium ion is rapidly reduced by the cyanoborohydride to give the amine. Reactions like this, using ammonia in a reductive amination, are often carried out with ammonium chloride or acetate as convenient sources of ammonia. At pH 6, ammonia will be mostly protonated anyway as the  $pK_a$  of  $\text{NH}_4^+$  is about 10.



► You will again meet the highly electrophilic iminium ions produced by reaction of formaldehyde with amines in Chapter 26, where we introduce you to the Mannich reaction.

In the second step of the synthesis, amine plus formaldehyde gives an imine, present as its protonated iminium form, which gets reduced. Formaldehyde is so reactive that it reacts again with the secondary amine to give an iminium ion; this too is reduced to the amine.



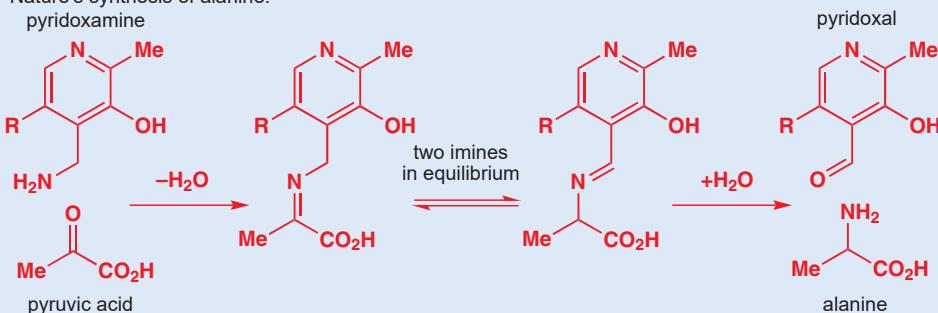
### Living things make amino acids using imines

The amino acid alanine can be made in moderate yield in the laboratory by reductive amination of pyruvic acid.



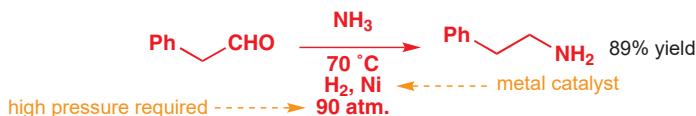
Living things use a very similar reaction to manufacture amino acids from keto acids, but do it much more efficiently. The key step is the formation of an imine between pyruvic acid and the vitamin B<sub>6</sub>-derived amine pyridoxamine.

Nature's synthesis of alanine:



This imine (biochemists call imines Schiff bases) is in equilibrium with an isomeric imine, which can be hydrolysed to pyridoxal and alanine. These reactions are, of course, all controlled by enzymes and coupled to the degradation of unwanted amino acids (the latter process converts the pyridoxal back to pyridoxamine). Nature was doing reductive aminations a long time before sodium cyanoborohydride was invented! We will come back to this in Chapter 42.

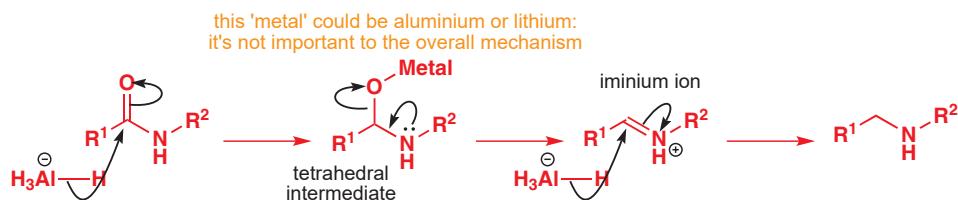
An alternative method for reductive amination uses hydrogenation (hydrogen gas with a metal catalyst) to reduce the imine in the presence of the carbonyl compound. Most of these reductions do not require such high temperatures or pressures.



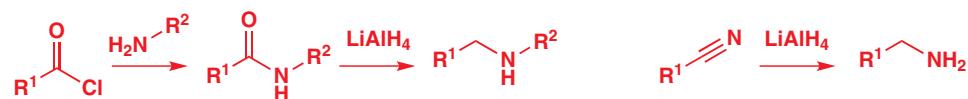
■ Hydrogenation is a good way of reducing a number of different functional groups, but not (usually) carbonyl groups. In Chapter 23 we will look in more detail at reducing agents (and other types of reagent) that demonstrate selectivity for one functional group over another (**chemoselectivity**).

### Lithium aluminium hydride reduces amides to amines

We've talked about reduction of iminium ions formed from carbonyl compounds plus amines. Iminium ions can also be formed by reducing amides with lithium aluminium hydride. A tetrahedral intermediate is formed that collapses to the iminium ion.

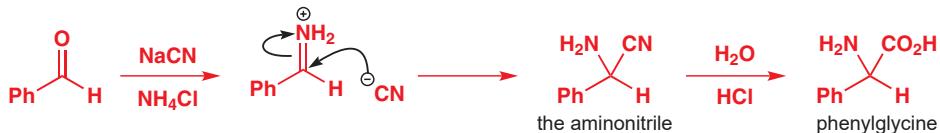


The iminium ion is, of course, more electrophilic than the starting amides (amide carbonyl groups are about the least electrophilic of any!), so it gets reduced to the secondary amine. This reaction can be used to make secondary amines from primary amines and acyl chlorides. A similar reduction with lithium aluminium hydride gives a primary amine from a nitrile.



### Cyanide will attack iminium ions: the Strecker synthesis of amino acids

Cyanide will react with iminium ions to form  $\alpha$  amino nitriles. Although these compounds are relatively unimportant in their own right, a simple hydrolysis step produces  $\alpha$  amino acids. This route to amino acids is known as the Strecker synthesis. Of course, it's not usually necessary to make the amino acids that Nature produces for us in living systems: they can be extracted from hydrolysed proteins. This Strecker synthesis is of phenylglycine, an amino acid not found in proteins. Cyanide reacts more rapidly with the iminium ion generated in the first step than it does with the starting benzaldehyde.

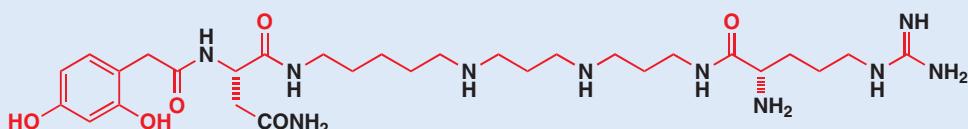


- Make sure that you can write a mechanism for the hydrolysis of the nitrile to the carboxylic acid! (If you need reminding it is given in Chapter 10.)

### The synthesis of a spider toxin: reductive amination

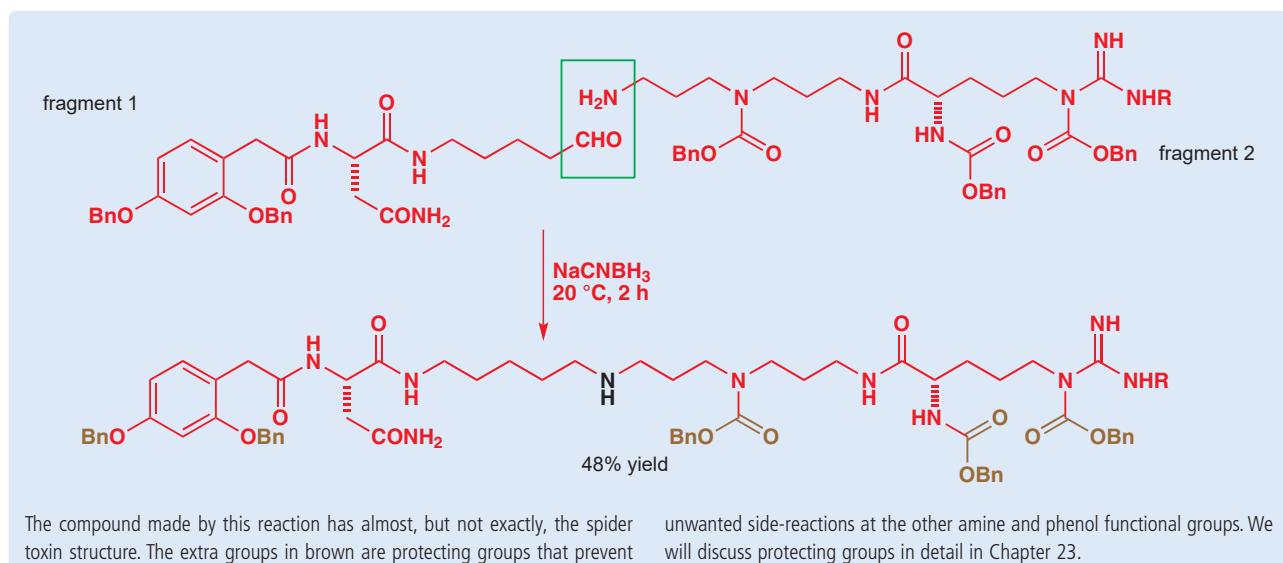
This compound is the toxin used by the orb weaver spider to paralyse its prey. Notice that it has a guanidine at its right-hand end. These are stable imines,

and their powerful basicity was discussed in Chapter 8.



Since the spider produces only minute quantities of the compound, chemists at the University of Bath set about synthesizing it in the laboratory so that they could study its biological properties. The toxin contains several amide and

amine functional groups, and the chemists decided that the best way to make it was to link two molecules together at one of the secondary amine groups using a reductive amination.



### Substitution of C=O for C=C: a brief look at the Wittig reaction

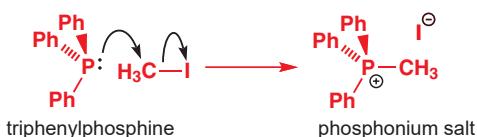
Before we leave substitution reactions of carbonyl groups, there is one more reaction that we must introduce. It is an important one and we will come back to it again later in this book, particularly in Chapter 27. It also has a rather different mechanism from most you have met in recent chapters, but we talk about it here because the overall consequence of the **Wittig reaction** is the substitution of a C=C bond for a C=O bond.

We don't normally tell you the name of a reaction before even mentioning how to do it, but here we make an exception because the reagents are rather unusual and need explaining in detail. The Wittig reaction is a reaction between a carbonyl compound (aldehyde or ketone only) and a species known as a **phosphonium ylid**. An ylid (or ylide) is a species with positive and negative charges on adjacent atoms, and phosphonium ylids are made from **phosphonium salts** by deprotonating them with a strong base.

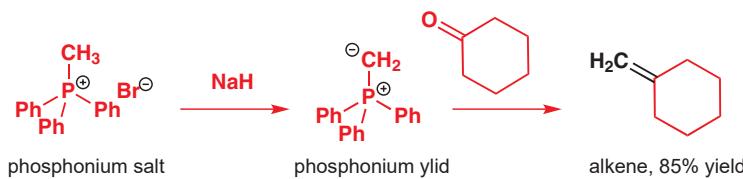
You have already met phosphonium salts in Chapter 5, where you saw the reaction of a phosphine (triphenylphosphine) with an alkyl halide (methyl iodide) to give the tetrahedral phosphonium salt.



The Wittig reaction is named after its discoverer, the Nobel Prize winner Georg Wittig (1897–1987; Nobel Prize 1979).



So here is a typical Wittig reaction: it starts with a phosphonium salt, which is treated with a strong base such as BuLi or sodium hydride, and then with a carbonyl compound; the alkene forms in 85% yield.

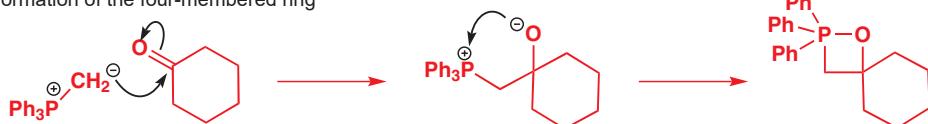


■ The positively charged P atom stabilizes the negative charge on carbon, making phosphonium salts another class of 'carbon acids' (to add to those you met in Chapter 8) that can be deprotonated by strong base. The hydride ion  $\text{H}^-$  is the conjugate base of  $\text{H}_2$  which has a  $\text{pK}_a$  of about 35.

What about the mechanism? We warned you that the mechanism is rather different from all the others you have met in this chapter, but nonetheless it begins with attack on the

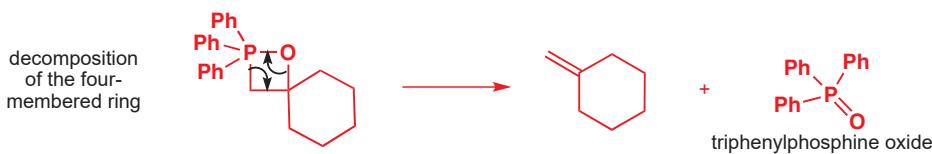
carbonyl group by a nucleophile; the nucleophile is the carbanion part of the phosphonium ylid. This reaction generates a negatively charged oxygen that attacks the positively charged phosphorus and gives a four-membered ring called an oxaphosphetane.

formation of the four-membered ring



Now, this four-membered ring (like many others) is unstable, and it can collapse in a way that forms two double bonds. Here are the curly arrows: the mechanism is cyclic and gives the alkene, which is the product of the reaction along with a phosphine oxide.

Interactive mechanism for the Wittig reaction



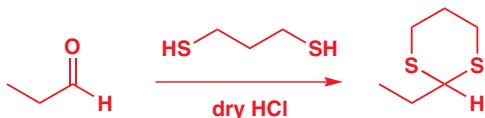
► We will look at the Wittig reaction again in more detail in Chapter 27.

The chemistry of some elements is dominated by one particular property, and a theme running right through the chemistry of phosphorus is its exceptional affinity for oxygen. The P=O bond, with its bond energy of 575 kJ mol<sup>-1</sup>, is one of the strongest double bonds in chemistry, and the Wittig reaction is irreversible and is driven forward by the formation of this P=O bond. No need here for the careful control of an equilibrium necessary when making acetals or imines.

## Summary

In this chapter, as in Chapter 10, you have met a wide variety of reactions, but we hope you have again been able to see that they are all related mechanistically. Of course, we have not been exhaustive: it would be impossible to cover every possible reaction of a carbonyl group, but having read Chapters 6, 9, and 10 you should feel confident in writing a *reasonable mechanism* for any reaction involving nucleophilic attack on a carbonyl group. You could try thinking about this, for example.

■ Hint. Consider sulfur's location in the periodic table.



In the next chapter we examine in a little more detail the phrase ‘a reasonable mechanism’: how do we know what mechanisms are reasonable, and what can we do to understand them? We shall look in more detail at some of the topics raised in this chapter, such as equilibria and rates of reactions. Carbonyl groups next star in Chapter 20 where they reveal a thus far hidden *nucleophilic* side to their character.

## 延伸阅读

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Section 3, 'Nucleophilic substitution to the carbonyl group with complete removal of carbonyl oxygen', in S. Warren, *Chemistry of the Carbonyl Group*, Wiley, Chichester, 1974.

## Check your understanding

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To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 12 平衡、速率和机理

## 联系

### ► 基础

- Structure of molecules **ch4**
- Drawing mechanisms **ch5**
- Nucleophilic attack on carbonyl groups **ch6 & ch9**
- Acidity and  $pK_a$  **ch8**
- Substitutions at carbonyl groups **ch11 & ch12**

### 目标

- What controls equilibria
- Free energy, enthalpy, and entropy
- What controls the rates of reactions
- Intermediates and transition states
- How catalysts work
- Effects of temperature on reactions
- Why the solvent matters
- Rate equations and their link to mechanism

### ► 展望

- Substitution reactions at saturated C **ch15**
- Conformational equilibria **ch16**
- Elimination reactions **ch17**
- How mechanisms are discovered **ch39**

'One could no longer just mix things; sophistication in physical chemistry was the base from which all chemists—including the organic—must start.' Christopher Ingold (1893–1970). Ingold uncovered many of the mechanisms we now take for granted in organic chemistry.

If you go into a chemistry laboratory, you will see some reactions being heated in boiling solvent (perhaps 80 to 120 °C), and you will see others being performed at maybe –80 °C or below. Some reactions are over in a few minutes; others are left for hours. In some reactions the amounts of reagents are critical; in others large excesses are used. Some reactions use water as a solvent; in others it must be rigorously excluded, and perhaps toluene, ether, ethanol, or DMF is essential for the success of the reaction. Why such a diverse range of conditions? How can conditions be chosen to favour the reaction we want? To explain all this we will need to work through some thermodynamic principles. We will take a practical, visual approach to the topic, and we will avoid detailed algebraic discussion: for that you are welcome to turn to a textbook of physical chemistry—there are some suggestions at the end of this chapter. In fact, we will use only two algebraic equations. Both are so important that you should memorize them; the second in particular can be extremely valuable when we think about how to get reactions to work.

## How far and how fast?

In previous chapters we have said things about the *reversibility of reactions*:

'Cyanohydrin formation is reversible: just dissolving a cyanohydrin in water can give back the aldehyde or ketone you started with' (Chapter 6); 'HCl transfers its proton almost completely to water, and is a strong acid. But the transfer of protons to water from carboxylic acids is only partial' (Chapter 8); 'This step is irreversible because SO<sub>2</sub> and HCl are gases that are lost from the reaction mixture' (Chapter 10); 'The tetrahedral intermediate can collapse either way, giving back ester or going forward to acid plus alcohol.' (Chapter 10);

about the *relative stability* of different compounds:

'The most important factor in the strength of an acid is the stability of the conjugate base' (Chapter 8); ' $\text{F}^-$  is much more stable than  $\text{CH}_3^-$  because fluorine is much more electronegative than carbon' (Chapter 8); 'Oximes are more stable than imines because the electronegative substituent can participate in delocalization of the imine double bond' (Chapter 11);

and about the *rate of reactions*:

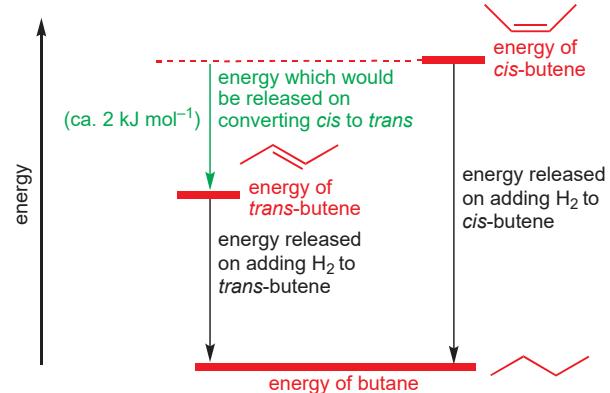
'Benzaldehyde is reduced about 400 times faster than acetophenone in isopropanol' (Chapter 6); 'While amines react with acetic anhydride quite rapidly at room temperature (reaction complete in a few hours), alcohols react extremely slowly in the absence of a base' (Chapter 10); 'Secondary and tertiary amides are difficult to hydrolyse but a similar mechanism is successful with only a little water and plenty of a strong base' (Chapter 10); 'Acyclic hemiacetals form relatively slowly from an aldehyde or or ketone plus an alcohol, but their rate of formation is greatly increased either by acid or by base' (Chapter 11).

We are now going to consider in detail why some reactions can run forwards or backwards, why some form products irreversibly, why some reach an equilibrium, why some reactions go fast and some go slow, and what stability has to do with all of this. Understanding these factors will allow you to make the reactions you want to happen go faster and the reactions you don't want to happen go slower, giving you a product in a useful yield. We shall be breaking reaction mechanisms down into steps and working out which step is the most important. But first we must consider what we really mean by the 'stability' of molecules and what determines how much of one substance you get when it is in equilibrium with another.

→ We looked at the problem of how to make ketones from esters by increasing the rate of one reaction at the expense of another in Chapter 10, p. 218.

## Stability and energy levels

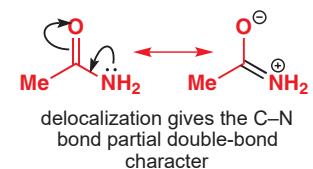
So far we have been rather vague about the term 'stability', just saying things like 'this compound is more stable than that compound'. What we really mean is that this compound has **less energy** than that one. For example, as you know from Chapters 4 and 7 alkenes can come in two forms we can call *cis* and *trans*. In general *trans*-alkenes are more stable than *cis*-alkenes. How do we know? Well, we can convert both *cis*- and *trans*-butene to the same alkane, butane, by adding a molecule of hydrogen. Energy is given out during the reaction, and if we measure how much energy we get from hydrogenation of *trans*-butene and compare it with the amount we get from *cis*-butene, we find that the *cis*-alkene give us about  $2 \text{ kJ mol}^{-1}$  more. *Cis*-butene is higher in energy, and must therefore be less stable. We can represent this in the energy profile diagram on the right. The two red lines show the energies of the molecules, and the black arrows the amount of energy released when hydrogen is added.

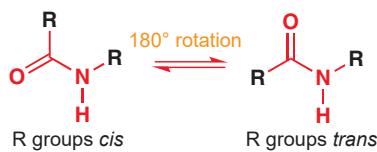


→ We used a similar argument to compare the stabilities of benzene and cyclooctatetraene (see p. 157).

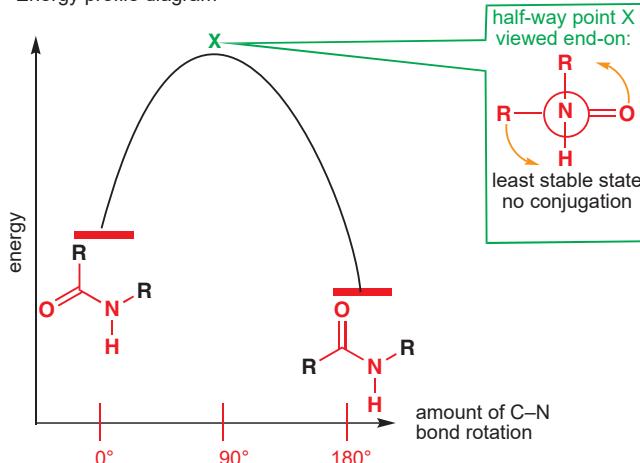
This comparison of energy is most interesting when two compounds can interconvert. For example, as you saw in Chapter 7, rotation about the C–N bond of an amide is slow because delocalization of the N lone pair gives it some double-bond character.

The C–N bond can rotate, but the rotation is slow and can be measured by NMR spectroscopy. We might expect to find two forms of an amide of the type  $\text{RNH}-\text{COR}$ : one with the two R groups *trans* to one another, and one with them *cis*. Depending on the size of R we should expect one form to be more stable than the other and we can represent this on an energy profile diagram showing the relationship between the two molecules in energy terms.





Energy profile diagram



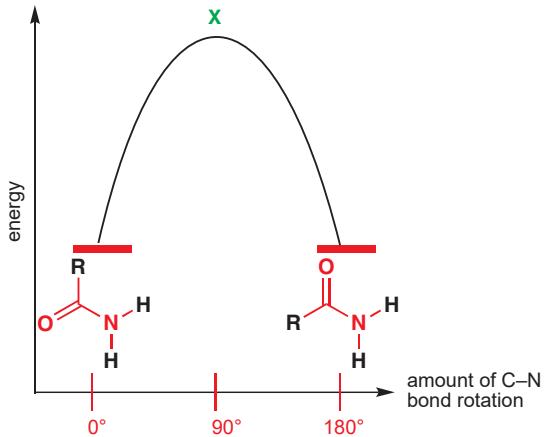
■ **Cis- and trans-alkenes** don't usually interconvert without catalysis. You can read more about this on p. 105.

This time there is an axis along the bottom indicating the extent of rotation about the C–N bond. The two red lines show the energies of the molecules and the curved black line shows what must happen in energy terms as the two forms interconvert. Energy goes up as the C–N bond starts to rotate and reaches a maximum at point X when rotation by 90° has removed the conjugation (the nitrogen lone pair can't delocalize into the C=O bond because it is perpendicular to the C=O  $\pi^*$  orbital) before falling again as the conjugation is regained.

The relative energies of the two states will depend on the nature of R. The situation we have shown, with the *cis* arrangement being much less stable than the *trans*, would apply to large R groups. We can define an equilibrium constant K for this process. For large R groups, K will be very large:

$$K = \frac{[\text{amide with R groups } \textit{trans}]}{[\text{amide with R groups } \textit{cis}]}$$

At the other extreme is the case when both substituents on nitrogen are H. Then the two arrangements would have equal energies. The process which interconverts the structures is the same but there is now no difference between them. If you could measure an equilibrium constant, it would now be exactly  $K = 1$ .



In more general terms, amide rotation is a simple example of an equilibrium reaction. If we replace 'amount of C–N bond rotation' with 'reaction coordinate' we have a picture of a typical reaction in which reagents and products are in equilibrium.

### How the equilibrium constant varies with the difference in energy between reactants and products

You saw that when the energies of the two forms of the amide were the same, the equilibrium constant for their interconversion must be  $K = 1$ . When one was higher in energy than the other, we just said that  $K$  was 'large'. But we can be more specific. For any reaction in equilibrium, the equilibrium constant  $K$  is related to the difference in energy between the starting materials and the products by the following equation:

$$\Delta G = -RT \ln K$$

where  $\Delta G$  (the **free energy** of the reaction) is the difference in energy between the two states (in  $\text{kJ mol}^{-1}$ ),  $T$  is the temperature (in kelvin, not  $^{\circ}\text{C}$ ), and  $R$  is a constant known as the **gas constant** and equal to  $8.314 \text{ J K}^{-1} \text{ mol}^{-1}$ .

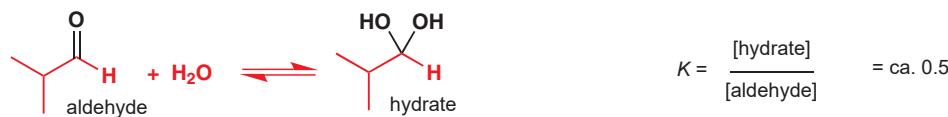
This equation tells us that we can work out the **equilibrium composition** (how much of each component there is at equilibrium) provided we know the difference in energy between the products and reactants.

The **reaction coordinate** is simply an arbitrary measure of the progress of a molecule of starting material as it turns into a molecule of product. You will see it in several diagrams in this chapter.

This relationship was derived by the American physical chemist J. Willard Gibbs in the 1870s.

### An example: hydration of an aldehyde

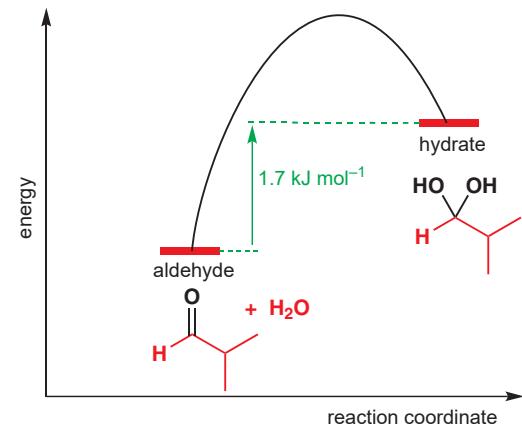
In Chapter 6 we showed you that water adds reversibly to the carbonyl group of an aldehyde: the aldehyde and the hydrate are in equilibrium. Here's the example with isobutyraldehyde (2-methylpropanal). The equilibrium constant is the concentration of hydrate at equilibrium divided by the concentration of aldehyde, also at equilibrium.



Although water is involved in the reaction, you saw on p. 169 that the concentration of neat water effectively remains constant at  $55.5 \text{ mol dm}^{-3}$  and is usually not included in the equilibrium constant.

The concentrations of hydrate and aldehyde at equilibrium in water may be determined by measuring the UV absorption of known concentrations of aldehyde in water and comparing these with the absorptions in a solvent such as cyclohexane where no hydrate formation is possible. Such experiments reveal that the equilibrium constant for this reaction in water at  $25^{\circ}\text{C}$  is approximately 0.5 so that there is about twice as much aldehyde as hydrate in the equilibrium mixture.

Using the equation above, we find that the corresponding value for  $\Delta G$  is  $-8.314 \times 298 \times \ln(0.5) = +1.7 \text{ kJ mol}^{-1}$ . In other words, the solution of the hydrate in water is  $1.7 \text{ kJ mol}^{-1}$  higher in energy than the solution of the aldehyde in water. All this can be shown on an energy profile diagram.



### The sign of $\Delta G$ tells us whether products or reactants are favoured at equilibrium

In the equilibrium above, the hydrate is higher in energy than the aldehyde: at equilibrium there is more aldehyde than hydrate, and the equilibrium constant is therefore less than 1. Whenever this is the case (i.e. the equilibrium lies to the side of the reactants, rather than the

The **reaction coordinate** is an arbitrary scale used for diagrammatic purposes only.

The sign of  $\Delta G$  for a reaction tells us whether the starting materials or products are favoured at equilibrium, but it tells us nothing about how long it will take before equilibrium is reached. The reaction could take hundreds of years! This will be dealt with later.

products)  $K$  will be less than 1. This means that its logarithm must be negative and, because  $\Delta G = -RT\ln K$ ,  $\Delta G$  must be positive. Conversely, for a reaction in which products are favoured over reactants,  $K$  must be greater than 1, its logarithm will be positive, and hence  $\Delta G$  must be negative. When  $K$  is exactly 1, since  $\ln 1 = 0$ ,  $\Delta G$  will be zero.

●  **$\Delta G$  tells us about the position of equilibrium.**

- If  $\Delta G$  for a reaction is negative, the products will be favoured at equilibrium.
- If  $\Delta G$  for a reaction is positive, the reactants will be favoured at equilibrium.
- If  $\Delta G$  for a reaction is zero, the equilibrium constant for the reaction will be 1.

### A small change in $\Delta G$ makes a big difference in $K$

The tiny difference in energy between the hydrate and the aldehyde ( $1.7 \text{ kJ mol}^{-1}$  is small: the strength of a typical C–C bond is about  $350 \text{ kJ mol}^{-1}$ ) gave an appreciable difference in the equilibrium composition. This is because of the logarithm term in the equation  $\Delta G = -RT\ln K$ : relatively small energy differences have a very large effect on  $K$ . The table below shows the equilibrium constants,  $K$ , that correspond to energy differences,  $\Delta G$ , between 0 and  $50 \text{ kJ mol}^{-1}$ . These are relatively small energy differences, but the equilibrium constants change by enormous amounts.

Energies in older or American books are sometimes quoted in kcal (kilocalories)  $\text{mol}^{-1}$ .  
 $1 \text{ kcal} = 4.184 \text{ kJ}$ . The 'calories' counted by nutritionists are in fact kilocalories; the typical energy output of a human adult is  $10,000 \text{ kJ}$  per day.

Variation of  $K$  with  $\Delta G$

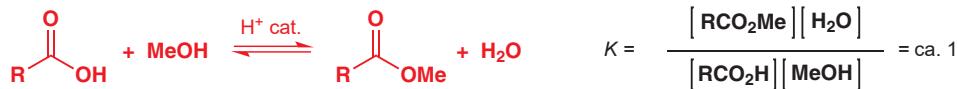
$\Delta G, \text{ kJ mol}^{-1}$	$K$	% of more stable state at equilibrium
0	1.0	50
1	1.5	60
2	2.2	69
3	3.5	77
4	5.0	83
5	7.5	88
10	57	98
15	430	99.8
20	3200	99.97
50	580 000 000	99.999998

In a typical chemical reaction, 'driving an equilibrium over to products' might mean getting, say, 98% of the products and only 2% of starting materials. You can see in the table that this requires an equilibrium constant of just over 50 and an energy difference of only  $10 \text{ kJ mol}^{-1}$ . This small energy difference is quite enough—after all, a yield of 98% is rather good!

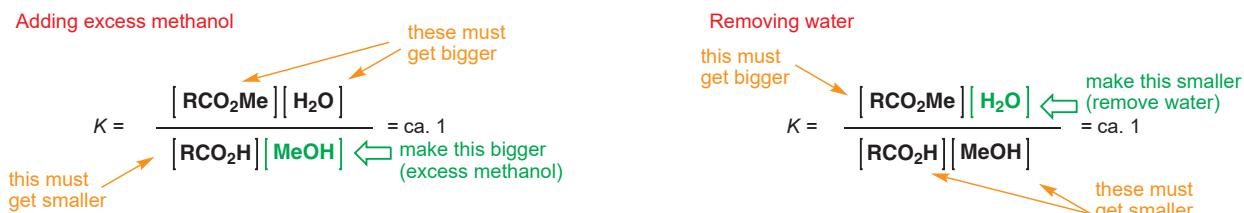
### How to make the equilibrium favour the product you want

#### The direct formation of esters

The formation and hydrolysis of esters was discussed in Chapter 10 where we established that acid and ester are in equilibrium and that the equilibrium constant is about 1. Since the position of the equilibrium favours neither the starting materials nor the products, how can we manipulate the conditions of the reaction if we actually want to make 100% ester?



The important point is that, at any one particular temperature, the equilibrium constant is just that—*constant*. This gives us a means of forcing the equilibrium to favour the products (or reactants) since the ratio between them must remain constant. Imagine what happens if we add more methanol to the reaction above.  $[MeOH]$  increases, but the overall value of  $K$  has to stay the same. The only way this can happen is if more of the ester converts to the acid. Alternatively, imagine removing water from the equilibrium.  $[H_2O]$  goes down, so to bring  $K$  back to the value of 1, the concentrations of acid and methanol are going to have to go down too, by converting themselves to ester and water.



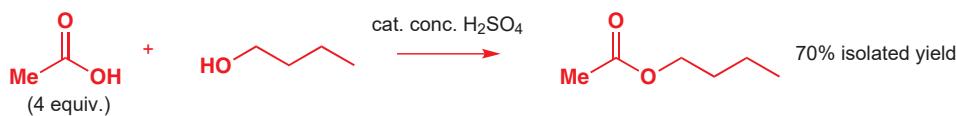
This is exactly how the equilibrium is manipulated in practice. One way to make esters in the laboratory is to use a large excess of the alcohol and remove water continually from the system as it is formed, for example by distilling it out. This means that in the equilibrium mixture there is a tiny quantity of water, lots of the ester, lots of the alcohol, and very little of the carboxylic acid; in other words, we have converted the carboxylic acid into the ester. We must still use an acid catalyst, but the acid must be anhydrous since we do not want any water present—commonly used acids are toluenesulfonic acid (tosic acid, TsOH), concentrated sulfuric acid ( $H_2SO_4$ ), or gaseous HCl. The acid catalyst does not alter the position of the equilibrium; it simply speeds up the rate of the reaction, allowing equilibrium to be reached more quickly. This is an important point that we will come back to shortly.

► There is more on TsOH on p. 227.

### Typical method for making an ester

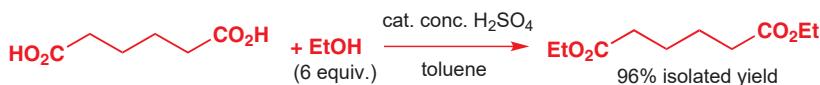
Reflux the carboxylic acid with an excess of the alcohol (or the alcohol with an excess of the carboxylic acid) with about 3–5% of a mineral acid (usually HCl or  $H_2SO_4$ ) as a catalyst and distil out the water that is formed in the reaction. For example, butanol was heated under reflux with a fourfold excess of acetic acid and a catalytic amount of concentrated  $H_2SO_4$  to give butyl acetate in a yield of 70%.

■ 'Reflux' means boil underneath a condenser, so that the boiling solvent constantly runs back into the reaction and is not lost.



It may also help to distil out the water that is formed in the reaction: diethyl adipate (the diethyl ester of hexanedioic acid) can be made in toluene solution using a sixfold excess of ethanol, concentrated  $H_2SO_4$  as catalyst, heating in toluene, and distilling out the water using a Dean Stark apparatus. You can tell from the yield that the equilibrium is very favourable.

► The Dean Stark apparatus for removing water from a refluxing mixture is described on p. 228.



In these cases the equilibrium is made more favourable by using an excess of reagents and/or removing one of the products. The equilibrium *constant* remains the same.

■ The high temperatures and acid catalysis are used to speed up *arrival* at equilibrium, which would otherwise take several days. This aspect of reactivity—the rate of the reaction, rather than the position of the equilibrium—will be dealt with shortly.

### Typical method for hydrolysing an ester

Almost all methods for hydrolysing an ester in order to convert it back to an acid and an alcohol simply make use of excess water. Increasing  $[H_2O]$  forces more acid and alcohol to form to restore the equilibrium, and in favourable situations high yields of the acid and alcohol are formed.

## Entropy is important in determining equilibrium constants

The equation we introduced on p. 243 tells us that an equilibrium favours whichever of the reactants or products has lower energy. But you might reasonably ask this question: why does it just *favour* the components with lower energy? Why do you get *any* of the higher energy ones at all? For the hydration on p. 243, for example, the hydrate is 1.7 kJ mol<sup>-1</sup> higher in energy than the starting aldehyde, so why does the aldehyde react at all? Surely the equilibrium would attain a lower energy state, not with just an excess of aldehyde over hydrate, but with no hydrate at all?

The answer is due to *entropy*, a measure of disorder. Even when there is a difference in energy between the starting materials and products in an equilibrium, you still get *some* of the less stable components. Put simply, having a mixture of components is favourable because a mixture has higher entropy than a pure compound, and equilibria tend to maximize overall entropy. This may be quite a new concept to you, so we will now work our way stepwise through these ideas.

### Energy, enthalpy, and entropy: $\Delta G$ , $\Delta H$ , and $\Delta S$

The equation in the margin just above tells us that the sign and magnitude of the energy  $\Delta G$  are the only things that matter in deciding whether an equilibrium goes in one direction or another. If  $\Delta G$  is negative the equilibrium will favour the products and if  $\Delta G$  is large and negative the reaction can go to completion. The table on p. 244 tells us that it is enough for  $\Delta G$  to be only about -10 kJ mol<sup>-1</sup> to get complete reaction. But we haven't yet considered what  $\Delta G$  actually corresponds to *physically*.

To do this we need to introduce our second equation. The free energy of a reaction,  $\Delta G$ , is related to two other quantities, the enthalpy of reaction,  $\Delta H$ , and the entropy of reaction,  $\Delta S$ , by the equation:

$$\Delta G = \Delta H - T\Delta S$$

As before,  $T$  is the temperature of the reaction in kelvin. Enthalpy,  $H$ , is a measure of heat, and the change in enthalpy,  $\Delta H$ , in a chemical reaction is the **heat given out or taken up** in that reaction. Reactions which give out heat are called *exothermic*, and have negative  $\Delta H$ ; reactions which take in heat are called *endothermic* and have positive  $\Delta H$ . Since breaking bonds requires energy and making bonds liberates energy, the enthalpy change gives an indication of whether the products have more stable bonds than the starting materials or not.

Entropy,  $S$ , is a measure of the **disorder in the system**, so  $\Delta S$  represents the entropy difference—the change in disorder—between the starting materials and the products. More disorder gives a positive  $\Delta S$ ; less disorder a negative  $\Delta S$ .

So  $\Delta G$  represents a combination of heat and disorder. But what does this mean for you as a chemist wanting to get a reaction to work the way you want it to? We know that for a favourable change (i.e. an equilibrium favouring products)  $\Delta G$  must be negative—in fact the more negative the better, as this gives a larger equilibrium constant. Since  $\Delta G = \Delta H - T\Delta S$ , we get a large, negative  $\Delta G$  most readily if:

- $\Delta H$  is negative, i.e. the reaction is exothermic.

and

- $\Delta S$  is positive (and hence  $-T\Delta S$  is negative), i.e. the reaction becomes more disordered.

■ That equation again:

$$\Delta G = -RT\ln K$$

■ If you are interested in the derivation of this equation, which is an expression of the second law of thermodynamics, you will need to consult a textbook of physical chemistry. But you will be able to follow the explanations below without knowing the background to the equation.

Of course, we can still get a negative  $\Delta G$  from an endothermic reaction (i.e. from a positive  $\Delta H$ ) but only if the reaction products are more disordered than the starting materials; likewise a reaction which becomes more ordered as it proceeds can still be favourable, but only if it is exothermic to compensate for the loss of entropy.

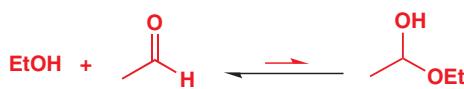
Because of the factor  $T$  multiplying the entropy term, both the equilibrium constant  $K$  (which depends on  $\Delta G$ ) and the relative importance of the two quantities ( $\Delta H$  and  $\Delta S$ ) will vary with temperature (entropy changes are more important at higher temperatures). We'll now look at some examples to see how this works in practice.

### Enthalpy versus entropy—some examples

Entropy dominates equilibrium constants in the difference between inter- and intramolecular reactions. In Chapter 6 we explained that hemiacetal formation is often an equilibrium, with neither starting materials nor products strongly favoured. The addition of ethanol to acetaldehyde shown below on the left, for example, has an equilibrium constant not far from 1. Overall,  $\Delta G$  must therefore be approximately 0 (in fact it's very slightly positive). The *enthalpy* change associated with the reaction is the result of the change in bonding: in this case, a C=O double bond becomes two C–O single bonds, and these two single bonds are marginally more stable than the C=O double bond, therefore  $\Delta H$  is slightly negative. But working against this is the fact that every molecule of hemiacetal that forms consumes two molecules of starting material. Decreasing the number of molecules (and moving from a mixture of aldehyde and alcohol towards pure hemiacetal) leads to an increase in the order of the mixture—in other words a *decrease* in entropy.  $\Delta S$  is negative, so the  $-T\Delta S$  is positive, just about counterbalancing the small negative  $\Delta H$ , and giving a slightly positive  $\Delta G$ .

A mixture has more entropy than a pure substance because there are many more ways of arranging a mixture. Imagine lining up every molecule in a mole of substance and a mole of a 1:1 mixture. For the pure substance, each member of the line of molecules has to be the same. For the mixture, at every position in the line there is a choice of two alternatives, giving a huge number of possible arrangements.

intermolecular hemiacetal formation

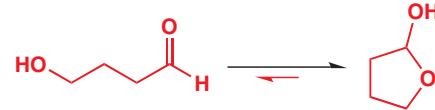


$\Delta H$  is small and negative because C=O double bond is slightly less stable than 2 x C–O single bonds

$\Delta S$  is negative because the one molecule of product is intrinsically less disordered than the two molecules of starting material

Since  $\Delta G = \Delta H - T\Delta S$ ,  $\Delta G$  is positive and the equilibrium lies to the left

intramolecular hemiacetal formation



$\Delta H$  is again small and negative because C=O double bond is slightly less stable than 2 x C–O single bonds

$\Delta S$  is no longer negative: there is no decrease in the number of molecules in this reaction

Since  $\Delta G = \Delta H - T\Delta S$ ,  $\Delta G$  is negative and the equilibrium lies to the right

The reaction on the right is different because it is an *intramolecular* reaction: the hydroxyl group and aldehyde lie in the same molecule.  $\Delta H$  will have essentially the same value as in the intermolecular reaction on the left, but as the intramolecular reaction progresses, one molecule stays one molecule—there is consequently a much less significant decrease in entropy. Our  $T\Delta S$  term no longer weighs against the negative  $\Delta H$  term, making  $\Delta G$  negative overall and allowing the equilibrium to lie to the right.

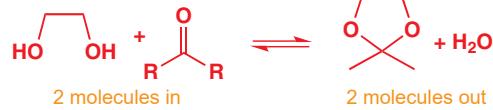
In Chapter 11 we showed you how acetals can be used as base-stable protective groups to prevent nucleophiles attacking carbonyl groups. The acetals we chose to use were cyclic compounds known as dioxolanes, for a very good reason: cyclic acetals are more resistant to hydrolysis than their acyclic counterparts. They are also easier to make—they form quite readily, even from ketones. Again, we have entropic factors to thank for their stability. For the formation of an acyclic acetal (below on the left), three molecules go in and two come out, but for a cyclic one, a cyclic acetal, two molecules go in (ketone plus diol) and two molecules come out (acetal plus water), so the usually unfavourable  $\Delta S$  factor is no longer against us.

► Look back at p. 227 to remind yourself of this.

acyclic acetal formation

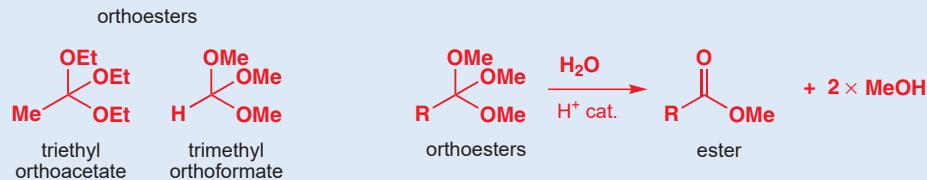


cyclic acetal formation

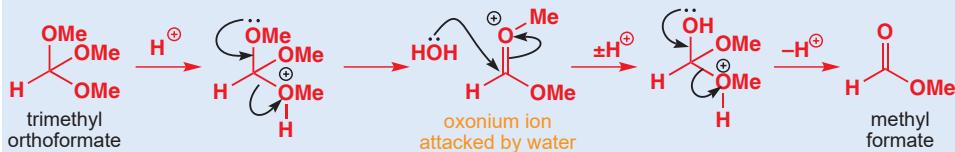


### Overcoming entropy: orthoesters

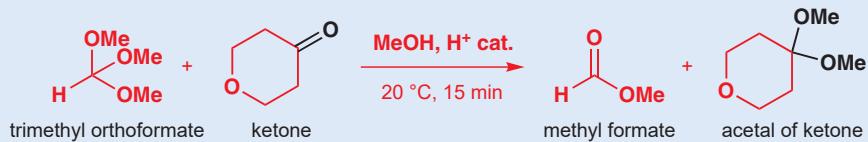
There is a neat way of sidestepping the entropic problem associated with making acyclic acetals: we can use an *orthoester* as a source of alcohol. Orthoesters can be viewed as the 'acetals of esters', which are hydrolysed by water, when catalysed by acid, to an ordinary ester and two molecules of alcohol.



Here is the mechanism for the hydrolysis—you should be feeling quite familiar with this sort of thing by now.



Ketones or aldehydes undergo acetal exchange with orthoesters. The mechanism starts off as if the orthoester is going to hydrolyse but the alcohol released adds to the ketone and acetal formation begins. The water produced is taken out of the equilibrium by hydrolysis of the orthoester, and we get two molecules from two: entropy is no longer our enemy.



### Equilibrium constants vary with temperature

We have said (p. 245) that the equilibrium constant is a constant only as long as the temperature does not change. We can work out exactly how the equilibrium constant varies with temperature by putting our two all-important equations  $\Delta G = -RT\ln K$  and  $\Delta G = \Delta H - T\Delta S$  together to make

$$-RT\ln K = \Delta H - T\Delta S$$

If we divide throughout by  $-RT$  we have

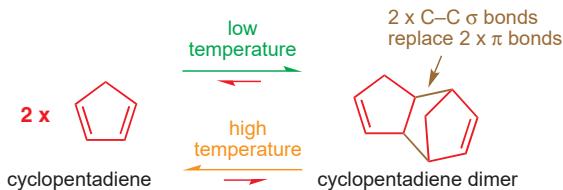
$$\ln K = -\frac{\Delta H}{RT} + \frac{\Delta S}{R}$$

This equation separates the equilibrium constant  $K$  into enthalpy and entropy terms, but it is the enthalpy term that determines how  $K$  varies with temperature. Plotting  $\ln K$  against  $1/T$  would give us a straight line with slope  $-\Delta H/R$  and intercept  $\Delta S/R$ . Since  $T$  (the temperature in kelvin) is always positive, whether the slope is positive or negative depends on the sign of  $\Delta H$ : if  $\Delta H$  is negative then, as temperature increases,  $\ln K$  (and hence  $K$ ) increases. In other words, if the reaction is exothermic (that is, gives out heat) then at higher temperatures the equilibrium constant will be smaller. For an endothermic reaction, as the temperature is increased, the equilibrium constant increases.

### Some reactions are reversible on heating: cracking

Notice that the equation above also tells us that enthalpy becomes a less important contributor to the equilibrium constant as temperature increases, so the higher the temperature, the more important is the entropy term. This fact means that some reactions favour one side of the equilibrium at low temperature but the other at high temperature. Here is an example: the dimerization of cyclopentadiene. You will meet the mechanism of this reaction in Chapter 34, but for

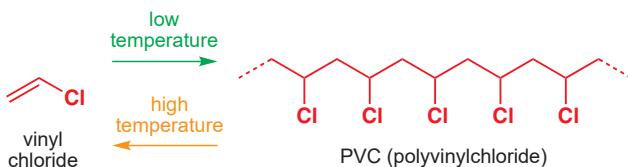
now we can just treat it as a simple dimerization reaction in which two C=C  $\pi$  bonds are replaced by two C–C  $\sigma$  bonds—enthalpically a very favourable process because  $\sigma$  bonds are stronger than  $\pi$  bonds. On standing at low temperature, cyclopentadiene converts to the dimer even though two monomer molecules have more entropy than one molecule of the dimer.



But on heating, the dimer breaks down to give monomeric cyclopentadiene: the equilibrium constant now favours the starting materials. As we predicted, because the reaction is exothermic, heating it makes it less favourable. You can also think of it in terms of our earlier equation  $\Delta G = \Delta H - T\Delta S$ : at low temperature, the large negative  $\Delta H$  term dominates, and  $\Delta G$  is large and negative too. But as  $T$  increases, the positive  $\Delta S$  becomes more important, and eventually  $T\Delta S$  overtakes  $\Delta H$  and  $\Delta G$  becomes positive, and the reaction now favours starting materials.

If you want to use cyclopentadiene, you have to heat the dimer to ‘crack’ it (‘cracking’ is the term used for getting monomers from dimers or polymers). If you lazily leave the monomer overnight and plan to do your reaction tomorrow, you will return in the morning to find dimer.

This idea becomes even more pointed when we look at polymerization. Polyvinyl chloride is the familiar plastic PVC and is made by reaction of large numbers of monomeric vinyl chloride molecules. There is, of course, an enormous decrease in entropy in this reaction any polymerization will not occur above a certain temperature. Some polymers can be depolymerized at high temperatures and this can be the basis for recycling.



Everything decomposes at a high enough temperature eventually, giving atoms. This is because the entropy for lots of particles all mixed up is much greater than that of fewer larger particles.

### ● Summary: Practical points from thermodynamic theory

- The free energy change  $\Delta G$  in a reaction is proportional to  $\ln K$  (that is,  $\Delta G = -RT\ln K$ ).
- $\Delta G$  and  $K$  are made up of enthalpy and entropy terms (that is,  $\Delta G = \Delta H - T\Delta S$ ).
- The enthalpy change  $\Delta H$  is the difference in stability (bond strength) of the reagents and products.
- The entropy change  $\Delta S$  is the difference between the disorder of the reagents and that of the products.
- The enthalpy term alone determines how  $K$  varies with temperature.
- The entropy change come to dominate control of equilibrium as temperature is raised.

### Le Châtelier's principle

You may well be familiar with a rule that helps to predict how a system at equilibrium responds to a change in external conditions—**Le Châtelier's principle**. This says that if we disturb a system at equilibrium it will respond so as to minimize the effect of the disturbance. An example of a disturbance is adding more starting material to a reaction mixture at equilibrium. What happens? More product is formed to use up this extra material. This is a consequence of the equilibrium constant being, well . . . , constant and hardly needs anybody's principle.

Another disturbance is heating. If a reaction under equilibrium is heated, how the equilibrium changes depends on whether the reaction is exothermic or endothermic. If it is exothermic (that is, gives out heat), Le Châtelier's principle would predict that, since heat is consumed in the reverse reaction, more of the starting materials will be formed. Again no ‘principle’ is needed—this change occurs because the equilibrium constant is smaller at higher temperatures in an exothermic reaction. Avoid using principles and rules without understanding the science underneath them or you may find yourself playing with fire (which incidentally most definitely does not obey Le Châtelier's principle, for very good reasons . . .).

## Introducing kinetics: how to make reactions go faster and cleaner

Although in chemistry laboratories you will see lots of reactions being heated, very rarely will this be to alter the equilibrium position. This is because most reactions are not carried out reversibly and so the ratio of products to reactants is not an equilibrium ratio. The main reason chemists heat up reactions is simple—it speeds them up. The study of the rates of reactions, as opposed to their equilibrium states, is known as **kinetics**.

- Thermodynamics is concerned with equilibria; kinetics is concerned with rates.

### How fast do reactions go? Activation energies

The combustion of the hydrocarbon shown below, the major component of petrol (gasoline) trivially known as ‘isooctane’, proceeds with  $\Delta G = -1000 \text{ kJ mol}^{-1}$  at 298 K.

■ ‘Isooctane’ is the trivial name of 2,2,4-trimethylpentane.



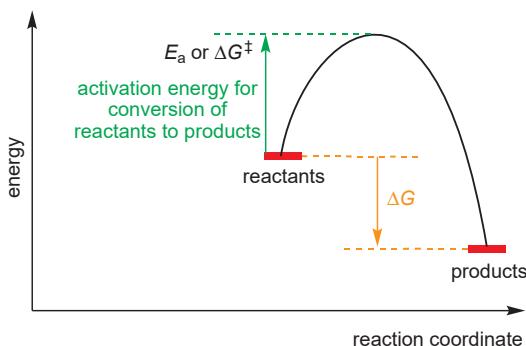
The table on p. 244 shows that even a  $\Delta G$  of only  $-50 \text{ kJ mol}^{-1}$  gives rise to a huge equilibrium constant:  $-1000 \text{ kJ mol}^{-1}$  gives an equilibrium constant of  $10^{175}$  (at 298 K), a number too vast to contemplate (there are ‘only’ about  $10^{86}$  atoms in the observable universe). This value of  $\Delta G$  (or the corresponding value for the equilibrium constant) suggests that isooctane simply could not exist in the presence of oxygen. Yet we put it into the fuel tanks of our cars every day—clearly something is wrong.

Since isooctane can exist in an atmosphere of oxygen despite the fact that the equilibrium position really would be completely on the side of the combustion products, the only conclusion we can draw must be that a mixture of isooctane and oxygen cannot be at equilibrium. A small burst of energy is needed to reach equilibrium: in a car engine, the spark plug provides this energy and combustion occurs. Without this burst of energy, the petrol is stable and no combustion occurs (as you will ruefully be aware if you have ever tried to start a car with a flat battery).

The mixture of petrol and oxygen is said to be *thermodynamically* unstable with respect to the products of the reaction,  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , but *kinetically* stable. We can be certain that they are thermodynamically unstable because even if the same small energy burst were applied to the products  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , they would never convert back to petrol and oxygen.

*Kinetically stable* means that although the mixture *could* convert to a more stable set of products, it doesn’t do so because an energy barrier separates it from those products. An energy level diagram for a reaction such as the combustion of isooctane is shown below. The products are more stable (lower in energy) than the reactants, but to become the products, the reactants have to overcome a barrier to reaction. This barrier is called the **activation energy** and is usually given the symbol  $E_a$  or  $\Delta G^\ddagger$ .

The differences between  $E_a$  and  $\Delta G^\ddagger$  need not concern us here; you will find the details in a textbook of physical chemistry.



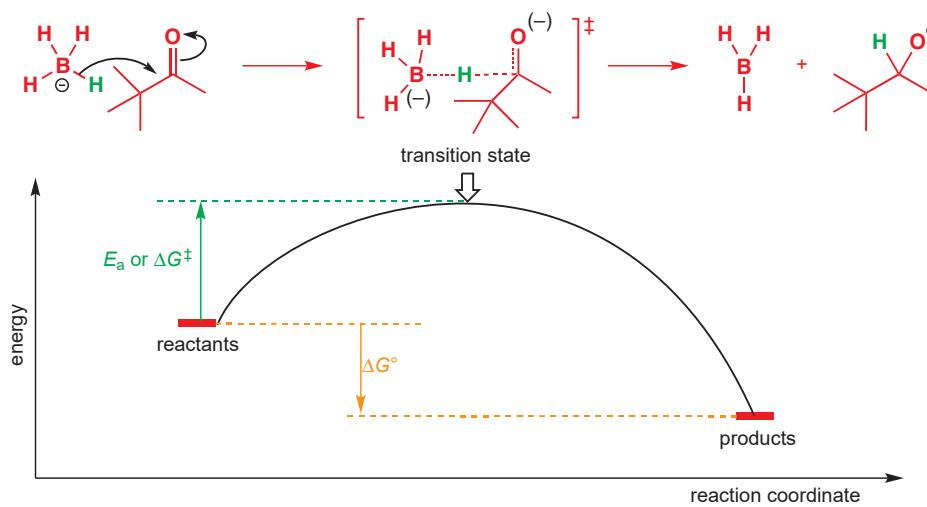
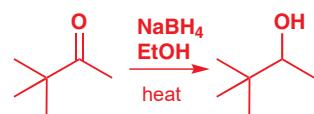
If a reaction cannot proceed until the reactants have sufficient energy to overcome the activation energy barrier, it is clear that, the smaller the barrier, the easier it will be for the reaction to proceed. Likewise, the more energy we give the starting materials in the form of temperature, the more likely it is that they will collide with sufficient combined energy to cross the activation energy barrier. Unlike equilibria, which can change in either direction, reaction rates *always* increase at higher temperatures.

A word of warning, however: heating is not all good for the chemist—not only does it speed up the reaction we want, it will also probably speed up lots of other reactions that we don't want, including perhaps decomposition of the product! We shall see how we can get round this, but first we shall take a closer look at what determines how fast a reaction takes place.

### The route from reactants to products: the transition state

The combustion of kinetically stable fuel releases lots of energy by a very complex mechanism. To understand how energy is involved in the progress of a reaction we will need to take a much more simple and familiar mechanism. The reduction of a ketone to an alcohol with sodium borohydride will do. You met this reaction in Chapters 5 and 6 and it should by now be a familiar part of your chemical vocabulary. An example is shown in the margin: in this particular case, the ketone is rather hindered by the adjacent *tert*-butyl group, and the reaction must be heated to form the product. Evidently, then, there is an activation barrier that must be overcome.

Let's think about what that barrier might be. Although the final product is an alcohol, as you know well, the first step is transfer of a hydrogen atom from boron to the carbonyl group, as shown in the mechanism below. Overall, as shown in the energy profile diagram, the products of this step are more stable than the starting materials ( $\Delta G$  is negative), but to get there the reaction has to pass through the activation energy barrier ( $\Delta G^\ddagger$ ). This barrier—the highest energy point on the profile—must correspond to some structure (which we have shown in square brackets) in which the hydrogen atom is only partly transferred from B to C, and the carbonyl group is only partly broken. We call this structure—the highest energy form through which the molecules must pass to get from reactants to products—the **transition state**. It is often represented in square brackets, frequently with a double dagger symbol  $\ddagger$  (to match the activation energy  $\Delta G^\ddagger$ ).



To draw a structure representing a transition state is easy: first put in all the bonds that are not affected by the reaction, then use dotted bonds for all those which break or form as the reaction proceeds. You will need to spread charge over appropriate atoms, putting a + or - in brackets to indicate a partial charge.

Interactive mechanism for borohydride reduction

Notice that the transition state has some features of the reactants and some features of the products. The B–H bond is partly broken, so we represent it as a dotted line, and the new H–C bond is partly formed, so likewise that is dotted too, as is the breaking C=O bond. The negative charge, which starts associated with B and ends on the oxygen atom, is shown in brackets in both locations, to indicate that it is shared between them. It takes energy to get to the transition state because the H has to move away from the B without significant compensation.

Conventionally, charges in brackets indicate a significant proportion, usually about 1/2, of a charge, unlike ' $\delta+$ ' or ' $\delta-$ ', which might represent only 1/10 or 1/5 of a charge.

But once the transition state is passed, the formation of a stable C–H bond and the migration of a charge to electronegative oxygen means that stability is regained.

A transition state is always unstable and can never be isolated: if the reaction proceeds just a little more forwards or backwards, the energy of the system is lower. Isolating a transition state would be like balancing a marble on top of a bowling ball.

### ● Transition state

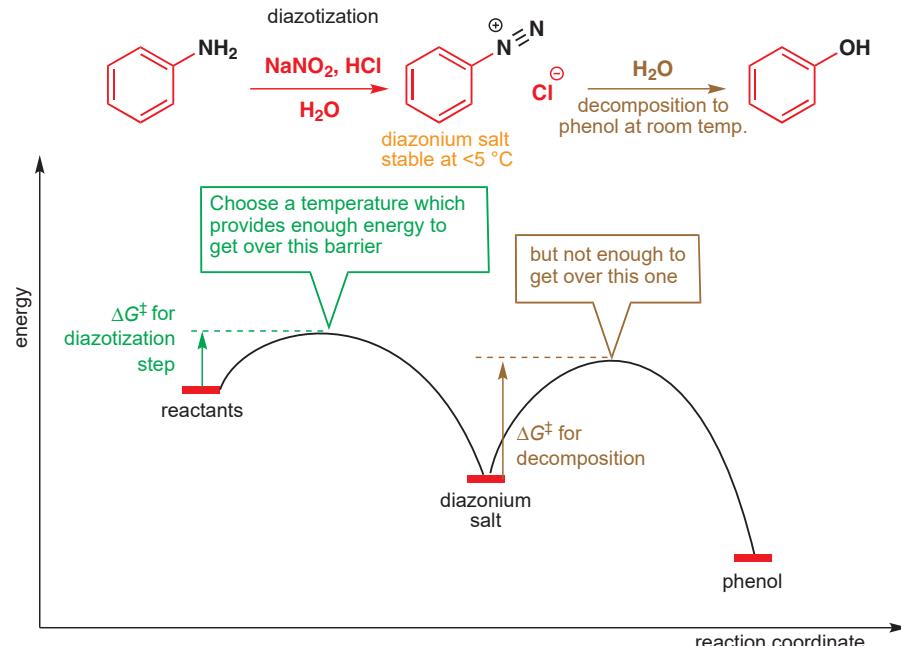
A transition state is a structure that represents an energy maximum on passing from reactants to products. It is not a real molecule in that it may have partially formed or broken bonds and may have more atoms or groups around the central atom than allowed by valence bond rules. It cannot be isolated because it is an energy maximum and any change in its structure leads to a more stable arrangement. A transition state is often shown by putting it in square brackets with a double-dagger superscript.

### Why some reactions are done at low temperature

So far in this chapter you have seen that while heating a reaction can change the position of an equilibrium, the usual reason for heating a reaction is to speed it up by giving the reactants more energy to allow them to overcome the activation barrier. But as we said in the introduction, in a typical laboratory you will see many reactions being carried out at low temperatures. Why might a chemist want to *slow a reaction down*?

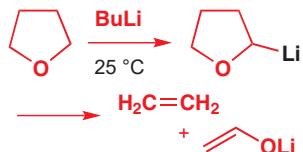
Well, often molecules can react in several different ways. A good reaction will have a lower activation energy than these alternatives. But often there are other unavoidable reactions waiting in the wings that will compete with the one that is wanted if the molecules have enough energy. The ideal situation is to give the starting materials enough energy to do the reaction we want, but not enough to do anything else: and that means keeping the reaction cold.

A famous example of a reaction which must be kept cold is the diazotization of anilines to make diazonium salts. The reaction involves treating the amine with nitrous acid ( $\text{HONO}$ ) made from  $\text{NaNO}_2$  and  $\text{HCl}$ . You need not think about the mechanism at this stage—you will meet it in Chapter 22—but the key point is that the product is a rather unstable but very useful diazonium salt. The diazotization takes place readily at room temperature, but unfortunately so does the decomposition of the product to give a phenol. By lowering the temperature, we supply insufficient energy for the phenol formation, but the diazotization still works just fine.



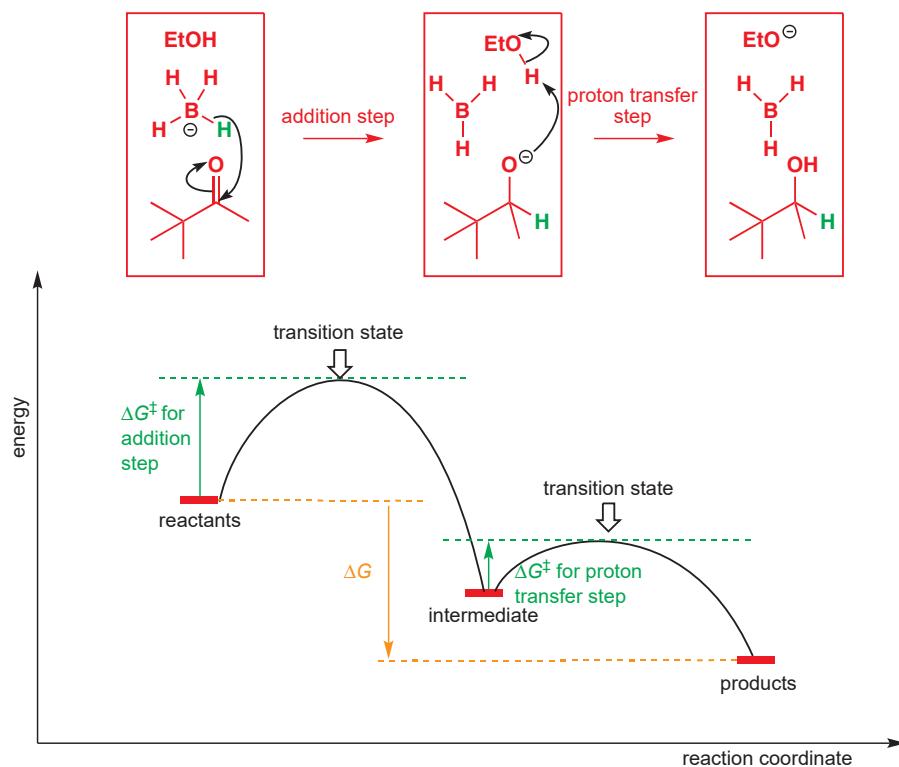
The use of organolithiums (which you saw in Chapter 9) typically involves low temperatures, often as low as  $-78^{\circ}\text{C}$ . Organolithiums are very reactive, and the addition or deprotonation reactions they undergo have activation energies sufficiently low that they proceed even at such temperatures. However, they do also have a tendency to attack some of the solvents which they dissolve best in, such as THF. If lithiations are attempted at higher temperatures, THF also reacts with *s*-BuLi to give the surprising by-products discussed in Chapter 35.

■  $-78^{\circ}\text{C}$  is the convenient temperature of a bath of acetone containing pellets of slowly evaporating solid  $\text{CO}_2$ .



## Reaction intermediates

Our mechanism for reduction of the ketone with borohydride is of course not yet complete: there is another step to follow—the protonation of the alkoxide by the ethanol solvent. We can add this step to our energy profile diagram.



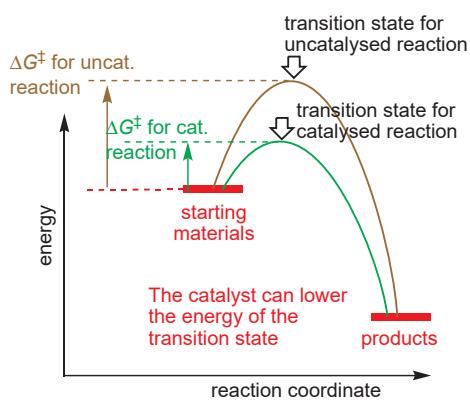
Interactive mechanism for borohydride reduction

Now the product of the first stage of the reaction is the starting material for the second, which follows on straightaway because the activation energy for the second reaction, the proton transfer, is smaller than for the first one. Notice that we have now labelled the middle set of structures, which includes the alkoxide ‘intermediate’. An intermediate is a staging post in a reaction pathway: it is stable for a finite (if short) period. Unlike a transition state it is a minimum rather than a maximum on the reaction energy profile, and therefore has a finite existence—an intermediate *could*, in principle, be isolated, and many have been (particularly at low temperature).

■ You can think of the diazonium salt on p. 252 as an isolable intermediate en route to the phenol. Notice how the energy profile for that sequence matches the one here.

### ● Intermediates and transition states

- A **transition state** represents an energy maximum—any small displacement leads to a more stable product. It can never be isolated.
- An **intermediate** is a molecule or ion that represents a localized energy minimum—an energy barrier must be overcome before the intermediate forms something more stable. An intermediate can in principle be isolated (although in practice its high energy can make this difficult).



## Catalysis

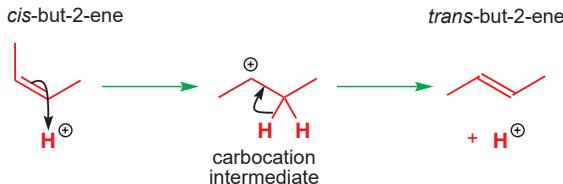
You've met the idea in several places in this book (and probably elsewhere) that a catalyst increases the rate of a reaction. From what you have just read, it must therefore be the case that a catalyst lowers the activation energy for a reaction. It can do this in one or both of two ways: it can lower the energy of the transition state (as shown in the diagram on the left, or it can raise the energy of the starting materials.

- Catalysts work by lowering the activation energy for a reaction.

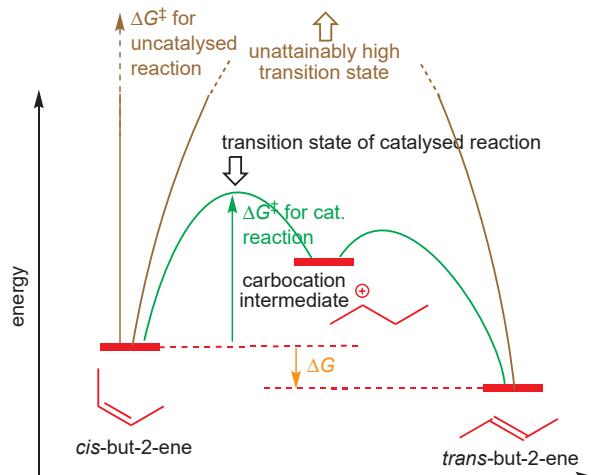
To illustrate the point with one simple example, let's take a reaction which simply does not work without a catalyst: the isomerization of butene. As you saw on p. 105, *cis* but-2-ene is about 2 kJ mol<sup>-1</sup> higher in energy than *trans* but-2-ene. This small energy difference would correspond to a 2.2:1, 70:30, *trans:cis* ratio of alkenes if they were in equilibrium. But it's a big *if*: the activation energy needed to get from one to the other is of the order of 260 kJ mol<sup>-1</sup>, which is practically unattainable. A quick calculation predicts that the half-life for the reaction would be approximately 10<sup>25</sup> years at room temperature, a time many orders of magnitude longer than the age of the universe. At 500 °C, however, the half-life is a more reasonable 4 hours, but unfortunately, when most alkenes are heated to these sorts of temperatures other unwanted reactions occur.

In order to interconvert the *cis* and *trans* isomers we must use a different strategy: catalysis. You will meet several ways of doing this in Chapter 27, but for the moment we will use just one: catalytic acid. As you saw in Chapter 5, alkenes are nucleophiles, and either isomer of but-2-ene can react with H<sup>+</sup> from acid to form a transient species known as a carbocation. The activation energy for formation of the carbocation is much less than that for rotation about the C=C bond. The carbocation can now easily lose a proton again, to reform either *cis*- or *trans*-but-2-ene, regenerating the catalyst and allowing the interconversion to take place. Overall, the activation energy is much lower than in the uncatalysed reaction. We will come back to other examples of catalysis later in the chapter.

### Acid catalysed isomerization:



You have already seen a case in this chapter, and you met many in Chapter 9, where THF (or diethyl ether) was used as the solvent for organolithium reactions: it coordinates to Li and solubilizes the organometallic compounds. Alcohol solvents cannot be used with organolithiums because they are deprotonated by the strong organolithium bases.



## Solvents

The nature of the solvent used in reactions often has a profound effect on how the reaction proceeds. Sometimes, if the solvent is also a reagent, the choice is easy: it's a good idea to carry out hydrolyses of esters in water and formations of esters in the appropriate alcohol because

the large concentration of the solvent drives the reaction towards the product, as explained on p. 208. Likewise, the solvent may also catalyse a reaction: ester formation from an acid chloride and an alcohol is often carried out in pyridine as a solvent because pyridine acts as a base catalyst of the reaction (p. 199).

On occasions, the choice of solvent is limited by simple features of the starting materials and products, such as their solubility or reactivity. Simple examples are cases where an inorganic salt is a reagent: ionic compounds are relatively insoluble in most organic solvents. Sodium bromide, for example, dissolves well in water, reasonably well in methanol, a little in ethanol, and hardly at all in most other organic solvents.

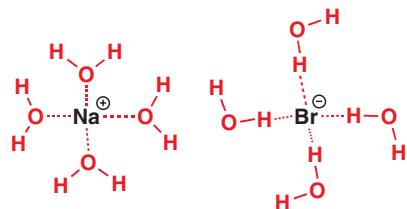
The insolubility of some salts in organic solvents can be used to drive an equilibrium in the direction required. For example, in the synthesis of this alkyl iodide from the alkyl bromide by reaction with sodium iodide, acetone is used as the solvent. Why? Well, sodium iodide is rather more soluble in acetone than is sodium bromide, so as sodium bromide is removed from the equilibrium mixture, more of the starting materials have to convert to the products to restore the equilibrium constant. You will meet more on this reaction in Chapter 15.



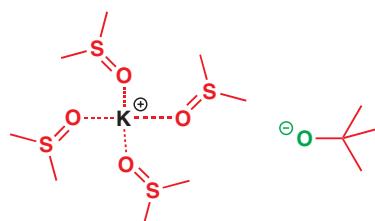
Solubilities of sodium bromide in protic solvents

Solvent	Solubility, g/100 g of solvent
H <sub>2</sub> O	90
MeOH	16
EtOH	6

Water dissolves sodium bromide well because it solvates both cations and anions: electrostatic interactions with its  $\delta-$  oxygen atoms can stabilize the positive sodium ions, while attraction to its  $\delta+$  hydrogen atoms can stabilize the negative bromide ion. Solvents which have polarized bonds like this are known as *polar*. Water and other alcohols are also called protic solvents because they have  $\delta+$  protons that can interact readily with anions.



Water solvates cations and anions



DMSO (a polar aprotic solvent) solvates only cations

Another group of polar solvents lack  $\delta+$  protons: these are the polar aprotic solvents, such as DMSO or DMF. Although they have a localized  $\delta-$  at oxygen, which can solvate cations, they are much less good at solvating anions because their molecules do not have a localized accessible  $\delta+$  region. In Chapter 10 (p. 213) you met a specific combination of *t*-BuOK and DMSO to help hydrolyse an amide. This is why DMSO is used here: it solvates the K<sup>+</sup> cation, leaving the *t*-BuO<sup>-</sup> unstabilized by solvation. It is desperate to become neutral by finding a proton. Metal alkoxides in DMSO are extremely basic, and when even sodium chloride is dissolved in DMSO the usually innocuous chloride ion becomes quite a powerful nucleophile, as you will see in Chapter 25.

A third group of solvents are not polar at all, but may still dissolve organic molecules quite well. These include hydrocarbons, chlorinated solvents (chloroform), and aromatic solvents (toluene, benzene).

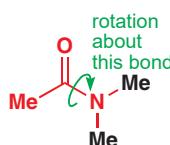
The table below groups common solvents in classes with shared features, and also indicates their polarity. Polarity is measured in various ways—here we give the ‘dielectric constants’—but you do not need to remember the numbers. Learning the general position of a solvent in this sequence of polarity will, however, be a wise investment of your time.

■ Alternatives for chloroform or benzene should be used where possible as there is evidence that these solvents have cancer-causing properties.

Polarity of some common solvents (dielectric constants)

Polar protic solvents		Polar aprotic solvents		Non-polar solvents	
water	80	DMSO	47	chloroform ( $\text{CHCl}_3$ )	4.8
methanol	33	DMF	38	diethyl ether	4.3
ethanol	25	acetonitrile	38	toluene	2.4
acetic acid	6	acetone	21	benzene	2.3
		dichloromethane	9.1	cyclohexane	2.0
		tetrahydrofuran (THF)	7.5	hexane	1.9
		ethyl acetate	6.0	pentane	1.8

increasing polarity ↑



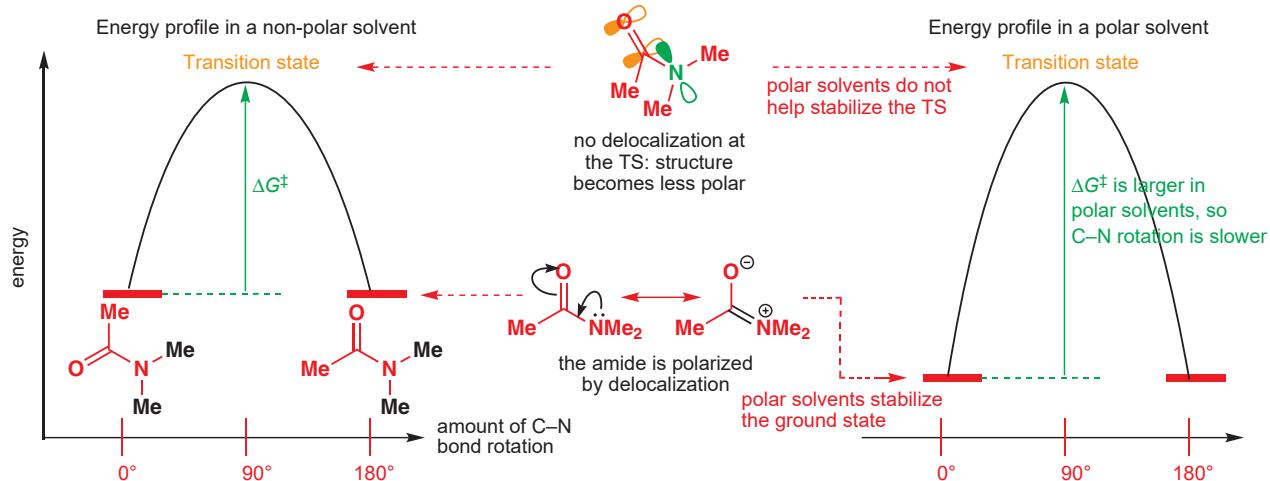
Rate constants for amide C–N bond rotation in dimethylacetamide

Solvent	$\Delta G^\ddagger$ , kJ mol <sup>-1</sup>
water	80.1
DMSO	76.5
acetone	74.5
cyclohexane	70.0

By virtue of their ability or inability to solvate charged species, solvents can affect the course of reactions by stabilizing or destabilizing a transition state or an intermediate. Here's a very simple example: the effect of solvent on one of the first 'reactions' in this chapter—the rotation about the C–N bond of an amide. The table in the margin shows the activation energy  $\Delta G^\ddagger$  for C–N bond rotation in dimethylacetamide (DMA) in a range of solvents. You can immediately deduce that the rate of the rotation is fastest in the least polar solvent, cyclohexane, because the barrier is lowest. Why might this be?

To understand rates, we have to think about activation energies, in other words the difference in energy between the starting materials and the transition state. As you know, an amide in its ground state (in other words, its lowest energy state) is delocalized because of conjugation between the nitrogen's lone pair and the carbonyl group. This delocalization leads to a degree of charge separation and polarization of the amide. But as the C–N bond rotates, the conjugation is broken because the molecule has to pass through a transition state in which the N lone pair is perpendicular to the  $\pi$  system of the carbonyl group. The transition state is therefore less polar than the ground state.

Now, if we compare the effect on this rotation of a non-polar solvent and a polar solvent, this is what will happen. The polar ground state will be stabilized by the polar solvent, and so will be lower in energy, as you see on the right of the diagram below. But the less polar transition state will have about the same energy, whatever the polarity of the solvent. So, in a polar solvent, the amount of energy required to get from the ground state to the transition state (this is the activation energy,  $E_a$  or  $\Delta G^\ddagger$ ) is greater than in a non-polar solvent, and bond rotation is slower.



In Chapter 15 you will go on to meet a pair of mechanisms in which the polarity of the transition state is very different. You will now be prepared to expect some very significant solvent effects when such reactions take place.

● Solvents can affect the rate of a reaction by:

- participating as a reagent
- acting as a catalyst
- dissolving the reagents
- differentially stabilizing the ground state and transition state.

## Rate equations

We've pointed out that reactions go faster at higher temperature because the starting materials have more energy. But temperature is not the sole controller of rate. Two molecules might well collide with plenty of energy, but unless they are two molecules that can actually react, that energy will be lost as heat. Going back again to the reduction of p. 251 (a reminder in the margin), it's obvious that only collisions between ketone (A) and borohydride (B) get us anywhere—there will be plenty of non-productive collisions between A and A or B and B. Obviously the chance of a collision between A and B is increased the more of each you have, and especially if you have lots of A *and* lots of B. In fact, the chance of a successful reaction is proportional to the product of the concentration of A and the concentration of B. We can express this in a simple *rate equation*:

$$\text{rate of reaction} = k \times [A] \times [B]$$

where the value *k* represents the *rate constant* for the reaction. The value of *k* is different for different reactions, and it also varies with temperature. The size of *k* also contains information about how likely it is that the molecules will collide with the right orientation. We call this analysis of the factors affecting the rate of the reactions the **kinetics** of the reaction.

There is of course a link between the activation energy of a reaction and its rate, and the connection between them is known as the Arrhenius equation, after the Swedish chemist Svante Arrhenius (1859–1927) who formulated it and won the Nobel Prize in 1903.

$$k = A e^{-E_a/RT}$$

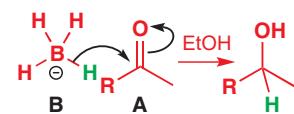
where *k* is the rate constant for the reaction, *R* is the gas constant (see p. 243), *T* is the temperature (in kelvin), and *A* is a quantity known as the pre-exponential factor. Because of the minus sign in the exponential term, the larger the activation energy, *E<sub>a</sub>*, the slower the reaction but the higher the temperature, the faster the reaction.

As we discussed on p. 253, the reaction between borohydride and the ketone to make an alkoxide is only the first step of this reaction. Since ethanol likewise has to collide with the alkoxide for this second step to take place, you might very reasonably ask yourself why the rate of formation of the alcohol product does not also depend on [EtOH]: why is the rate equation not

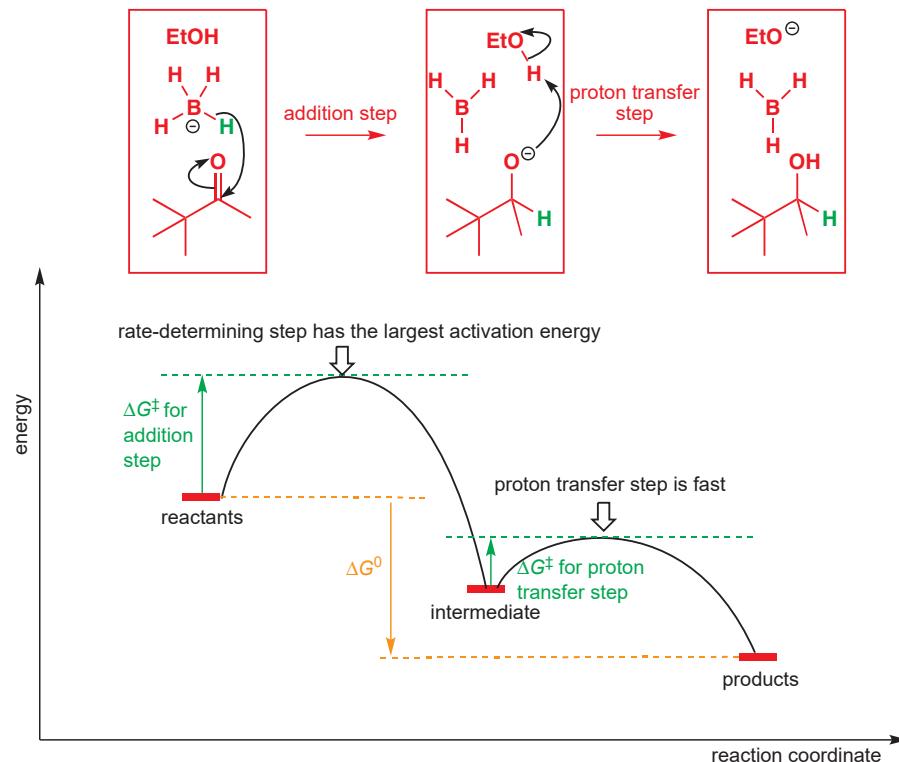
$$\text{rate of reaction} = k \times [\text{ketone}] \times [\text{borohydride}] \times [\text{EtOH}] ?$$

The answer is hinted at in the energy profile diagram you saw on p. 253, which is reproduced below. The activation energy for the proton transfer step is lower than for the addition step, so it happens faster. It fact, it can happen fast *whatever the concentration of ethanol*, so ethanol does not appear in the rate equation. The overall rate of any reaction is determined only by what happens in the mechanistic step that is slowest, known as the **rate-determining step** or **rate-limiting step**. This is a general point about anything that happens in several

► We discussed the simple ideas about what must happen for a reaction to take place between two molecules at the start of Chapter 5. We're now adding more detail to those simple concepts.



steps: if you want to empty a football stadium through a set of turnstiles, it is only the rate at which the turnstiles operate that limits the emptying speed—it doesn't matter how quickly or slowly people walk away after they are through.



Proton transfers to or from carbon may be slow.

At several points in Chapters 6, 9, 10, and 11 we have said things like 'don't worry about the details of the proton transfers' and now you know why: proton transfers between N and O atoms are fast, and other steps are almost always rate determining. It doesn't really matter how you get a proton from one electronegative atom to another—in reality it will be flitting all over the place and any reasonable route is just as correct as any other.

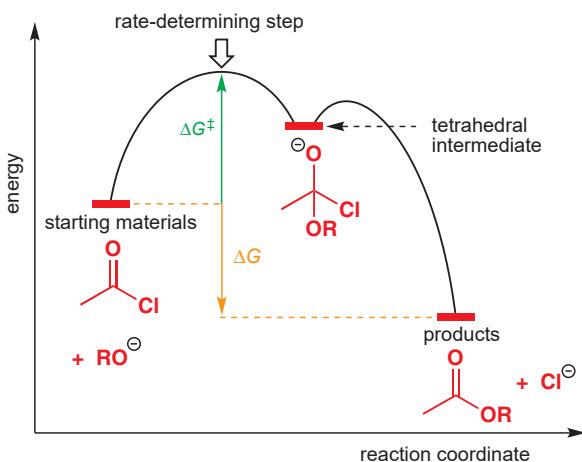
- Proton transfers, particularly between O or N, are always fast and only rarely rate determining.

### Kinetics gives us an insight into the mechanism of a reaction

In Chapters 10 and 11 you met some other multistep reactions with intermediates. Take this example: an alkoxide  $\text{RO}^-$  will react with an acid chloride to form an ester. If we measure how the rate of the formation of the ester varies with the concentration of the alkoxide and of the acid chloride, we discover a rate equation

$$\text{rate} = k[\text{MeCOCl}][\text{RO}^-]$$

Both the acid chloride and alkoxide must therefore be involved in the rate-determining step, which, as you know from Chapter 10, must be the formation of the tetrahedral intermediate. This intermediate is less stable than the starting materials, so the reaction energy profile takes the form shown below, with the highest transition state corresponding to the addition step.



The presence of two species in the rate equation confirms that the reaction is bimolecular (i.e. it involves two molecules), and we call such rate equations *second order*.

Numerous kinetic studies have confirmed that this mechanism, with a tetrahedral intermediate, is the normal pathway by which substitution reactions at carbonyl groups take place, as we explained in Chapter 10. You could draw a similar pathway, and a similar energy profile, for all of the reactions shown on p. 215, adjusting the energies of the starting materials, products, and intermediates appropriately, but all of them are second order, with rate-limiting attack on the carbonyl group.

However, there are occasional exceptions. These are not important enough for you to consider them likely when you write substitution mechanisms, but they do illustrate the fact that *kinetics* tells us about *mechanism*.

Here is one: when an acid chloride is heated with an alcohol in the absence of base, an ester forms. However, it turns out that under these conditions the rate equation is first order: it does not matter how much or how little alcohol is added, the rate depends only on the concentration of the acid chloride:

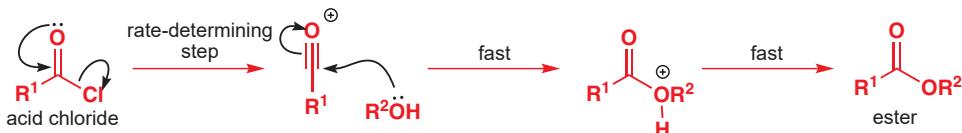
$$\text{rate of reaction} = k[\text{R}^1\text{COCl}]$$



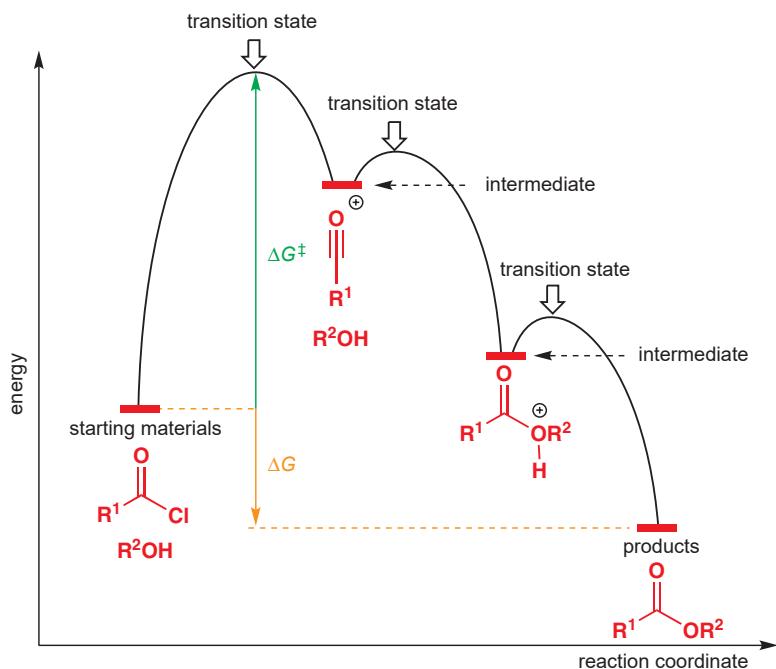
This is not the recommended way to make an ester: the reaction is much better if a base is added, in which case it follows the usual addition-elimination mechanism.

Evidently, from the rate equation, no collision between the acid chloride and the alcohol is required for this reaction to go. The rate-determining step must be *unimolecular*. What actually happens is that the acid chloride decomposes by itself to give a reactive cation with the loss of the good leaving group Cl<sup>-</sup>.

#### Unusual unimolecular mechanism for ester formation



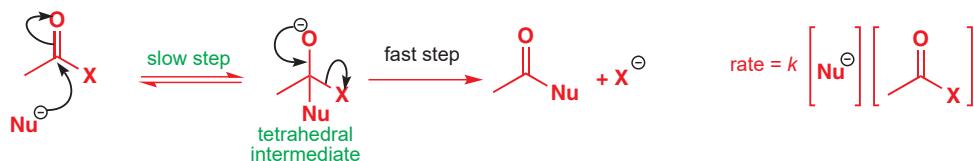
There are three steps in this reaction scheme, although the last is a trivial deprotonation. The energy barrier must be highest in the first step, which involves the acid chloride alone. The cation is an intermediate (although a short-lived one) with a real existence that reacts rapidly with the alcohol in a step that does not affect the rate of the reaction. The easiest way to picture this detail is in an energy profile diagram:



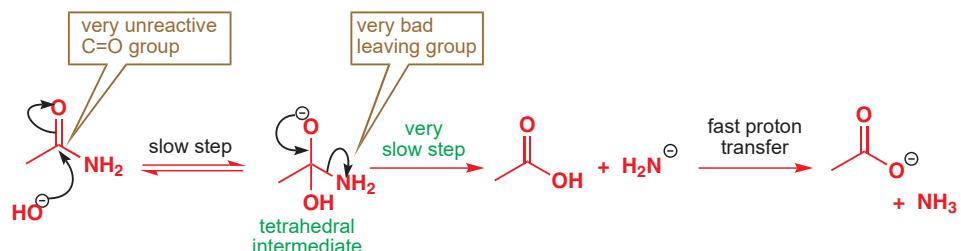
Notice that the products are again lower in energy than the starting materials, and although there are three transition states in this reaction, only the highest-energy transition state (the first one here) matters in determining the reaction rate. The reaction now passes through two intermediates (local minima). It is often the case that when intermediates are involved in a reaction, the highest-energy transition state is associated with the formation of the highest-energy intermediate.

### What does third-order kinetics mean?

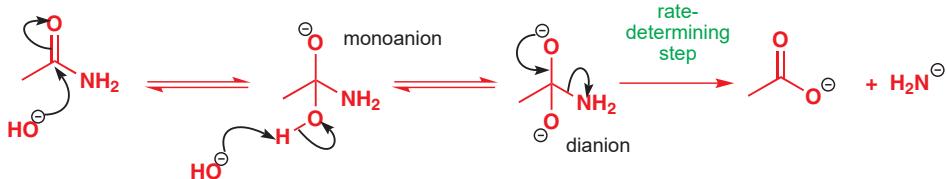
The first-order kinetics of this unusual substitution reaction is here to illustrate a point, but it should not distract you from the fact that most nucleophilic substitutions of carboxylic acid derivatives (the reactions you met in Chapter 10) are bimolecular reactions with rate-determining formation of the tetrahedral intermediate.



However, something different again happens when we come to reactions of amides. Because of the delocalization of the nitrogen lone pair into the carbonyl group, nucleophilic attack on the carbonyl group is very difficult. In addition, the leaving group ( $\text{NH}_2^-$ , with  $\text{p}K_a$  of  $\text{NH}_3$  about 35) is very bad indeed.



What happens as a consequence is that in the hydrolysis of amides the second step—the breakdown of the tetrahedral intermediate—becomes rate determining. But this offers the opportunity for base catalysis of this step. If a second hydroxide ion removes the proton from the tetrahedral intermediate, the loss of NH<sub>2</sub> from what is now a dianion is made easier, and a stable carboxylate ion is formed directly.



In Chapter 10 (p. 213) you met a method for hydrolysing amides that exploits this second deprotonation.

Notice that in the first mechanism just one hydroxide ion is involved, whereas now two are involved: one is consumed to form product, but the second is in fact regenerated when the product NH<sub>2</sub><sup>-</sup> anion reacts with water—in other words the second hydroxide ion is a catalyst.

The rate equation for the amide hydrolysis reflects this involvement of two hydroxide ions: the rate depends on the square of the hydroxide ion concentration and it is *third order*. We'll label the rate constant  $k_3$  to emphasize this:

$$\text{rate} = k_3[\text{MeCONH}_2] \times [\text{HO}^-]^2$$

But you may be asking yourself where this third-order kinetics comes from, since the hydroxide ions are not actually involved in the rate-determining step. In fact, third-order kinetics hardly ever mean the real simultaneous termolecular collision of three molecules at once—such events are just too rare.

The rate-determining step here is actually unimolecular—the collapse of the dianion. So we expect

$$\text{rate} = k[\text{dianion}]$$

We don't know the concentration of the dianion but we do know that it's in equilibrium with the monoanion—we'll call this equilibrium constant  $K_2$ :

$$K_2 = \frac{[\text{dianion}]}{[\text{monoanion}][\text{HO}^-]}$$

and so [dianion] =  $K_2[\text{monoanion}][\text{HO}^-]$ .

This sort of helps, but we still don't know what [monoanion] is, other than that it's again in equilibrium, this time with the amide—we'll call this equilibrium constant  $K_1$ :

$$K_1 = \frac{[\text{monoanion}]}{[\text{amide}][\text{HO}^-]}$$

and so [monoanion] =  $K_1[\text{amide}][\text{HO}^-]$ .

Substituting these values in the simple rate equation we discover that

$$\text{rate} = k[\text{dianion}] \text{ becomes}$$

$$\text{rate} = kK_1K_2[\text{amide}][\text{HO}^-]^2$$

The third-order kinetics result from two equilibria starting with the amide and involving two hydroxide ions, followed by a unimolecular rate-determining step, and the 'third-order rate constant'  $k_3$  is actually a product of the two equilibrium constants and a first-order rate constant:

$$k_3 = k \times K_1 \times K_2$$

This often happens with reactions with late rate-determining steps: the rate constant can depend on the concentrations of any species involved before the rate-determining step (although not necessarily in that step itself) but never depends on species involved after the rate-determining step.

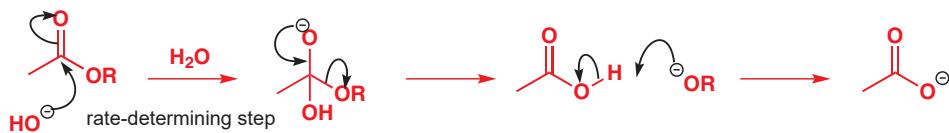
In Chapter 39 we will discuss in much more detail how such experiments are designed; much sooner, in Chapter 15, you will meet another pair of mechanisms—one first order and one second order—that tell us a lot about the reactivity of the molecules involved.

Just because a proposed mechanism gives a rate equation that fits the experimental data, it does not necessarily mean that it is the *right* mechanism; all it means is that it is consistent with the experimental facts so far, but there may be other mechanisms that also fit. It is then up to the experimenter to design cunning experiments to try to rule out other possibilities.

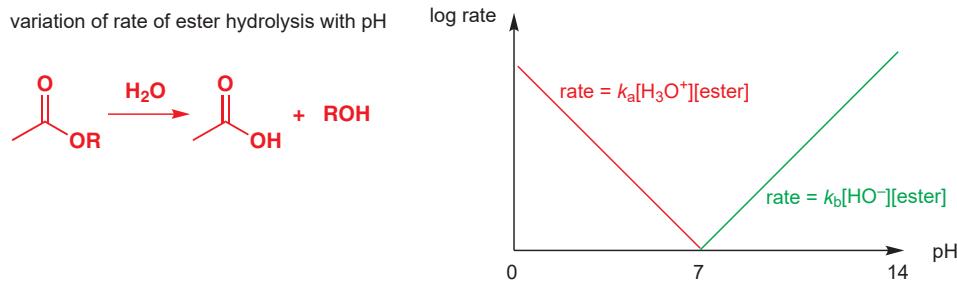
Mechanisms are given throughout this book—eventually you will learn to predict what mechanism to expect for a given type of reaction, but this is because earlier experimentalists have worked out the mechanisms by a study of kinetics and other methods.

## Catalysis in carbonyl substitution reactions

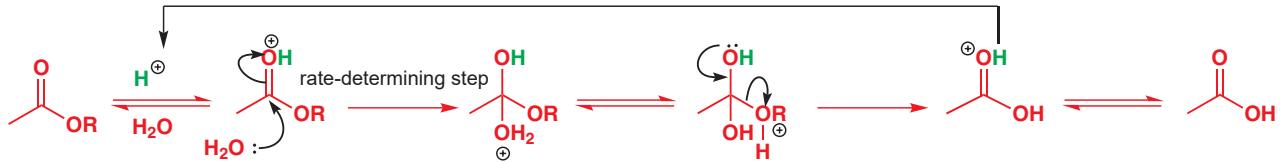
The amide hydrolysis you have just met is much faster in base because base (in this case hydroxide) deprotonates the intermediate and makes it more reactive. The same is true for many other base-catalysed processes: often it is the nucleophile that is made more reactive by deprotonation to form an anion. For example, ester hydrolysis is faster at higher pH because the higher the pH the more hydroxide there is to act as a nucleophile.



We can plot this on a graph of rate vs. pH:



The rate equation at high pH is second order, as you expect, and depends on the concentration of hydroxide and the concentration of the ester. Notice, though, that below pH 7 the rate starts to increase again as the concentration of  $\text{H}^+$  increases. This is because ester hydrolysis is also acid catalysed, as you saw in Chapter 10. At acidic pH, a new mechanism takes over in which protonation of the carbonyl group accelerates attack of weakly nucleophilic water.



You will also see rate constants labelled in other ways—this is a matter of choice. A common method is to use  $k_1$  for first-order,  $k_2$  for second-order, and  $k_3$  for third-order rate constants, for example.

This mechanism is discussed on p. 231.

The reaction is still bimolecular but the rate constant is different: we can represent the two processes by two rate equations, labelling the rate constants  $k_a$  and  $k_b$  with the suffixes 'a' for acid and 'b' for base to show more clearly what we mean:

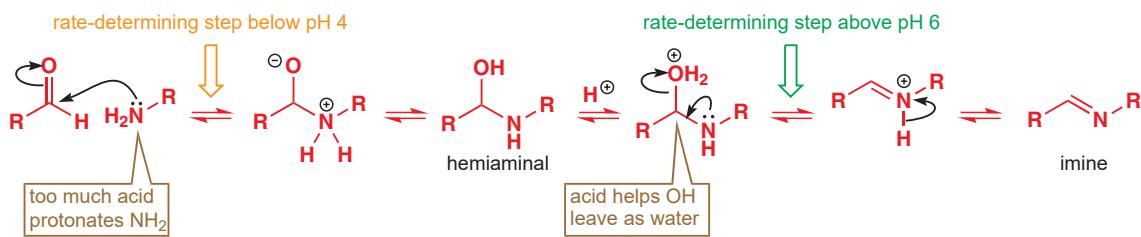
$$\text{rate of ester hydrolysis in acid (pH < 7) solution} = k_a[\text{MeCO}_2\text{R}][\text{H}_3\text{O}^+]$$

$$\text{rate of ester hydrolysis in basic (pH > 7) solution} = k_b[\text{MeCO}_2\text{R}][\text{HO}^-]$$

This is typical acid–base catalysis, known as ‘specific acid–base catalysis’ because the specific acid and base involved are  $\text{H}^+$  (or  $\text{H}_3\text{O}^+$ ) and  $\text{OH}^-$ . The form of the pH dependence of the rate tells us that there is a choice of two mechanisms—the one that is faster is the one that is observed.

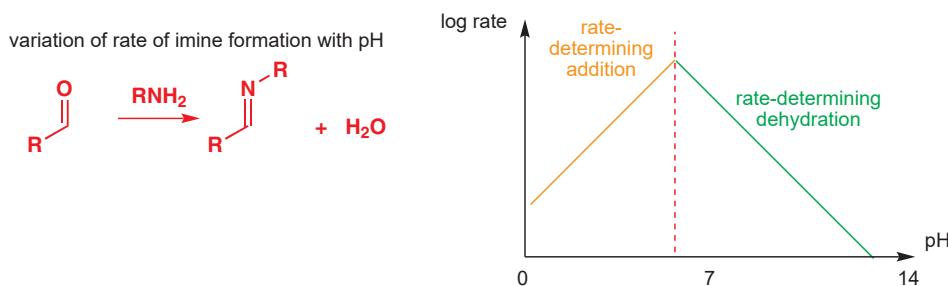
You met a reaction in Chapter 11 whose rate has a very different pH dependence: imine formation. To remind you, here is the mechanism again. We pointed out in Chapter 11 that

the reaction is acid catalysed because acid is needed to help water leave. But too much acid is a problem because it protonates the starting amine and slows the reaction down.



For these reasons, the pH–rate profile for imine formation looks like this: there is a maximum rate around pH 6, and either side the reaction goes more slowly.

Interactive mechanism for imine formation



The difference now is that at low pH, the rate-determining step changes from being the dehydration step (which can then go very fast because of the high concentration of acid) to being the addition step, which is slowed down by protonation of the amine. Whereas a reaction will always go by the fastest of the available mechanisms, it is also bound to go at the rate of the slowest step in that mechanism.

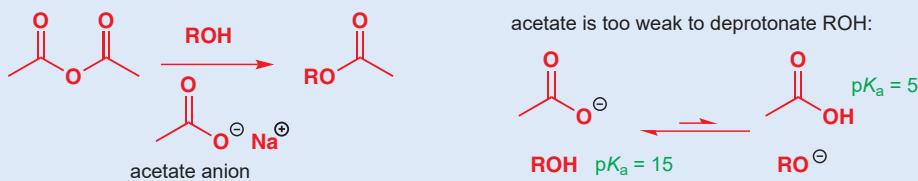
### ● Multistep reaction rates

The overall rate of a multistep reaction is decided by:

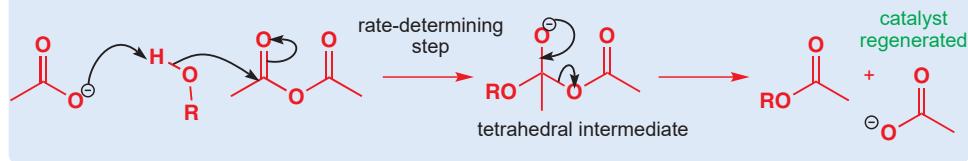
- the **fastest** of the available mechanisms
- the **slowest** of the possible rate-determining steps.

### Catalysis by weak bases

In Chapter 10 we used pyridine as a catalyst in carbonyl substitution reactions, even though it is only a weak base. Catalysis by pyridine involves two mechanisms, and is discussed on p. 200. Acetate ion is another weak base which can catalyse the formation of esters from anhydrides:



The problem is, it is far too weak a base (acetic acid has a  $pK_a$  of 5) to deprotonate the alcohol ( $pK_a$  15), so it can't be forming alkoxide (in the way that hydroxide would for example). But what it can do is to remove the proton from the alcohol as *the reaction occurs*.



This type of catalysis, which is available to any base, not only strong bases, is called *general base catalysis* and will be discussed more in Chapter 39. It does not speed the reaction up very much but it does lower the energy of the transition state leading to the tetrahedral intermediate by avoiding the build-up of positive charge as the alcohol adds. The disadvantage of general base catalysis is that the first, rate-determining, step really is termolecular (unlike in the amide hydrolysis mechanism you met on p. 261). It is inherently unlikely that three molecules will collide with each other simultaneously. In this case, however, if ROH is the solvent, it will always be nearby in any collision so a termolecular step is just about acceptable.

## Kinetic versus thermodynamic products

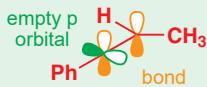
We started this chapter with a discussion of thermodynamics: the factors that govern equilibria. We then moved onto rates: the factors that determine the *rate* at which reactions proceed. Depending on the reaction, either may be more important, and in general:

- Reactions under **thermodynamic control** have outcomes that depend on the position of an equilibrium and therefore the relative stability of the possible products.
- Reactions under **kinetic control** have outcomes that depend on the rate at which the reaction proceeds, and therefore on the relative energies of the transition states leading to the alternative products.

► There are further examples of contrasting kinetic and thermodynamic control in Chapters 19 and 22.

■ Hydrogen chloride is a gas, but it can be absorbed onto the surface of the alumina for convenient handling.

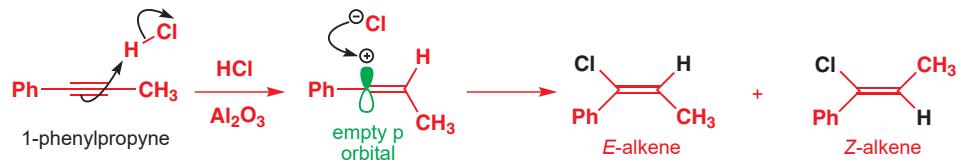
■ It's worth taking a moment to think about the structure of the intermediate cation here: the cationic carbon is *sp* hybridized (linear) with an empty p orbital perpendicular to the p orbitals of the double bond (it is the p orbital that used to be involved in the second  $\pi$  bond of the alkyne).



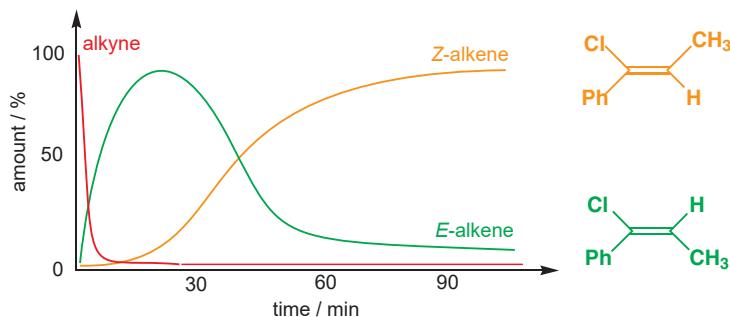
Before we leave this chapter, we will introduce an example of a reaction where thermodynamic control and kinetic control lead to different outcomes—in other words, where the fastest reaction does not give the most stable possible product.

The reaction is one you have not yet met, but it is quite a simple one, and it follows an unsurprising mechanism. It is the reaction of an alkyne with hydrogen chloride in the presence of alumina ( $\text{Al}_2\text{O}_3$ ). The reaction produces two geometrical isomers of a chloroalkene.

Alkynes, like alkenes, are nucleophiles, and so the mechanism involves first of all attack by the alkyne on HCl, followed by recombination of the vinyl cation, which is formed with the chloride anion.



The two alkenes are labelled *E* and *Z*. After about 2 hours the main product is the *Z*-alkene. However, this is not the case in the early stages of the reaction. The graph below shows how the proportions of the starting material and the two products change with time.



Points to note:

- When the alkyne concentration drops almost to zero (10 minutes), the only alkene that has been formed is the *E*-alkene.

- As time increases, the amount of *E*-alkene decreases as the amount of *Z*-alkene increases.
- Eventually, the proportions of *E*- and *Z*-alkene do not change.

Since it is the *Z*-alkene that dominates at equilibrium, this must be lower in energy than the *E*-alkene. Since we know the ratio of the products at equilibrium, we can work out the difference in energy between the two isomers:

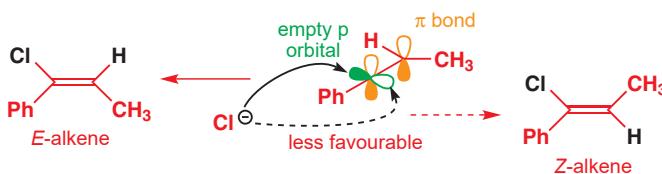
ratio of *E*:*Z*-alkenes at equilibrium = 1:35

$$K_{\text{eq}} = \frac{[\text{Z}]}{[\text{E}]} = 35$$

$$\Delta G = -RT \ln K = -8.314 \times 298 \times \ln(35) = -8.8 \text{ kJ mol}^{-1}$$

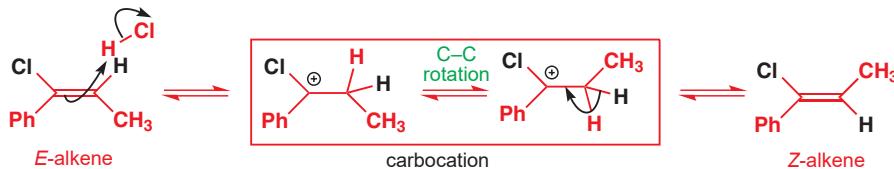
that is, the *Z*-alkene is 8.8 kJ mol<sup>-1</sup> lower in energy than the *E*-alkene.

However, although the *Z*-alkene is more stable, the *E*-alkene is formed faster under these conditions: the route to the *E*-alkene must have a smaller activation energy barrier than *trans* addition. This is quite easy to understand: the intermediate cation has no double-bond geometry because the cationic C is sp hybridized (linear). When chloride attacks, it prefers to attack from the side of the H atom rather than the (bigger) methyl group.

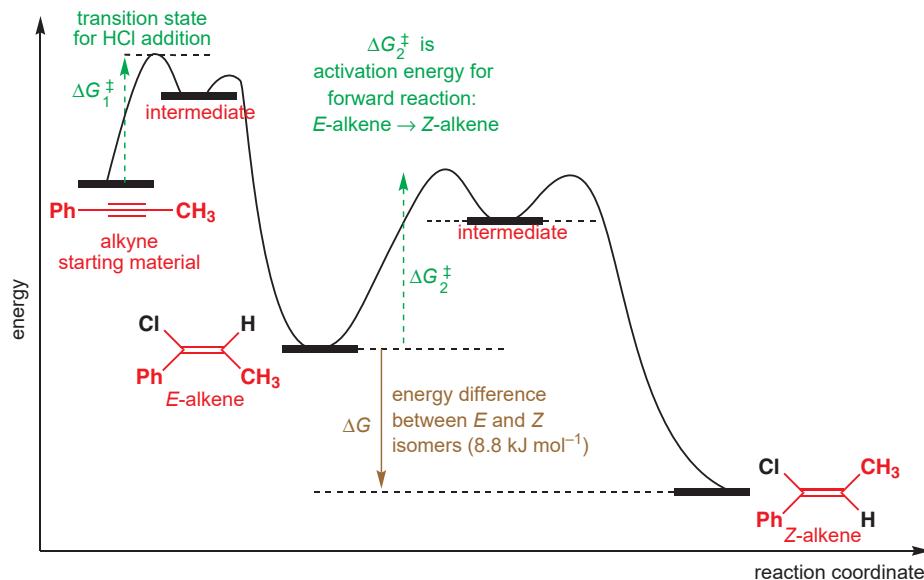


You might normally expect an *E*-alkene to be more stable than a *Z*-alkene—it just so happens here that Cl has a higher priority than Ph and the *Z*-alkene has the two largest groups (Ph and Me) *trans* (see p. 392 for rules of nomenclature).

There must then be some mechanism by which the quickly formed *E*-alkene is converted into the more stable *Z*-alkene. The conditions are acidic, so the most likely mechanism is the acid-catalysed alkene isomerization you saw earlier in the chapter:



This information can be summarized on an energy profile diagram:



Initially, the alkyne is converted into the *E*-alkene via the intermediate linear cation. The activation energy for this step is labelled  $\Delta G_1^\ddagger$ . The *E*-alkene can convert to the *Z* isomer via an intermediate, with activation energy  $\Delta G_2^\ddagger$ . Since  $\Delta G_1^\ddagger$  is smaller than  $\Delta G_2^\ddagger$ , the *E*-alkene forms faster than it isomerizes, and all the alkyne is rapidly converted to the *E*-alkene. But over the course of the reaction, the *E*-alkene slowly isomerizes to the *Z*-alkene. An equilibrium is eventually reached that favours the *Z*-alkene because it is more stable (by 8.8 kJ mol<sup>-1</sup>, as we calculated earlier). Why doesn't the *Z*-alkene form faster than the *E*? Well, as we suggested above, the transition state for its formation from the linear cation must be higher in energy than the transition state for formation of the *E*-alkene, because of steric hindrance.

### ● Kinetic and thermodynamic products

- The *E*-alkene is formed faster and is known as the **kinetic product** or the **product of kinetic control**.
- The *Z*-alkene is more stable and is known as the **thermodynamic product** or the **product of thermodynamic control**.

If we wanted to isolate the kinetic product, the *E*-alkene, we would carry out the reaction at low temperature and not leave it long enough for equilibration. If, on the other hand, we want the thermodynamic product, the *Z*-alkene, we would leave the reaction for longer at higher temperatures to make sure that the larger energy barrier yielding the most stable product can be overcome.

## Summary of mechanisms from Chapters 6–12

In Chapter 5 we introduced basic arrow-drawing. A lot has happened since then and this is a good opportunity to pull some strands together. You may like to be reminded:

- When molecules react together, one is the *electrophile* and one is the *nucleophile*.
- Electrons flow from an electron-rich to an electron-poor centre.
- Charge is conserved in each step of a reaction.

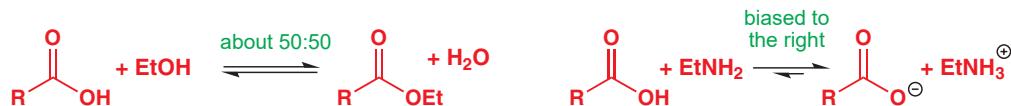
These three considerations will help you draw the mechanism of a reaction that you have not previously met.

### Types of reaction arrows

- Simple reaction arrows showing that a reaction goes from left to right or right to left.



- Equilibrium arrows showing the extent and direction of equilibrium.

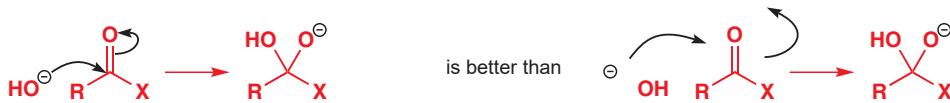


- Delocalization or conjugation arrows showing two different ways to draw the same molecule. The two structures ('canonical forms' or 'resonance structures') must differ only in the position of electrons.

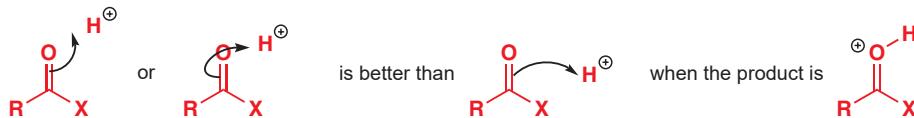


## Using curly arrows

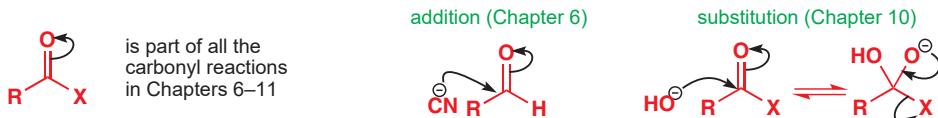
1. The curly arrow should show clearly where the electrons come from and where they go to.



2. If electrophilic attack on a  $\pi$  or  $\sigma$  bond leads to the bond being broken, the arrows should show clearly which atom bonds to the electrophile.

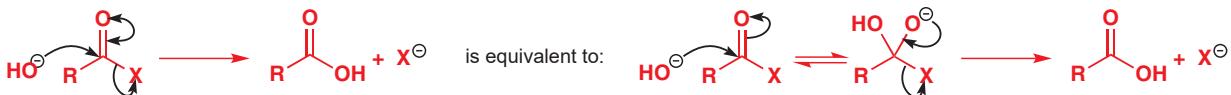


3. Reactions of the carbonyl group are dominated by the breaking of the  $\pi$  bond. If you use this arrow first on an unfamiliar reaction of a carbonyl compound, you will probably find a reasonable mechanism.



## Shortcuts in drawing mechanisms

1. The most important is the double-headed arrow on the carbonyl group used during a substitution reaction.



2. The symbol  $\pm H^+$  is shorthand for the gain and loss of a proton in the same step (usually involving N, O, or S; such steps are usually kinetically very fast).



## 延伸阅读

For a more in-depth description of reaction pathways, see J. Keeler and P. Wothers, *Why Chemical Reactions Happen*, OUP, Oxford, 2003.

A physical chemistry text such as *Physical Chemistry*, 9th edn, by P. Atkins and J. de Paula, OUP, Oxford, 2011, will give you much more mathematical detail.

An excellent modern and rather more advanced physical organic book is E. V. Anslyn and D. A. Dougherty, *Modern Physical Organic*

*Chemistry*, University Science Books, South Orange New Jersey, 2005.

Equilibrium constants for hemiacetal formation: J. P. Guthrie *Can J. Chem.* 1975, 898.

Solvent dependence of bond rotation in amides: T. Drakenberg, K. I. Dahlqvist, and S. Forsen *J. Phys. Chem.*, 1972, 76, 2178.

## Check your understanding

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To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# <sup>1</sup>H NMR: 核磁共振氢谱

## 联系

### → 基础

- X-ray crystallography, mass spectrometry, NMR, and infrared spectroscopy ch3

### 目标

- Proton (or <sup>1</sup>H) NMR spectra and their regions
- How <sup>1</sup>H NMR compares with <sup>13</sup>C NMR: integration
- How 'coupling' in <sup>1</sup>H NMR provides most of the information needed to find the structure of an unknown molecule

### → 展望

- Using <sup>1</sup>H NMR with other spectroscopic methods to solve structures rapidly ch18
- Using <sup>1</sup>H NMR to investigate the detailed shape (stereochemistry) of molecules ch31
- <sup>1</sup>H NMR spectroscopy is referred to in most chapters of the book as it is the most important tool for determining structure; you must understand this chapter before reading further

## The differences between carbon and proton NMR

We introduced nuclear magnetic resonance (NMR) in Chapter 3 as part of a three-pronged attack on the problem of determining molecular structure. We showed that mass spectrometry weighs the molecules, infrared spectroscopy tells us about functional groups, and <sup>13</sup>C and <sup>1</sup>H NMR tell us about the hydrocarbon skeleton. We concentrated on <sup>13</sup>C NMR because it's simpler, and we were forced to admit that we were leaving the details of the most important technique of all—proton (<sup>1</sup>H) NMR—until a later chapter because it is more complicated than <sup>13</sup>C NMR. This is that chapter and we must now tackle those complications. We hope you will see <sup>1</sup>H NMR for the beautiful and powerful technique that it surely is. The difficulties are worth mastering for this is the chemist's primary weapon in the battle to solve structures.

- We will make use of <sup>1</sup>H and <sup>13</sup>C NMR evidence for structure throughout this book, and it is essential that you are familiar with the explanations in this chapter before you read further.

Proton NMR differs from <sup>13</sup>C NMR in a number of ways.

- <sup>1</sup>H is the major isotope of hydrogen (99.985% natural abundance), while <sup>13</sup>C is only a minor isotope (1.1%).
- <sup>1</sup>H NMR is quantitative: the area under the peak tells us the number of hydrogen nuclei, while <sup>13</sup>C NMR may give strong or weak peaks from the same number of <sup>13</sup>C nuclei.
- Protons interact magnetically ('couple') to reveal the connectivity of the structure, while <sup>13</sup>C is too rare for coupling between <sup>13</sup>C nuclei to be seen.

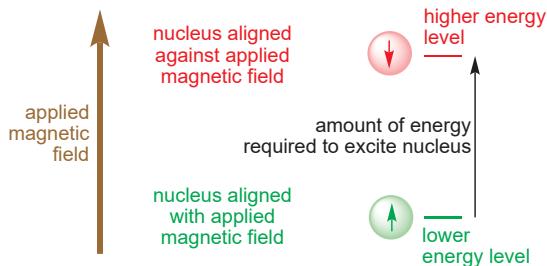
■ '<sup>1</sup>H NMR' and 'proton NMR' are interchangeable terms. All nuclei contain protons of course, but chemists often use 'proton' specifically for the nucleus of a hydrogen atom, either as part of a molecule or in its 'free' form as H<sup>+</sup>. This is how it will be used in this chapter.

- $^1\text{H}$  NMR shifts give a more reliable indication of the local chemistry than that given by  $^{13}\text{C}$  spectra.

We shall examine each of these points in detail and build up a full understanding of proton NMR spectra.

In Chapter 3 we illustrated the alignment of nuclei using the analogy of a compass needle in a magnetic field.

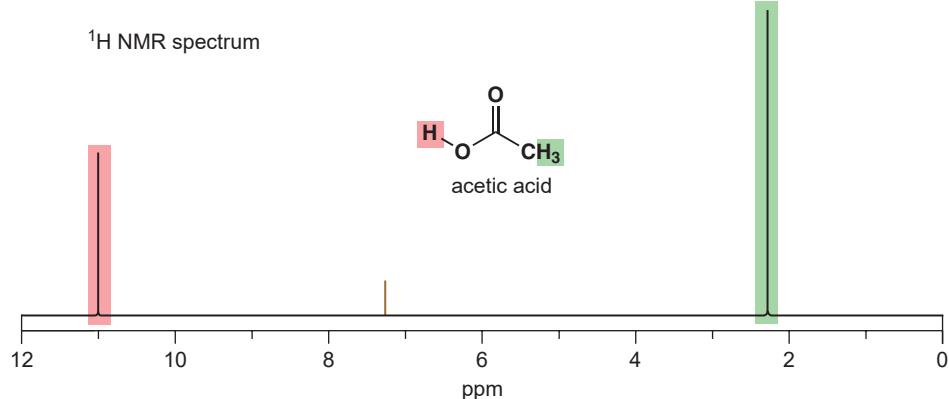
Proton NMR spectra are recorded in the same way as  $^{13}\text{C}$  NMR spectra: radio waves are used to study the energy level differences of nuclei in a magnetic field, but this time they are  $^1\text{H}$  and not  $^{13}\text{C}$  nuclei. Hydrogen nuclei in a magnetic field have two energy levels: they can be aligned either with or against the applied magnetic field.



All nuclei are characterized by their 'nuclear spin', a value known as  $I$ . The number of energy levels available to a nucleus of spin  $I$  is  $2I + 1$ .  $^1\text{H}$  and  $^{13}\text{C}$  both have  $I = 1/2$ .

This 10 ppm scale is not the same as any part of the  $^{13}\text{C}$  NMR spectrum. It is at a different frequency altogether.

$^1\text{H}$  and  $^{13}\text{C}$  spectra have many similarities: the scale runs from right to left and the zero point is given by the same reference compound, although it is the proton resonance of  $\text{Me}_4\text{Si}$  rather than the carbon resonance that defines the zero point. You will notice at once that the scale is much smaller, ranging over only about 10 ppm instead of the 200 ppm needed for carbon. This is because the variation in the chemical shift is a measure of the shielding of the nucleus by the electrons around it. There is inevitably less change possible in the distribution of two electrons around a hydrogen nucleus than in that of the eight valence electrons around a carbon nucleus. Here is the  $^1\text{H}$  NMR spectrum of acetic acid, which you first saw in Chapter 3.

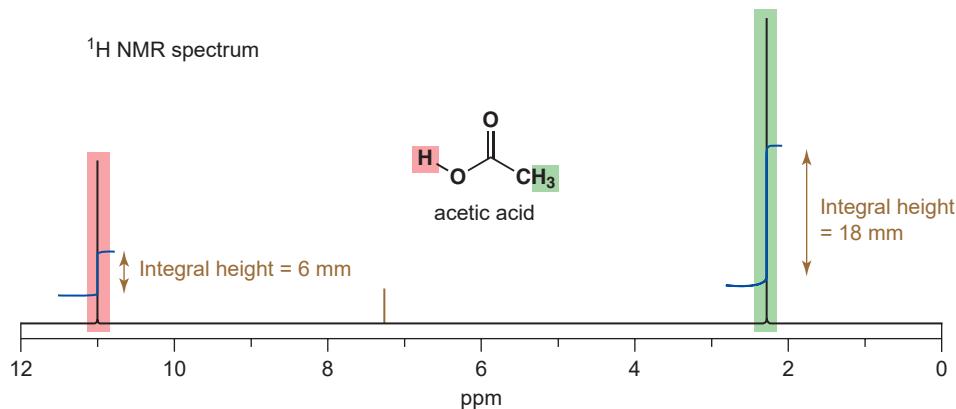


A reminder from Chapter 3: ignore the peak at 7.25 shown in brown. This is from the solvent, as explained on p.272.

## Integration tells us the number of hydrogen atoms in each peak

You know from Chapter 3 that the position of a signal in an NMR spectrum tells us about its environment. In acetic acid the methyl group is next to the electron-withdrawing carbonyl group and so is slightly deshielded at about  $\delta$  2.0 ppm and the acidic proton itself, attached to O, is very deshielded at  $\delta$  11.2 ppm. The same factor that makes this proton acidic—the O–H bond is polarized towards oxygen—also makes it resonate at low field. So far things are much the same as in  $^{13}\text{C}$  NMR. Now for a difference. In  $^1\text{H}$  NMR the size of the peaks is also important: the area under the peaks is exactly proportional to the number of protons. Proton spectra are normally integrated, that is, the area under the peaks is computed and recorded as a line with steps corresponding to the area, like this.

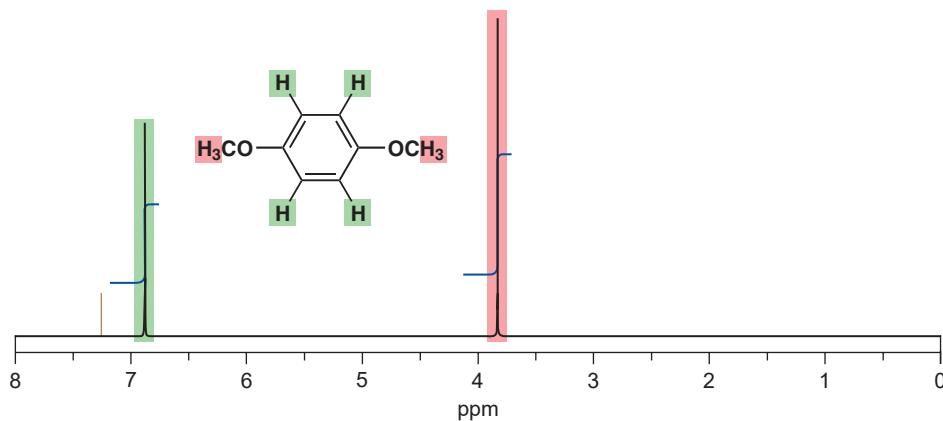
It is not enough simply to measure the relative heights of the peaks because, as here, some peaks might be broader than others. Hence the area under the peak is measured.



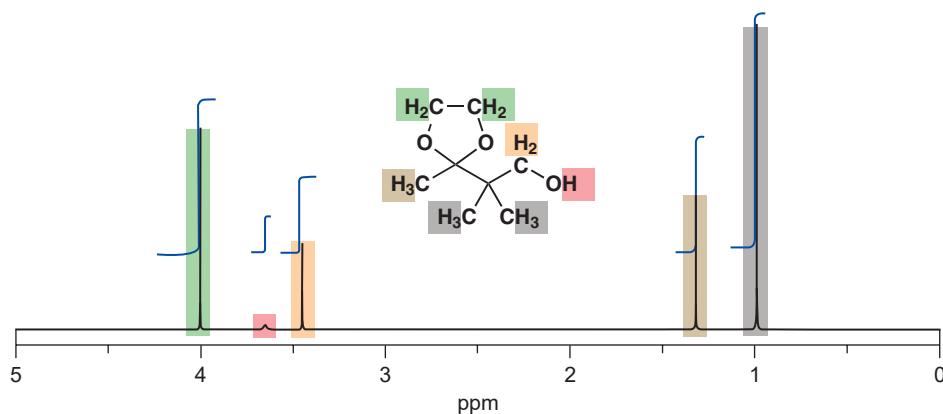
Simply measuring the height of the steps with a ruler gives you the *ratio* of the numbers of protons represented by each peak. In many spectra this will be measured for you and reported as a number at the bottom of the spectrum. Knowing the atomic composition (from the mass spectrum) we also know the distribution of protons of various kinds. Here the heights are 6 mm and 18 mm, a ratio of about 1:3. The compound is C<sub>2</sub>H<sub>4</sub>O<sub>2</sub> so, since there are four H atoms altogether, the peaks must contain 1 × H and 3 × H, respectively.

In the spectrum of 1,4-dimethoxybenzene there are just two signals in the ratio of 3:2. This time the compound is C<sub>8</sub>H<sub>10</sub>O<sub>2</sub> so the true ratio must be 6:4. The positions of the two signals are exactly where you would expect them to be from our discussion of the regions of the NMR spectrum in Chapter 3: the 4H aromatic signal is in the left-hand half of the spectrum, between 5 and 10 ppm, where we expect to see protons attached to sp<sup>2</sup> C atoms, while the 6H signal is in the right-hand half of the spectrum, where we expect to see protons attached to sp<sup>3</sup> C atoms.

→ We will come back to the regions of the <sup>1</sup>H NMR spectrum in more detail in just a moment, but we introduced them in Chapter 3 on p. 60.



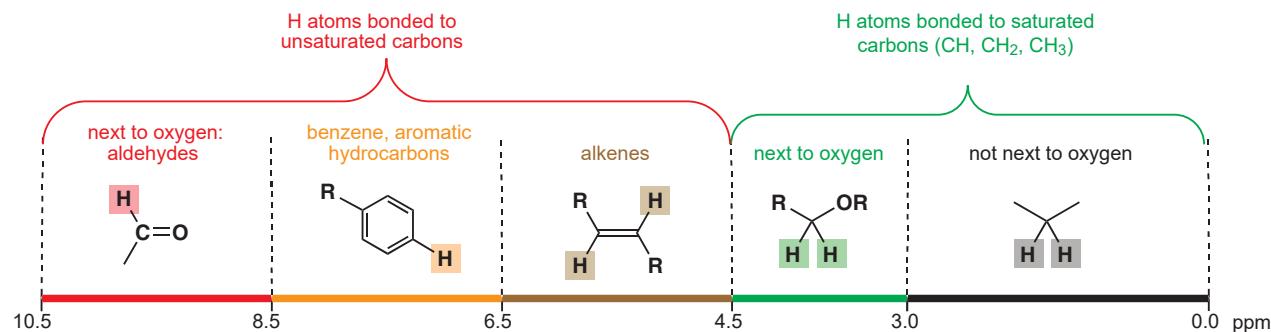
In this next example it is easy to assign the spectrum simply by measuring the steps in the integral. There are two identical methyl groups (CMe<sub>2</sub>) with six Hs, one methyl group by itself with three Hs, the OH proton (1 H), the CH<sub>2</sub> group next to the OH (two Hs), and finally the CH<sub>2</sub>CH<sub>2</sub> group between the oxygen atoms in the ring (four Hs).



Before we go on, a note about the solvent peaks shown in brown in these spectra. Proton NMR spectra are generally recorded in solution in deuteriochloroform ( $\text{CDCl}_3$ )—that is, chloroform ( $\text{CHCl}_3$ ) with the  $^1\text{H}$  replaced by  $^2\text{H}$  (deuterium). The proportionality of the size of the peak to the number of protons tells you why: if you ran a spectrum in  $\text{CHCl}_3$ , you would see a vast peak for all the solvent Hs because there would be much more solvent than the compound you wanted to look at. Using  $\text{CDCl}_3$  cuts out all extraneous protons.  $^2\text{H}$  atoms have different nuclear properties and so don't show up in the  $^1\text{H}$  spectrum. Nonetheless,  $\text{CDCl}_3$  is always unavoidably contaminated with a small amount of  $\text{CHCl}_3$ , giving rise to the small peak at 7.25 ppm. Spectra may equally well be recorded in other deuterated solvents such as water ( $\text{D}_2\text{O}$ ), methanol ( $\text{CD}_3\text{OD}$ ), or benzene ( $\text{C}_6\text{D}_6$ ).

## Regions of the proton NMR spectrum

All the H atoms in the last example were attached to  $\text{sp}^3$  carbons, so you will expect them to fall between 0 and 5 ppm. However, you can clearly see that H atoms that are nearer to oxygen are shifted downfield within the 0–5 ppm region, to larger  $\delta$  values (here as far as 3.3 and 3.9 ppm). We can use this fact to build some more detail into our picture of the regions of the  $^1\text{H}$  NMR spectrum.



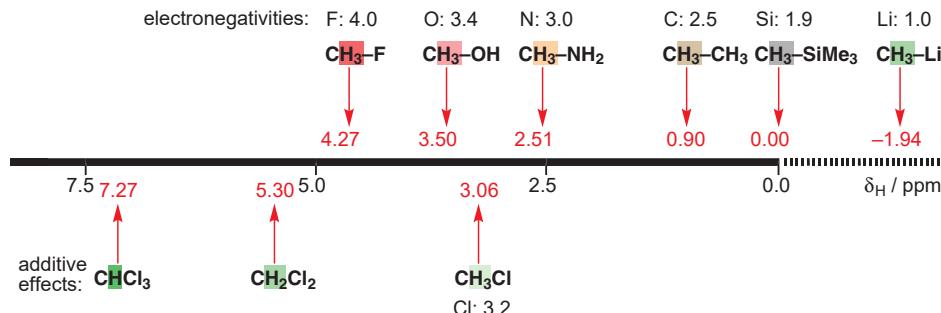
These regions hold for protons attached to C: protons attached to O or N can come almost anywhere on the spectrum. Even for C–H signals the regions are approximate and overlap quite a lot. You should use the chart as a basic guide, and you should aim to learn these regions. But you will also need to build up a more detailed understanding of the factors affecting proton chemical shift. To help you achieve this understanding, we now need to examine the classes of proton in more detail and examine the reasons for their particular shifts. It is important that you grasp these reasons.

In this chapter you will see a lot of numbers—chemical shifts and differences in chemical shifts. We need these to show that the ideas behind  $^1\text{H}$  NMR are securely based in fact. *You do not need to learn these numbers.* Comprehensive tables can be found at the end of Chapter 18, which we hope you will find useful for reference while you are solving problems.

## Protons on saturated carbon atoms

### Chemical shifts are related to the electronegativity of substituents

We shall start with protons on saturated carbon atoms. The top half of the diagram below shows how the protons in a methyl group are shifted more and more as the atom attached to them gets more electronegative.



When we are dealing with single atoms as substituents, these effects are straightforward and more or less additive. If we go on adding electronegative chlorine atoms to a carbon atom, electron density is progressively removed from it and the carbon nucleus and the hydrogen atoms attached to it are progressively deshielded. You can see this in the bottom half of the diagram above. Dichloromethane,  $\text{CH}_2\text{Cl}_2$ , and chloroform,  $\text{CHCl}_3$ , are commonly used as solvents and their shifts will become familiar to you if you look at a lot of spectra.

### Proton chemical shifts tell us about chemistry

The truth is that shifts and electronegativity are not perfectly correlated. The key property is indeed electron withdrawal but it is the electron-withdrawing power of the whole substituent in comparison with the carbon and hydrogen atoms in the CH skeleton that matters. Methyl groups joined to the same element—nitrogen, say—may have very different shifts if the substituent is an amino group ( $\text{CH}_3\text{—NH}_2$  has  $\delta_{\text{H}}$  for the  $\text{CH}_3$  group = 2.41 ppm) or a nitro group ( $\text{CH}_3\text{—NO}_2$  has  $\delta_{\text{H}}$  4.33 ppm). A nitro group is much more electron-withdrawing than an amino group.

What we need is a quick guide rather than some detailed correlations, and the simplest is this: all functional groups except very electron-withdrawing ones shift methyl groups from 1 ppm (where you find them if they are not attached to a functional group) downfield to about 2 ppm. Very electron-withdrawing groups shift methyl groups to about 3 ppm. This is the sort of thing it is worth learning.

You have seen  $\delta$  used as a symbol for chemical shift. Now that we have two sorts of chemical shift—in the  $^{13}\text{C}$  NMR spectrum and in the  $^1\text{H}$  NMR spectrum—we need to be able to distinguish them.  $\delta_{\text{H}}$  means chemical shift in the  $^1\text{H}$  NMR spectrum, and  $\delta_{\text{C}}$  is chemical shift in the  $^{13}\text{C}$  NMR spectrum.

#### ● Estimating the chemical shift of a methyl group

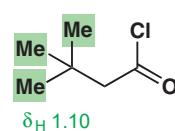
		Methyl group attached to no electron-withdrawing functional groups
		standard Me signal at about 1 ppm
move downfield by 2 ppm		
Methyl attached to very electron-withdrawing functional group	Methyl attached to electron-withdrawing or conjugating functional group	move downfield by 1 ppm
Me—X signal at about 3 ppm	Me—X signal at about 2 ppm	
X can be... oxygen-based functional groups: ethers (OR), esters (OCOR)	X can be... carbonyl groups: acids ( $\text{CO}_2\text{H}$ ), esters ( $\text{CO}_2\text{R}$ ), ketones (COR), nitriles (CN)	
amides ( $\text{NHCOR}$ ), sulfones ( $\text{SO}_2\text{R}$ )	amines (NHR), sulfides (SR)	
	alkene, arene, alkyne	

Rather than trying to fit these data to some atomic property, even such a useful one as electronegativity, we should rather see these shifts as a useful measure of the electron-withdrawing power of the group in question. The NMR spectra are telling us about the chemistry. The largest shift you are likely to see for a methyl group is that caused by the nitro group, 3.43 ppm, at least twice the size of the shift for a carbonyl group. This gives us our first hint of some important chemistry: one nitro group is worth two carbonyl groups when it comes to electron-withdrawing power. You have already seen that electron withdrawal and acidity are related (Chapter 8) and in later chapters you will see that we can correlate the anion-stabilizing power of groups like carbonyl, nitro, and sulfone with proton NMR.

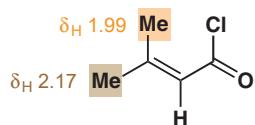
### Methyl groups give us information about the structure of molecules

It sounds rather unlikely that the humble methyl group could tell us much that is important about molecular structure—but just you wait. We shall look at four simple compounds and their NMR spectra—just the methyl groups, that is.

The first compound, the acid chloride in the margin, shows just one methyl signal containing nine Hs at  $\delta_{\text{H}}$  1.10. This tells us two things. All the protons in each methyl group are identical,



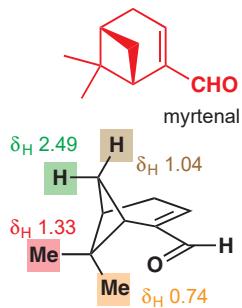
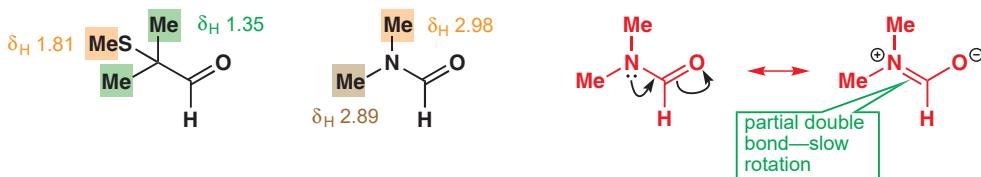
■ Rotation about single bonds is generally very fast (you are about to see an exception); rotation about double bonds is generally very, very slow (it just doesn't happen). We talked about rotation rates in Chapter 12.



and all three methyl groups in the tertiary butyl (*t*-butyl, or  $\text{Me}_3\text{C}-$ ) group are identical. This is because rotation about C–C single bonds, both about the  $\text{CH}_3-\text{C}$  bond and about the  $(\text{CH}_3)_3\text{C}-\text{C}$  bond, is fast. Although at any one instant the hydrogen atoms in one methyl group, or the methyl groups in the *t*-butyl group, may differ, on average they are the same. The time-averaging process is fast rotation about a  $\sigma$  bond.

The second compound shows two 3H signals, one at 1.99 and one at 2.17 ppm. Unlike a C–C bond, the C=C double bond does not rotate at all and so the two methyl groups are different. One is on the same side of the alkene as (or '*cis* to') the –COCl group while the other is on the opposite side (or '*trans*').

The next pair of compounds contain the CHO group. One is a simple aldehyde, the other an amide of formic acid: it is DMF, dimethylformamide. The first has two sorts of methyl group: a 3H signal at  $\delta_{\text{H}}$  1.81 for the SMe group and a 6H signal at  $\delta_{\text{H}}$  1.35 for the CMe<sub>2</sub> group. The two methyl groups in the 6H signal are the same, again because of fast rotation about a C–C  $\sigma$  bond. The second compound also has two methyl signals, at 2.89 and 2.98 ppm, each 3H, and these are the two methyl groups on nitrogen. Restricted rotation about the N–CO bond must be making the two Me groups different. You will remember from Chapter 7 (p. 155) that the N–CO amide bond has considerable double-bond character because of conjugation: the lone pair electrons on nitrogen are delocalized into the carbonyl group.



Like double bonds, cage structures prevent bond rotation and can make the two protons of a CH<sub>2</sub> group appear different. There are many flavouring compounds (terpenoids) from herbs that have structures like this. In the example here—myrtenal, from the myrtle bush—there is a four-membered ring bridged across a six-membered ring. The methyl groups on the other bridge are different because one is over the alkene while one is over the CH<sub>2</sub>. No rotation of any bonds within the cage is possible, so these methyl groups resonate at different frequencies (0.74 and 1.33 ppm). The same is true for the two H atoms of the CH<sub>2</sub> group.

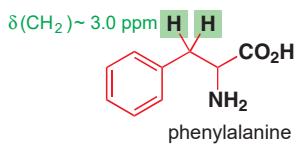
### CH and CH<sub>2</sub> groups have higher chemical shift than CH<sub>3</sub> groups

Electronegative substituents have a similar effect on the protons of CH<sub>2</sub> groups and CH groups, but with the added complication that CH<sub>2</sub> groups have *two* other substituents and CH groups *three*. A simple CH<sub>2</sub> (methylene) group resonates at 1.3 ppm, about 0.4 ppm further downfield than a comparable CH<sub>3</sub> group (0.9 ppm), and a simple CH group resonates at 1.7 ppm, another 0.4 ppm downfield. Replacing each hydrogen atom in the CH<sub>3</sub> group by a carbon atom causes a small downfield shift as carbon is slightly more electronegative (C 2.5; H 2.2) than hydrogen and therefore shields less effectively.

#### ● Chemical shifts of protons in CH, CH<sub>2</sub>, and CH<sub>3</sub> groups with no nearby electron-withdrawing groups.

CH group	CH <sub>2</sub> group	CH <sub>3</sub> group
1.7 ppm	1.3 ppm	0.9 ppm

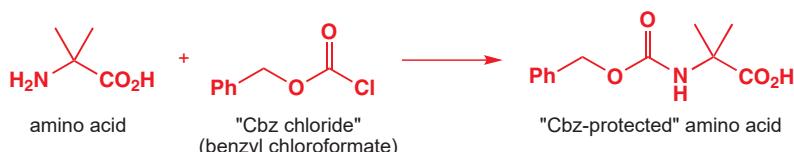
move downfield by 0.4 ppm      move downfield by 0.4 ppm



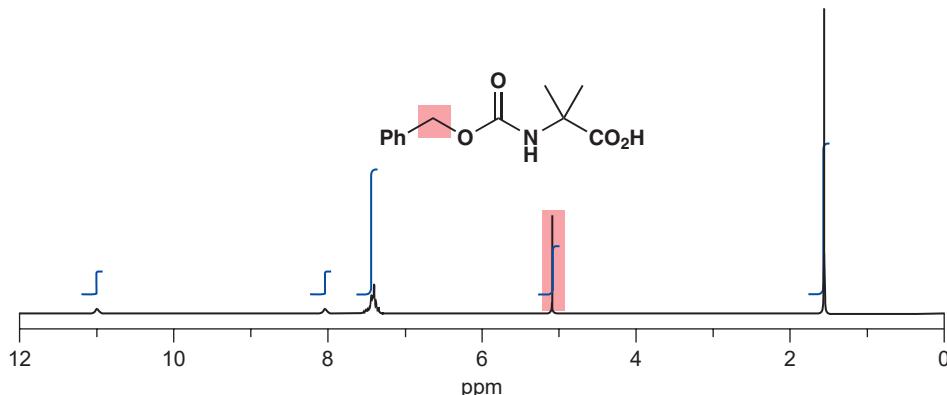
The benzyl group ( $\text{PhCH}_2-$ ) is very important in organic chemistry. It occurs naturally in the amino acid phenylalanine, which you met in Chapter 2. Phenylalanine has its CH<sub>2</sub> signal at 3.0 ppm and is moved downfield from 1.3 ppm mostly by the benzene ring.

Amino acids are often 'protected' as the Cbz (carboxybenzyl) derivatives by reaction with an acid chloride (we'll discuss this more in Chapter 23). Here is a simple example together

with the NMR spectrum of the product. Now the  $\text{CH}_2$  group has gone further downfield to 5.1 ppm as it is next to both oxygen and phenyl.

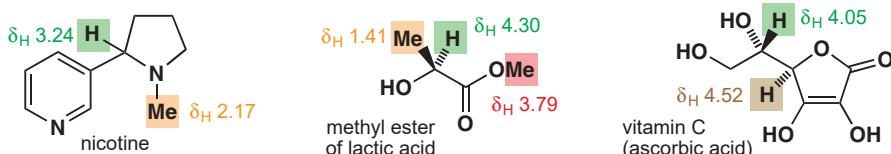


► You met this sort of amide-forming reaction in Chapter 10—here the amide is actually a carbamate as the  $\text{C}=\text{O}$  group is flanked by both O and N.



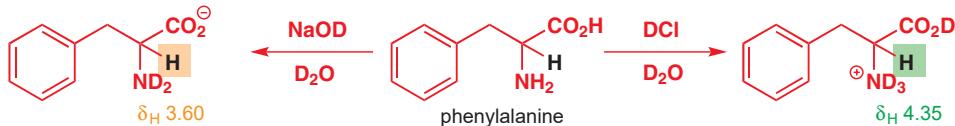
### Chemical shifts of CH groups

A CH group in the middle of a carbon skeleton resonates at about 1.7 ppm—another 0.4 ppm downfield from a  $\text{CH}_2$  group. It can have up to three substituents and these will cause further downfield shifts of about the same amount as we have already seen for  $\text{CH}_3$  and  $\text{CH}_2$  groups. Three examples from nature are nicotine, the methyl ester of lactic acid, and vitamin C. Nicotine, the compound in tobacco that causes the craving (although not the death, which is doled out instead by the carbon monoxide and tars in the smoke), has one hydrogen atom trapped between a simple tertiary amine and an aromatic ring at 3.24 ppm. The ester of lactic acid has a CH proton at 4.3 ppm. You could estimate this with reasonable accuracy using the guidelines in the two summary boxes on pp. 273 and 274. Take 1.7 (for the CH) and add 1.0 (for  $\text{C}=\text{O}$ ) plus 2.0 (for OH) = 4.7 ppm—not far out. Vitamin C (ascorbic acid) has two CHs. One at 4.05 ppm is next to an OH group (estimate 1.7 + 2.0 for OH = 3.7 ppm) and one is next to a double bond and an oxygen atom at 4.52 ppm (estimate 1.7 + 1 for double bond + 2 for OH = 4.7 ppm). Again, not too bad for a rough estimate.



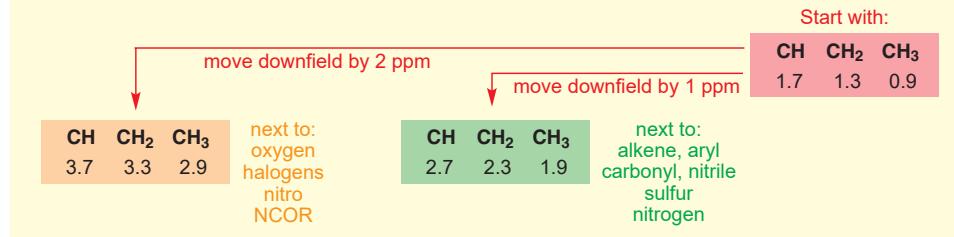
An interesting case is the amino acid phenylalanine whose  $\text{CH}_2$  group we looked at a moment ago. It also has a CH group between the amino and the carboxylic acid groups. If we record the  $^1\text{H}$  NMR spectrum in  $\text{D}_2\text{O}$ , in either basic ( $\text{NaOD}$ ) or acidic ( $\text{DCl}$ ) solutions, we see a large shift of that CH group. In basic solution the CH resonates at 3.60 ppm and in acidic solution it resonates at 4.35 ppm. There is a double effect here:  $\text{CO}_2\text{H}$  and  $\text{NH}_3^+$  are both more electron-withdrawing than  $\text{CO}_2^-$  and  $\text{NH}_2$  so both move the CH group downfield.

■  $\text{D}_2\text{O}$ ,  $\text{NaOD}$ , and  $\text{DCl}$  have to be used in place of their  $^1\text{H}$  equivalents to avoid swamping the spectrum with  $\text{H}_2\text{O}$  protons. All acidic protons are replaced by deuterium in the process—more on this later.



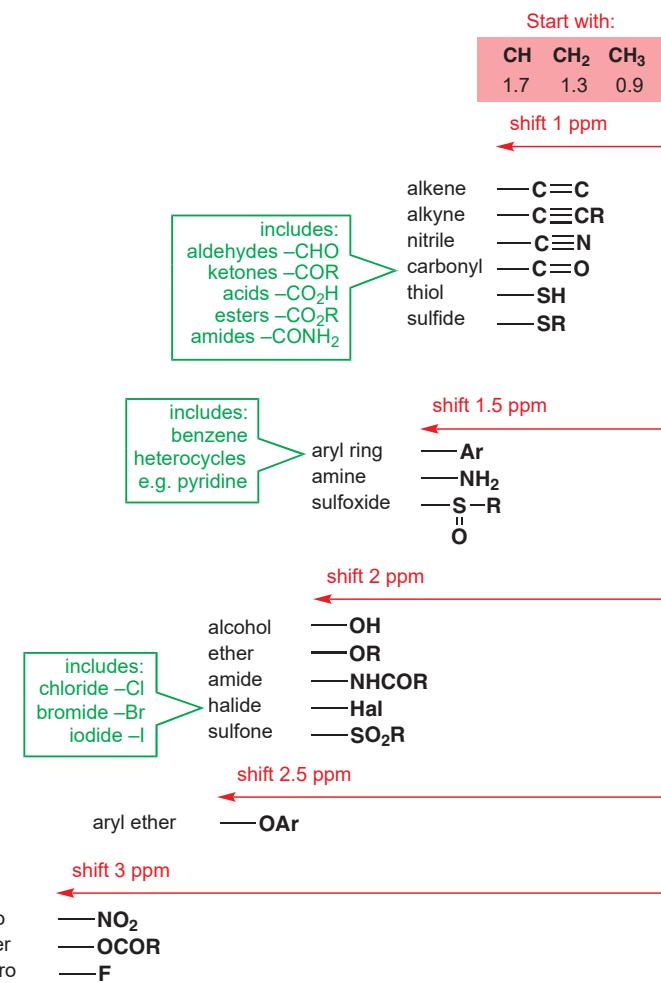
● A simple guide to estimating chemical shifts

We suggest you start with a very simple (and therefore necessarily oversimplified) picture, which should be the basis for any further refinements. Start methyl groups at 0.9, methylenes ( $\text{CH}_2$ ) at 1.3, and methines ( $\text{CH}$ ) at 1.7 ppm. Any functional group is worth a 1 ppm downfield shift except oxygen and halogen which are worth 2 ppm. This diagram summarizes this approach.

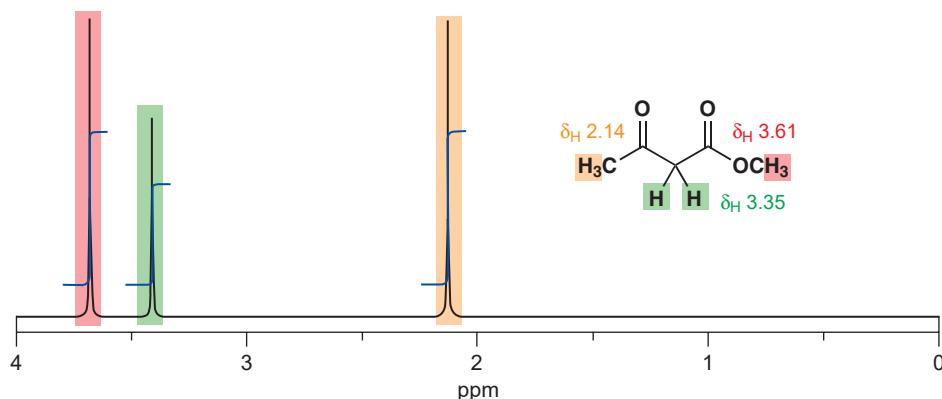


The guide above is very rough and ready, but is easily remembered and you should aim to learn it. However, if you want to, you can make it slightly more accurate by adding further subdivisions and separating out the very electron-withdrawing groups (nitro, ester OCOR, fluoride), which shift by 3 ppm. This gives us the summary chart on this page, which we suggest you use as a reference. If you want even more detailed information, you can refer to the tables in Chapter 18 or better still the more comprehensive tables in any specialized text (see the Further reading section).

### Summary chart of proton NMR shifts

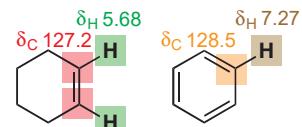


Answers deduced from this chart won't be perfect but will give a good guide. Remember—these shifts are additive. Take a simple example, the ketoester below. There are just three signals and the integration alone distinguishes the two methyl groups from the  $\text{CH}_2$  group. One methyl has been shifted from 0.9 ppm by about 1 ppm, the other by more than 2 ppm. The first must be next to  $\text{C}=\text{O}$  and the second next to oxygen. More precisely, 2.14 ppm is a shift of 1.24 ppm from our standard value (0.9 ppm) for a methyl group, about what we expect for a methyl ketone, while 3.61 ppm is a shift of 2.71 ppm, close to the expected 3.0 ppm for an ester joined through the oxygen atom. The  $\text{CH}_2$  group is next to an ester and a ketone carbonyl group and so we expect it at  $1.3 + 1.0 + 1.0 = 3.3$  ppm, an accurate estimate, as it happens. We shall return to these estimates when we look at the spectra of unknown compounds.



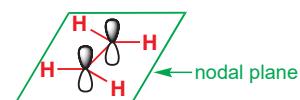
## The alkene region and the benzene region

In  $^{13}\text{C}$  NMR, alkene and benzene carbons came in the same region of the spectrum, but in the  $^1\text{H}$  NMR spectrum the H atoms attached to arene C and alkene C atoms sort themselves into two groups. To illustrate this point, look at the  $^{13}\text{C}$  and  $^1\text{H}$  chemical shifts of cyclohexene and benzene, shown in the margin. The two carbon signals are almost the same (1.3 ppm difference, < 1% of the total 200 ppm scale) but the proton signals are very different (1.6 ppm difference = 16% of the 10 ppm scale). There must be a fundamental reason for this.



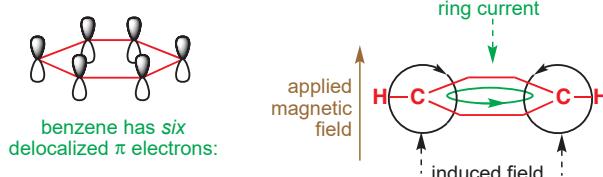
### The benzene ring current causes large shifts for aromatic protons

A simple alkene has an area of low electron density in the plane of the molecule because the  $\pi$  orbital has a node there, and the carbons and hydrogen nuclei lying in the plane gain no shielding from the  $\pi$  electrons.



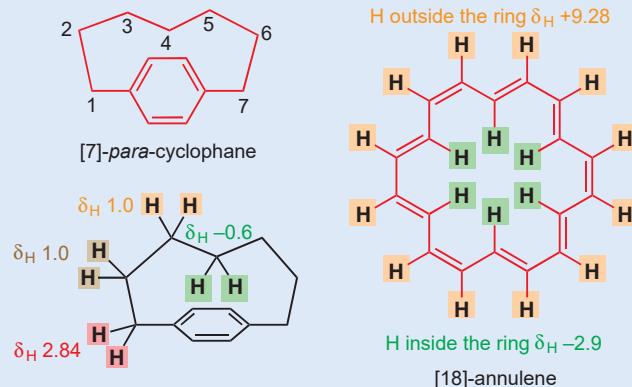
The benzene ring looks similar at first sight, and the plane of the molecule is indeed a node for all the  $\pi$  orbitals. However, as we discussed in Chapter 7, benzene is aromatic—it has extra stability because the six  $\pi$  electrons fit into three very stable orbitals and are delocalized round the whole ring. The applied field sets up a ring current in these delocalized electrons that produces a local field rather like the field produced by the electrons around a nucleus. Inside the benzene ring the induced field opposes the applied field, but outside the ring it reinforces the applied field. The carbon atoms are in the ring itself and experience neither effect, but the hydrogens are outside the ring, feel a stronger applied field, and appear less shielded (i.e. more deshielded; larger chemical shift).

■ Magnetic fields produced by circulating electrons are all around you: electromagnets and solenoids are exactly this.



### Cyclophanes and annulenes

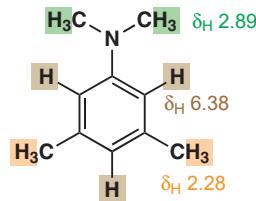
You may think that it is rather pointless imagining what goes on inside an aromatic ring as we cannot have hydrogen atoms literally inside a benzene ring. However, we can get close. Compounds called cyclophanes have loops of saturated carbon atoms attached at both ends to the same benzene rings. You see here a structure for [7]-*para*-cyclophane, which has a string of seven  $\text{CH}_2$  groups attached to the *para* positions of the same benzene ring. The four H atoms on the benzene ring itself appear as one signal at 7.07 ppm—a typical ring-current deshielded value for a benzene ring. The two  $\text{CH}_2$  groups joined to the benzene ring (C1) are also deshielded by the ring current at 2.64 ppm. The next two sets of  $\text{CH}_2$  groups on C2 and C3 are neither shielded nor deshielded at 1.0 ppm. But the middle  $\text{CH}_2$  group in the chain (C4) must be pointing towards the ring in the middle of the  $\pi$  system and is heavily shielded by the ring current at  $-0.6$  ppm.



Interactive structures of cyclophane and annulene

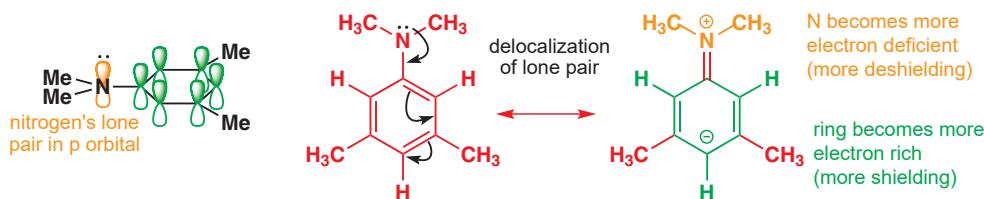
With a larger aromatic ring it is possible actually to have hydrogen atoms inside the ring. Compounds are aromatic if they have  $4n + 2$  delocalized electrons and this ring with nine double bonds, that is, 18  $\pi$  electrons, is an example. The hydrogens outside the ring resonate in the aromatic region at rather low field (9.28 ppm) but the hydrogen atoms inside the ring resonate at an amazing  $-2.9$  ppm, showing the strong shielding by the ring current. Such extended aromatic rings are called *annulenes*: you met them in Chapter 7.

### Uneven electron distribution in aromatic rings



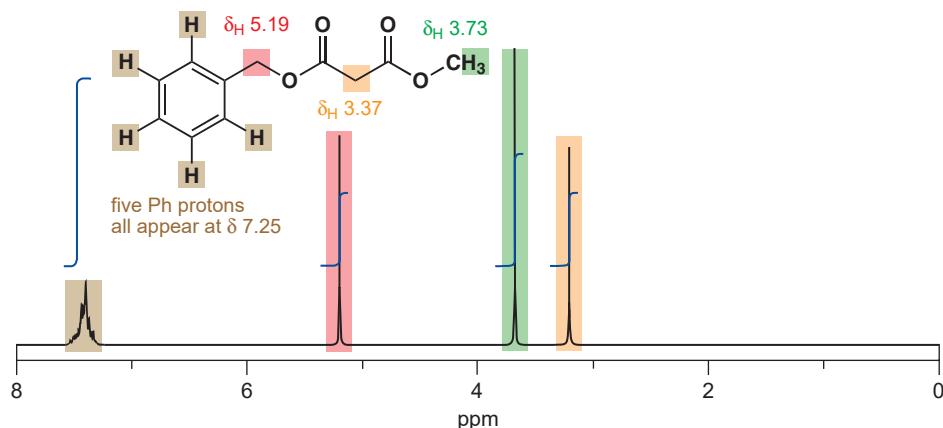
The greater electron density around the ring more than compensates for any change in the ring current.

The  $^1\text{H}$  NMR spectrum of this simple aromatic amine has three peaks in the ratio 1:2:2, which must correspond to 3H:6H:6H. The 6.38 ppm signal clearly belongs to the protons round the benzene ring, but why are they at 6.38 and not at around 7.2 ppm? We must also distinguish the two methyl groups at 2.28 ppm from those at 2.89 ppm. The chart on p. 276 suggests that these should both be at about 2.4 ppm, close enough to 2.28 ppm but not to 2.89 ppm. The solution to both these puzzles is the distribution of electrons in the aromatic ring. Nitrogen feeds electrons into the  $\pi$  system, making it electron rich: the ring protons are more shielded and the nitrogen atom becomes positively charged and its methyl groups more deshielded. The peak at 2.89 ppm must belong to the  $\text{NMe}_2$  group.



Why should you usually expect to see *three* types of protons for a monosubstituted phenyl ring?

Other groups, such as simple alkyl groups, hardly perturb the aromatic system at all and it is quite common for all five protons in an alkyl benzene to appear as one signal instead of the three we might expect. Here is an example with some non-aromatic protons too: there is another on p. 275—the Cbz-protected amino acid.



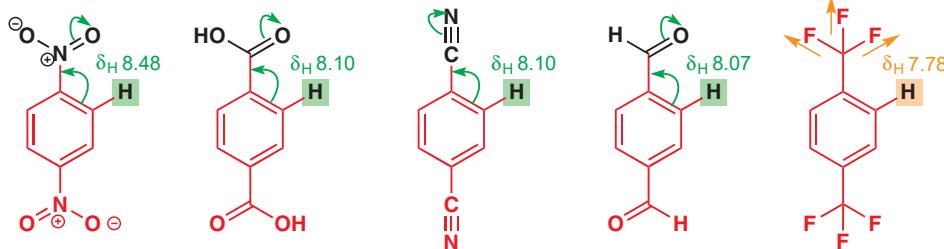
The five protons on the aromatic ring all have the same chemical shift. Check that you can assign the rest. The  $\text{OCH}_3$  group (green) is typical of a methyl ester (the chart on p. 276 suggests 3.9 ppm). One  $\text{CH}_2$  group (yellow) is between two carbonyl groups (compare 3.35 ppm for the similar  $\text{CH}_2$  group on p. 277). The other (red) is next to an ester and a benzene ring: we calculate  $1.3 + 1.5 + 3.0 = 5.8$  ppm for that—reasonably close to the observed 5.19 ppm. Notice how the Ph and the O together act to shift the Hs attached to this  $\text{sp}^3$  C downfield into what we usually expect to be the alkene region. Don't interpret the regions on p. 272 too rigidly!

### How electron donation and withdrawal change chemical shifts

We can get an idea of the effect of electron distribution by looking at a series of benzene rings with the same substituent in the 1 and 4 positions. This pattern makes all four hydrogens on the ring identical. Here are a few compounds listed in order of chemical shift: largest shift (lowest field; most deshielded) first. Conjugation is shown by the usual curly arrows, and inductive effects by a straight arrow by the side of the group. Only one hydrogen atom and one set of arrows are shown.

Conjugation, as discussed in Chapter 7, is felt through  $\pi$  bonds, while inductive effects are the result of electron withdrawal or donation felt simply by polarization of the  $\sigma$  bonds of the molecule. See p. 135.

the effect of electron-withdrawing groups  
by conjugation

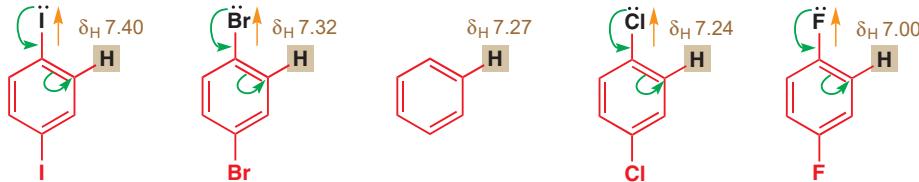


The largest shifts come from groups that withdraw electrons by conjugation. Nitro is the most powerful—this should not surprise you as we saw the same in non-aromatic compounds in both  $^{13}\text{C}$  and  $^1\text{H}$  NMR spectra. Then come the carbonyl and nitrile group followed by groups showing simple inductive withdrawal.  $\text{CF}_3$  is an important example of this kind of group—three fluorine atoms combine to exert a powerful effect.

► This all has very important consequences for the reactivity of differently substituted benzene rings: their reactions will be discussed in Chapter 21.

In the middle of our sequence, around the position of benzene itself at 7.27 ppm, come the halogens, whose inductive electron withdrawal and lone pair donation are nearly balanced.

balance between withdrawal by inductive effect and donation of lone pairs by conjugation

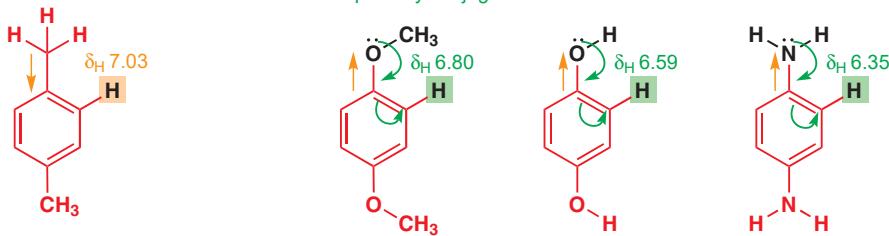


Alkyl groups are weak inductive donators, but the groups which give the most shielding—perhaps surprisingly—are those containing the electronegative atoms O and N. Despite being inductively electron withdrawing (the C–O and C–N  $\sigma$  bonds are polarized with  $\delta + \text{C}$ ), on balance conjugation of their lone pairs with the ring (as you saw on p. 278) makes them net electron donors. They *increase* the shielding at the ring hydrogens. Amino groups are the best. Note that one nitrogen-based functional group ( $\text{NO}_2$ ) is the best electron withdrawer while another ( $\text{NH}_2$ ) is the best electron donor.

the effect of electron-donating groups

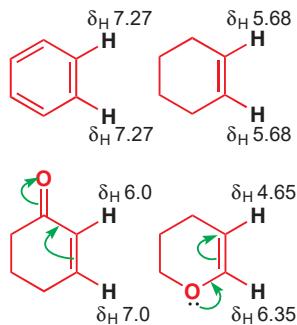
by inductive effect

balance between withdrawal by inductive effect and donation of lone pairs by conjugation—electron donation wins



As far as the donors with lone pairs are concerned (the halogens plus O and N), two factors are important—the size of the lone pairs and the electronegativity of the element. If we look at the four halides at the top of this page the lone pairs are in 2p (F), 3p (Cl), 4p (Br), and 5p (I) orbitals. In all cases the orbitals on the benzene ring are 2p so the fluorine orbital is of the right size to interact well and the others too large. Even though fluorine is the most electronegative, it is still the best donor. The others don't pull so much electron density away, but they can't give so much back either.

If we compare the first row of the p block elements—F, OH, and  $\text{NH}_2$ —all have lone pairs in 2p orbitals so now electronegativity is the only variable. As you would expect, the most electronegative element, F, is now the weakest donor.

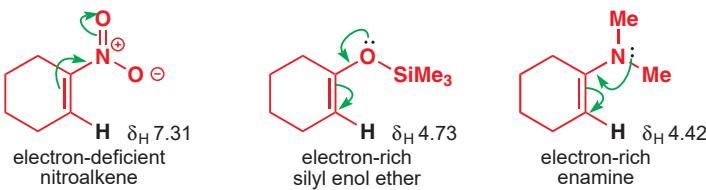


### Electron-rich and electron-deficient alkenes

The same sort of thing happens with alkenes. We'll concentrate on cyclohexene so as to make a good comparison with benzene. The six identical protons of benzene resonate at 7.27 ppm; the two identical alkene protons of cyclohexene resonate at 5.68 ppm. A conjugating and electron-withdrawing group such as a ketone removes electrons from the double bond as expected—but unequally. The proton nearer the  $\text{C}=\text{O}$  group is only slightly downfield from cyclohexene but the more distant one is over 1 ppm downfield. The curly arrows show the electron distribution, which we can deduce from the NMR spectrum.

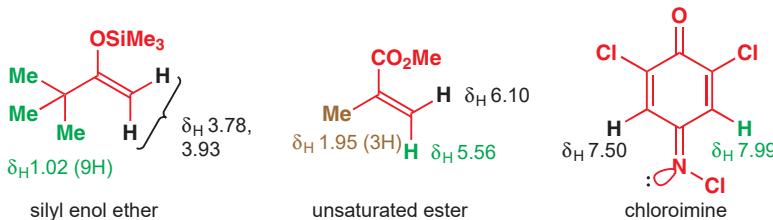
Oxygen as a conjugating electron donor is even more dramatic. It shifts the proton next to it downfield by the inductive effect but pushes the more distant proton upfield a whole 1 ppm by donating electrons. The separation between the two protons is nearly 2 ppm.

For both types of substituent, the effects are more marked on the more distant ( $\beta$ ) proton. If these shifts reflect the true electron distribution, we should be able to deduce something about the chemistry of the following three compounds. You might expect that nucleophiles will attack the electron-deficient site in the nitroalkene, while electrophiles will be attacked by the electron-rich sites in silyl enol ethers and enamines. These are all important reagents and do indeed react as we predict, as you will see in later chapters. Look at the difference—there are nearly 3 ppm between the shifts of the same proton on the nitro compound and the enamine!



### Structural information from the alkene region

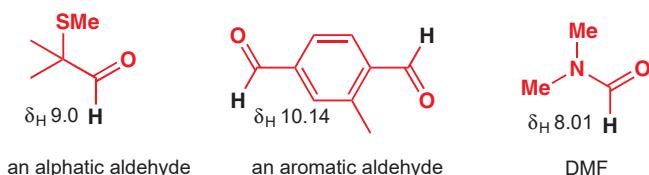
Alkene protons on different carbon atoms can obviously be different if the carbon atoms themselves are different and we have just seen examples of that. Alkene protons can also be different if they are on the same carbon atom. All that is necessary is that the substituents at the other end of the double bond should themselves be different. The silyl enol ether and the unsaturated ester below both fit into this category. The protons on the double bond must be different, because each is *cis* to a different group. We may not be able to assign which is which, but the difference alone tells us something. The third compound is an interesting case: the different shifts of the two protons on the ring prove that the N–Cl bond is at an angle to the C=N bond. If it were in line, the two hydrogens would be identical. The other side of the C=N bond is occupied by a lone pair and the nitrogen atom is trigonal ( $\text{sp}^2$  hybridized).



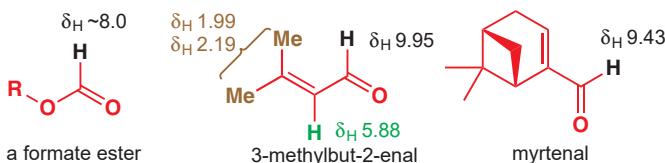
### The aldehyde region: unsaturated carbon bonded to oxygen

The aldehyde proton is unique. It is directly attached to a carbonyl group—one of the most electron-withdrawing groups that exists—and is very deshielded, resonating with the largest shifts of any CH protons, in the 9–10 ppm region. The examples below are all compounds that we have met before. Two are just simple aldehydes—aromatic and aliphatic. The third is the solvent DMF. Its CHO proton is less deshielded than most—the amide delocalization that feeds electrons into the carbonyl group provides some extra shielding.

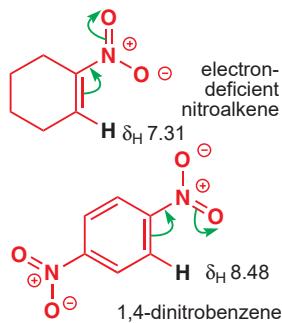
■ *Aliphatic* is a catch-all term for compounds that are not aromatic.



Conjugation with an oxygen lone pair has much the same effect—formate esters resonate at about 8 ppm—but conjugation with  $\pi$  bonds does not. The aromatic aldehyde above, simple conjugated aldehyde below, and myrtenal all have CHO protons in the normal region (9–10 ppm).

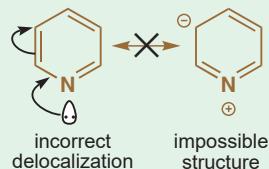


### Non-aldehyde protons in the aldehyde region: pyridines



► There is more on the electron-withdrawing nature of the nitro group on p. 176.

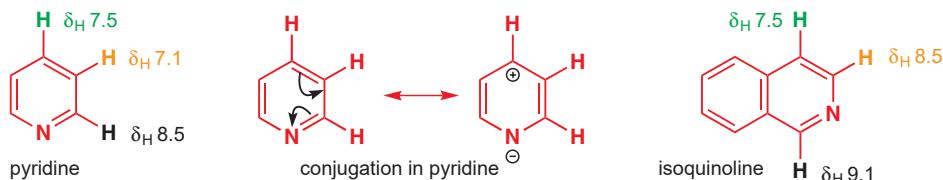
■ Note that the alternative ‘conjugation’ shown in the structure below is wrong. The structure with two adjacent double bonds in a six-membered ring is impossible and, in any case, as you saw in Chapter 8, the lone pair electrons on nitrogen are in an  $\text{sp}^2$  orbital orthogonal to the p orbitals in the ring. There is no interaction between orthogonal orbitals.



Two other types of protons resonate in the region around 9–10 ppm: some aromatic protons and some protons attached to heteroatoms like OH and NH. We will deal with NH and OH protons in the next section, but first we must look at some electron-deficient aromatic rings with distinctively large shifts.

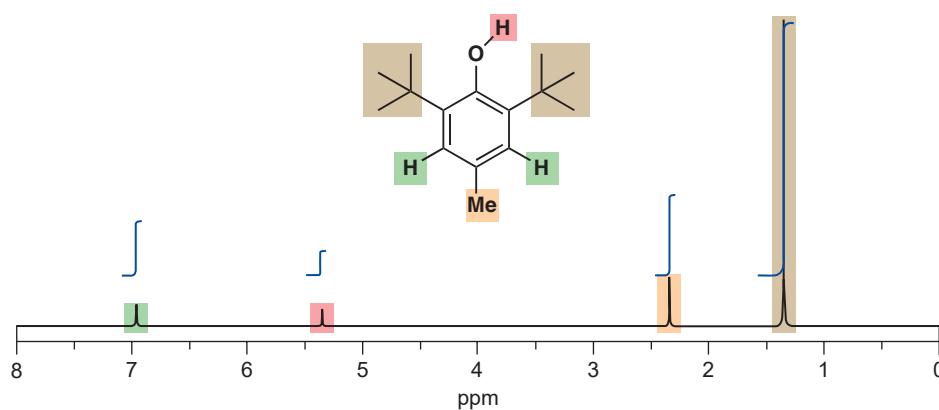
Protons on double bonds, even very electron-deficient double bonds like those of nitroalkenes, hardly get into the aldehyde region. However, some benzene rings with very electron-withdrawing groups do manage it because of the extra downfield shift of the ring current, so look out for nitrobenzenes as they may have signals in the 8–9 ppm region.

More important molecules with signals in this region are the aromatic heterocycles such as pyridine, which you saw functioning as a base in Chapters 8 and 10. The NMR shifts clearly show that pyridine is aromatic: one proton is at 7.1 ppm, essentially the same as benzene, but the others are more downfield and one, at C2, is in the aldehyde region. This is not because pyridine is ‘more aromatic’ than benzene but because nitrogen is more electronegative than carbon. Position C2 is like an aldehyde—a proton attached to  $\text{sp}^2$  C bearing a heteroatom—while C4 is electron deficient due to conjugation (the electronegative nitrogen is electron withdrawing). Isoquinoline is a pyridine and a benzene ring fused together and has a proton even further downfield at 9.1 ppm—this is an imine proton that experiences the ring current of the benzene ring.

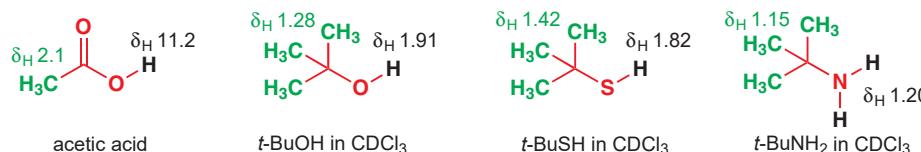


### Protons on heteroatoms have more variable shifts than protons on carbon

Protons directly attached to O, N, or S (or any other heteroatom, but these are the most important) also have signals in the NMR spectrum. We have avoided them so far because the positions of these signals are less reliable and because they are affected by exchange.



In Chapter 2 you met the antioxidant BHT. Its proton NMR is very simple, consisting of just four lines with integrals 2, 1, 3, and 18. The chemical shifts of the *tert*-butyl group (brown), the methyl group on the benzene ring (orange), and the two identical aromatic protons (green) should cause you no surprise. What is left, the 1 H signal at 5.0 ppm (pink), must be the OH. Earlier on in this chapter we saw the spectrum of acetic acid,  $\text{CH}_3\text{CO}_2\text{H}$ , which showed an OH resonance at 11.2 ppm. Simple alcohols such as *tert*-butanol have OH signals in  $\text{CDCl}_3$  (the usual NMR solvent) at around 2 ppm. Why such big differences?



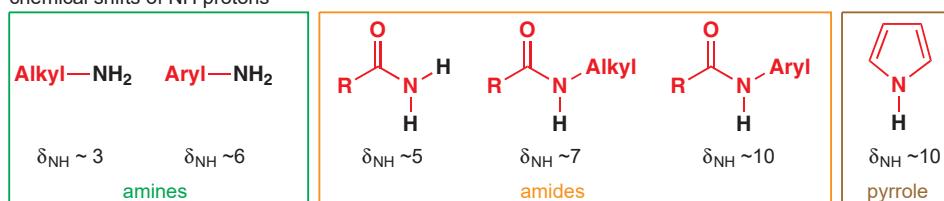
This is a matter of acidity. The more acidic a proton is—that is, the more easily it can escape as  $\text{H}^+$  (this is the definition of acidity from Chapter 8)—the more the OH bond is polarized towards oxygen. The more the RO—H bond is polarized, the closer we are to free  $\text{H}^+$ , which would have no shielding electrons at all, and so the further the proton goes downfield. The OH chemical shifts and the acidity of the OH group are—to a rough extent at least—related.

Thiols ( $\text{RSH}$ ) behave in a similar way to alcohols but are not so deshielded, as you would expect from the smaller electronegativity of sulfur (phenols are all about 5.0 ppm,  $\text{PhSH}$  is at 3.41 ppm). Alkane thiols appear at about 2 ppm and aryl thiols at about 4 ppm. Amines and amides show a big variation, as you would expect for the variety of functional groups involved, and are summarized below. Amides are slightly acidic, as you saw in Chapter 8, and amide protons resonate at quite low fields. Pyrroles are special—the aromaticity of the ring makes the NH proton unusually acidic—and they appear at about 10 ppm.

	ROH <sup>a</sup>	ArOH <sup>b</sup>	$\text{RCO}_2\text{H}^{\text{c}}$
$\text{pK}_a$	16	10	5
$\delta_{\text{H}}(\text{OH})$ , ppm	2.0	5.0	>10

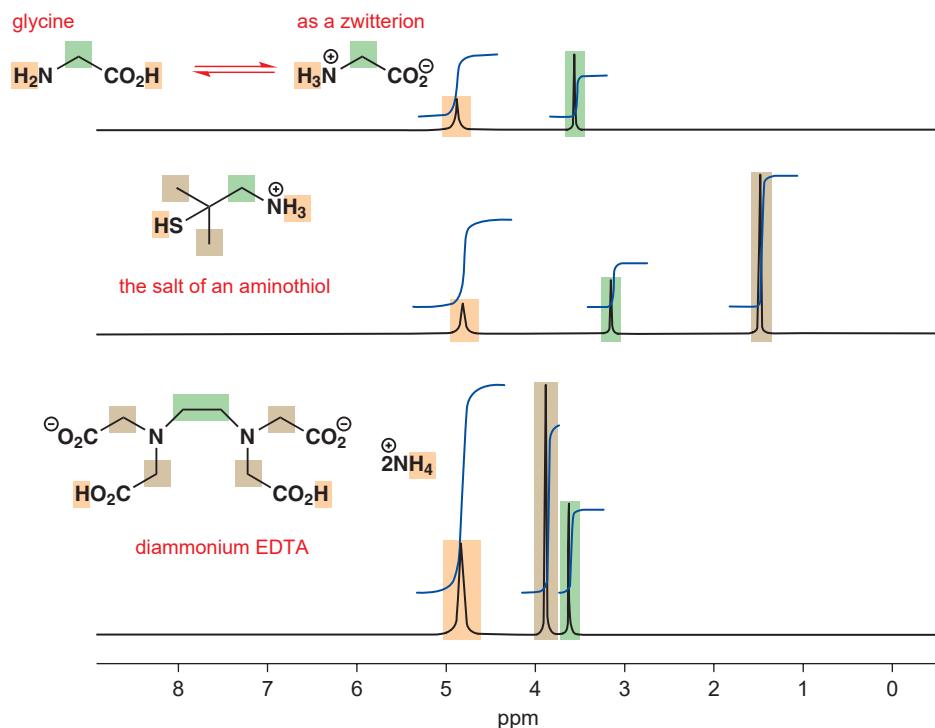
<sup>a</sup>alcohol <sup>b</sup>phenol <sup>c</sup>carboxylic acid

chemical shifts of NH protons



### Exchange of acidic protons is revealed in proton NMR spectra

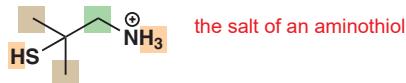
Compounds with very polar groups often dissolve best in water. NMR spectra are usually run in  $\text{CDCl}_3$ , but heavy water,  $\text{D}_2\text{O}$ , is an excellent NMR solvent. Here are some results in that medium.



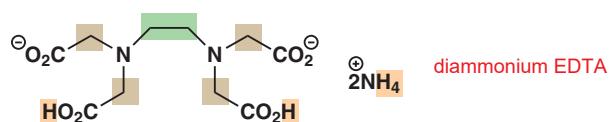
Glycine is expected to exist as a zwitterion (Chapter 8, p. 167). It has a 2H signal (green) for the  $\text{CH}_2$  between the two functional groups, which would do for either form. The 3H signal at 4.90 ppm (orange) might suggest the  $\text{NH}_3^+$  group, but wait a moment before making up your mind.



The aminothiol salt has the  $\text{CMe}_2$  and  $\text{CH}_2$  groups about where we would expect them (brown and green), but the  $\text{SH}$  and  $\text{NH}_3^+$  protons appear as one 4H signal.

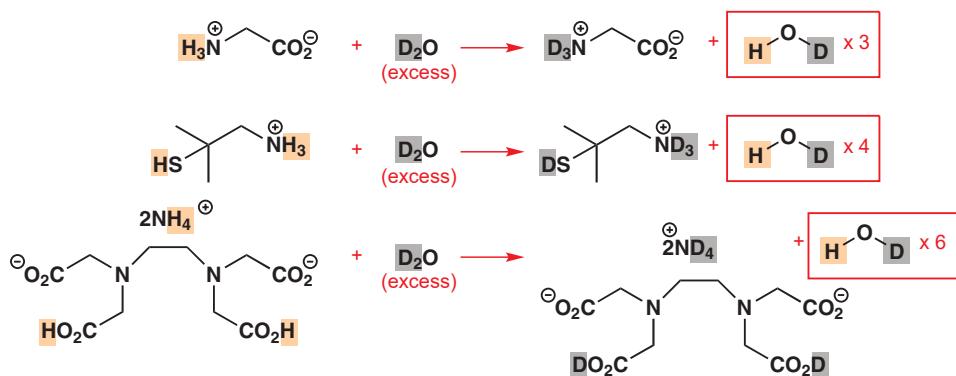


The double salt of EDTA has several curious features. The two (green)  $\text{CH}_2$  groups in the middle are fine, but the other four  $\text{CH}_2$  (brown) groups all appear identical, as do all the protons on both the  $\text{CO}_2\text{H}$  and  $\text{NH}_3^+$  groups.



The best clue to why this is so comes from the strange coincidence of the chemical shifts of the OH, NH, and SH protons in these molecules. They are all the same within experimental error: 4.90 ppm for glycine, 4.80 ppm for the aminothiol, and 4.84 ppm for EDTA. In fact all correspond to the same species: HOD, or monodeuterated water. Exchange between XH (where X=O, N, or S) protons is extremely fast, and the solvent,  $\text{D}_2\text{O}$ , supplies a vast excess of exchangeable *deuteriums*. These immediately replace all the OH, NH, and SH protons in the molecules with D, forming HOD in the process. Recall that we do not see signals for deuterium atoms (that's why deuterated solvents are used). They have their own spectra at a different frequency.

EDTA is ethylenediamine tetraacetic acid, an important complexing agent for metals. This is the salt formed with just two equivalents of ammonia.



The same sort of exchange between OH or NH protons with each other or with traces of water in the sample means that the OH and NH peaks in most spectra in  $\text{CDCl}_3$  are rather broader than the peaks for CH protons.

Two questions remain. First, can we tell whether glycine is a zwitterion in water or not? Not really: the spectra fit either or an equilibrium between both—other evidence leads us to expect the zwitterion in water. Second, why are all four  $\text{CH}_2\text{CO}$  groups in EDTA the same? This we can answer. As well as the equilibrium exchanging the  $\text{CO}_2\text{H}$  protons with the solvent, there will be an equally fast equilibrium exchanging protons between  $\text{CO}_2\text{D}$  and  $\text{CO}_2^-$ . This makes all four ‘arms’ of EDTA the same.

You should leave this section with an important chemical principle firmly established in your mind.

#### ● Proton exchange between heteroatoms is fast

Proton exchange between heteroatoms, particularly O, N, and S, is a very fast process in comparison with other chemical reactions, and often leads to averaged peaks in the  $^1\text{H}$  NMR spectrum.

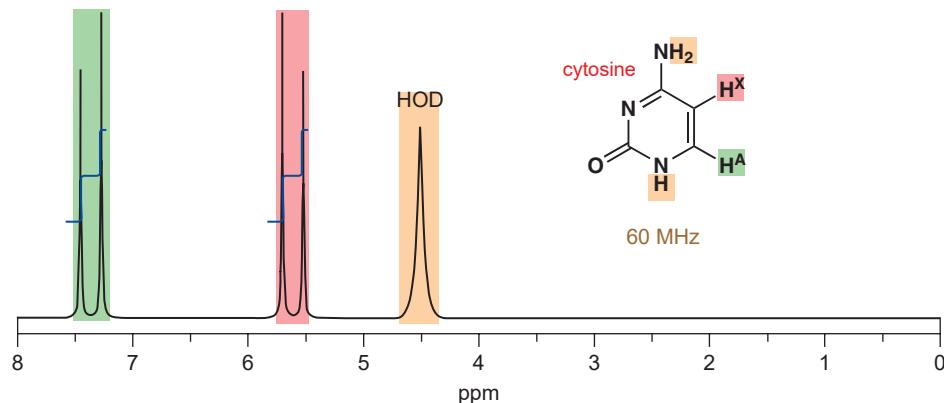
► We mentioned this fact before in the context of the mechanism of addition to a C=O group (p. 136), and we will continue to explore its mechanistic consequences throughout this book.

## Coupling in the proton NMR spectrum

### Nearby hydrogen nuclei interact and give multiple peaks

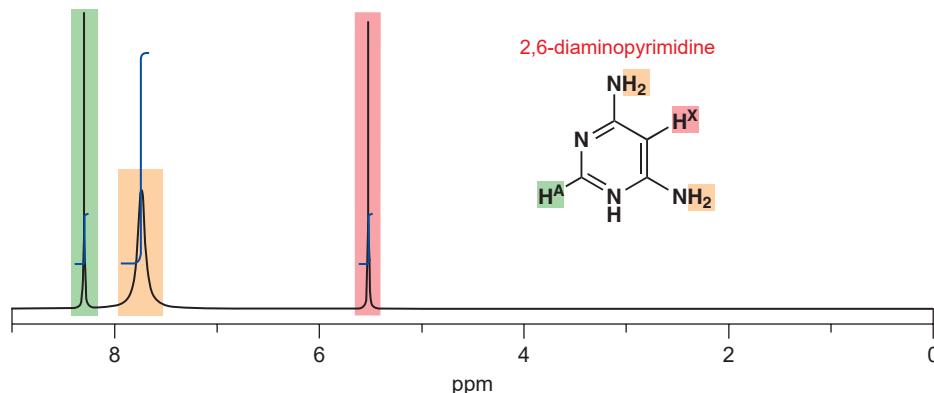
So far proton NMR has been not unlike carbon NMR on a smaller scale. However, we have yet to discuss the real strength of proton NMR, something more important than chemical shifts and something that allows us to look not just at individual atoms but also at the way the C–H skeleton is joined together. This is the result of the interaction between nearby protons, known as *coupling*.

An example we could have chosen in the last section is the nucleic acid component cytosine, which has exchanging  $\text{NH}_2$  and NH protons giving a peak for  $\text{HOD}$  at 4.5 ppm. We didn’t choose this example because the other two peaks would have puzzled you. Instead of giving just one line for each proton, they give two lines each—doublets as you will learn to call them—and it is time to discuss the origin of this ‘coupling’.



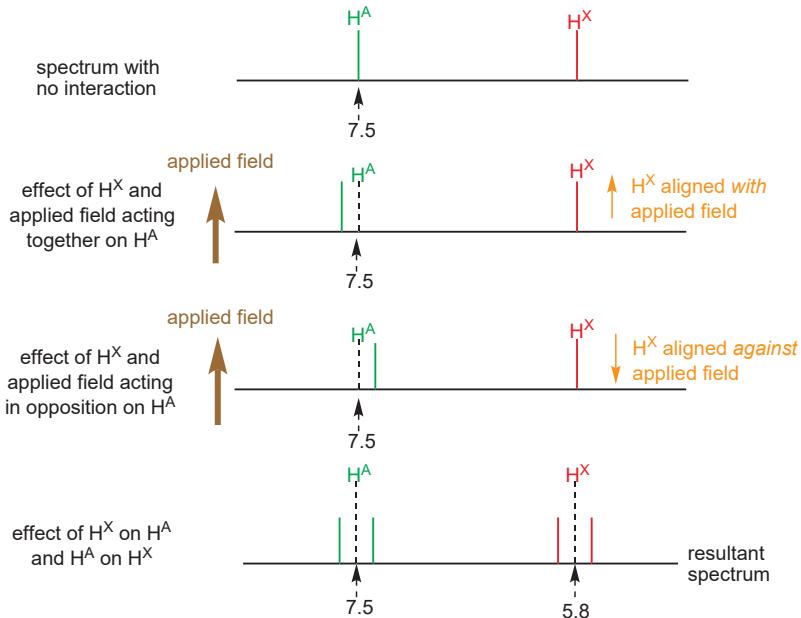
► Cytosine is one of the four bases that, in combination with deoxyribose and phosphate, make up DNA. It is a member of the class of heterocycles called pyrimidines. We come back to the chemistry of DNA towards the end of this book, in Chapter 42.

You might have expected a spectrum like that of the heterocycle below, which like cytosine is also a pyrimidine. It too has exchanging  $\text{NH}_2$  protons and two protons on the heterocyclic ring. But these two protons give the expected two lines instead of the four lines in the cytosine spectrum. It is easy to assign the spectrum: the green proton labelled  $\text{H}^{\text{A}}$  is attached to an aldehyde-like  $\text{C}=\text{N}$  and so comes at lowest field. The red proton labelled  $\text{H}^{\text{X}}$  is *ortho* to two electron-donating  $\text{NH}_2$  groups and so comes at high field for an aromatic proton (p. 272). These protons do not couple with each other because they are too far apart. They are separated by five bonds whereas the ring protons in cytosine are separated by just three bonds.



Understanding this phenomenon is so important that we are going to explain it in three different ways—you choose which appeals to you most. Each method offers a different insight.

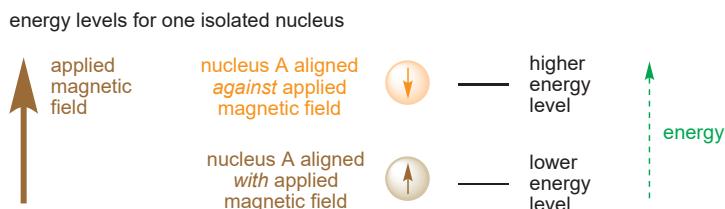
The diaminopyrimidine spectrum you have just seen has two single lines (*singlets* we shall call them from now on) because each proton,  $\text{H}^{\text{A}}$  or  $\text{H}^{\text{X}}$ , can be aligned either with or against the applied magnetic field. The cytosine spectrum is different because each proton, say  $\text{H}^{\text{A}}$ , is near enough to experience the small magnetic field of the other proton  $\text{H}^{\text{X}}$  as well as the field of the magnet itself. The diagram shows the result.



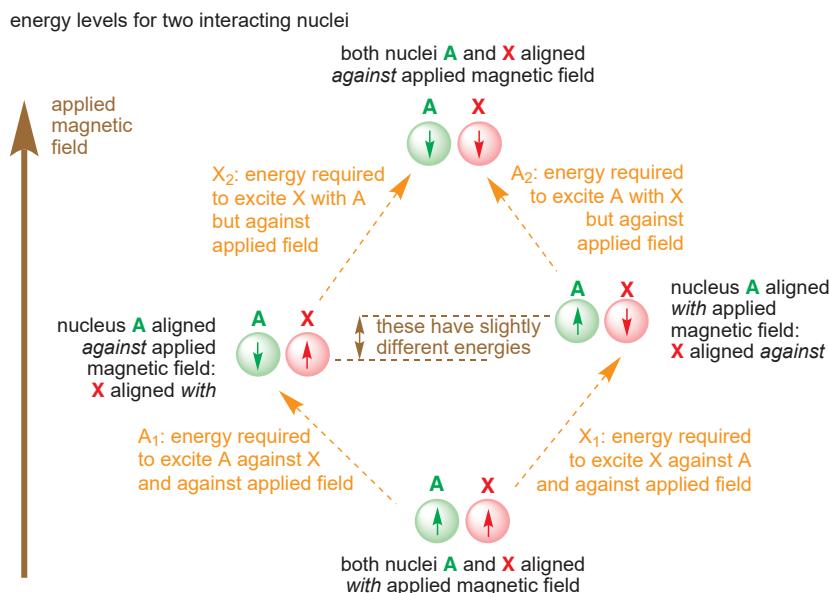
If each proton interacted only with the applied field we would get two singlets. But proton  $\text{H}^{\text{A}}$  actually experiences two slightly different fields: the applied field *plus* the field of

$H^X$  or the applied field *minus* the field of  $H^A$ .  $H^X$  acts either to increase or decrease the field experienced by  $H^A$ . The position of a resonance depends on the field experienced by the proton so these two situations give rise to two slightly different peaks—a *doublet* as we shall call it. And whatever happens to  $H^A$  happens to  $H^X$  as well, so the spectrum has two doublets, one for each proton. Each couples with the other. The field of a proton is a very small indeed in comparison with the field of the magnet and the separation between the lines of a doublet is very small. We shall discuss the size of the coupling later (pp. 294–300).

The second explanation takes into account the energy levels of the nucleus. In Chapter 4, when we discussed chemical bonds, we imagined electronic energy levels on neighbouring atoms interacting with each other and splitting to produce new molecular energy levels, some higher in energy and some lower in energy than the original atomic energy levels. When hydrogen *nuclei* are near each other in a molecule, the nuclear energy levels also interact and split to produce new energy levels. If a single hydrogen nucleus interacts with a magnetic field, we have the picture on p. 270 of this chapter: there are *two* energy levels as the nucleus can be aligned with or against the applied magnetic field, there is one energy jump possible, and there is a resonance at one frequency. This you have now seen many times and it can be summarized as shown below.



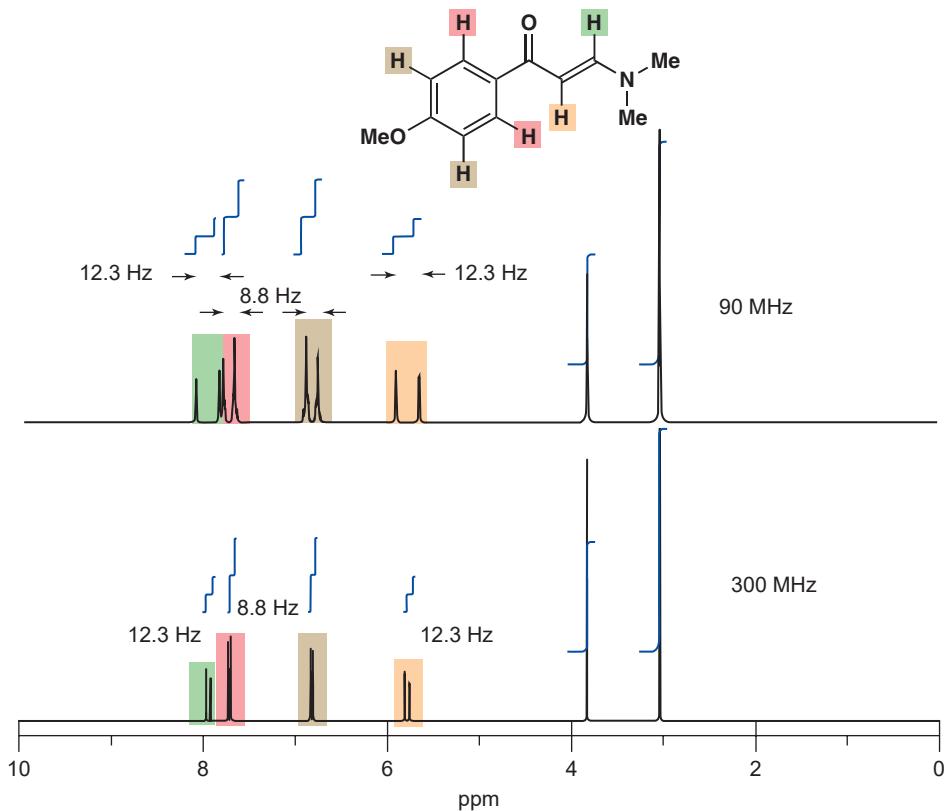
The spectrum of the pyrimidine on p. 286 shows exactly this situation: two protons well separated in the molecules and each behaving independently. Each has two energy levels, each gives a singlet, and there are two lines in the spectrum. But in cytosine, whose spectrum is shown on p. 285, the situation is different: each hydrogen atom has another hydrogen nucleus nearby and there are now *four* energy levels. Each nucleus  $H^A$  and  $H^X$  can be aligned with or against the applied field. There is one (lower) energy level where they are both aligned with the field and one (higher) level where they are both aligned against. In between there are two different energy levels in which one nucleus is aligned with the field and one against. Exciting H from alignment with to alignment against the applied field can be done in two slightly different ways, shown as  $A_1$  and  $A_2$  on the diagram. The result is two resonances very close together in the spectrum.



Please notice carefully that we cannot have this discussion about  $\text{H}^{\text{A}}$  without discussing  $\text{H}^{\text{X}}$  in the same way. If there are two slightly different energy jumps to excite  $\text{H}^{\text{A}}$ , there must also be two slightly different energy jumps to excite  $\text{H}^{\text{X}}$ .  $\text{A}_1$ ,  $\text{A}_2$ ,  $\text{X}_1$ , and  $\text{X}_2$  are all different, but the *difference* between  $\text{A}_1$  and  $\text{A}_2$  is exactly the same as the *difference* between  $\text{X}_1$  and  $\text{X}_2$ . Each proton now gives two lines (a doublet) in the NMR spectrum and the splitting of the two doublets is *exactly the same*. We describe this situation as coupling. We say ‘A and X are coupled’ or ‘X is coupled to A’ (and vice versa, of course). We shall be using this language from now on and so must you.

Now look back at the spectrum of cytosine at the beginning of this section. You can see the two doublets, one for each of the protons on the aromatic ring. Each is split by the same amount (this is easy to check with a ruler). The separation of the lines is the **coupling constant** and is called  $J$ . In this case  $J = 4$  Hz. Why do we measure  $J$  in hertz and not in ppm? We pointed out on p. 55 (Chapter 3) that we measure chemical shifts in ppm because we get the same number regardless of the rating of the NMR machine in MHz. We measure  $J$  in Hz because we also get the same number regardless of the machine.

The spectra below show  $^1\text{H}$  NMR spectra of the same compound run on two different NMR machines—one a 90 MHz spectrometer and one a 300 MHz spectrometer (these are at the lower and upper ends of the range of field strengths in common use). Notice that the peaks stay in the same place on the chemical shift scale (ppm) but the size of the coupling appears to change because 1 ppm is worth 90 Hz in the top spectrum but 300 Hz in the bottom.



#### Measuring coupling constants in hertz

To measure a coupling constant it is essential to know the rating of the NMR machine in MHz (megahertz). This is why you are told that each illustrated spectrum is, say, a ‘400 MHz  $^1\text{H}$  NMR spectrum’. Couplings may be marked on the spectrum, electronically, but if not then to measure the coupling, measure the distance between the lines by ruler or dividers and use the horizontal scale to find out the separation in ppm. The conversion is then easy—to turn parts per million of megahertz into hertz you just leave out the million! So 1 ppm on a 300 MHz machine is 300 Hz. On a 500 MHz machine, a 10 Hz coupling is a splitting of 0.02 ppm.

● Spectra from different machines

When you change from one machine to another, say, from a 200 MHz to a 500 MHz NMR machine, chemical shifts ( $\delta$ ) stay the same in ppm and coupling constants ( $J$ ) stay the same in Hz.

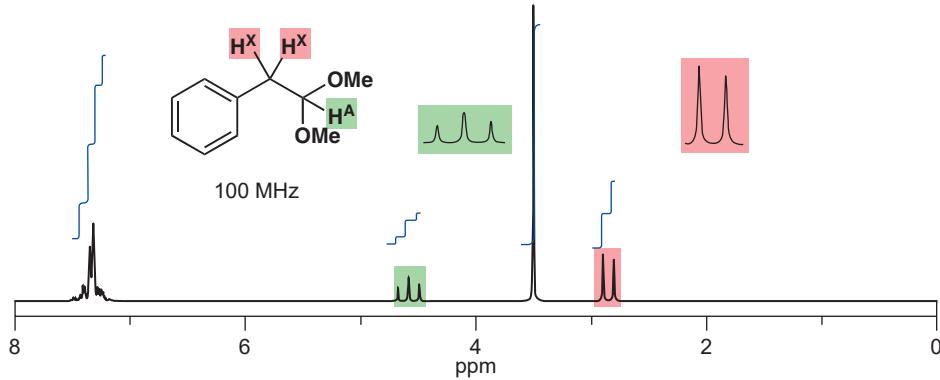
Now for the third way to describe coupling. If you look again at what the spectrum would be like without interaction between  $H^A$  and  $H^X$  you will see the pattern on the right, with the chemical shift of each proton clearly obvious.

But you don't see this because each proton couples with the other and splits its signal by an equal amount either side of the true chemical shift. The true spectrum has a pair of doublets each split by an identical amount. Note that no line appears at the true chemical shift, but it is easy to measure the chemical shift by taking the midpoint of the doublet.

So this spectrum would be described as  $\delta_H$  7.5 (1H, d,  $J$  4 Hz,  $H^A$ ) and 5.8 (1H, d,  $J$  4 Hz,  $H^X$ ). The main number gives the chemical shift in ppm and then, in brackets, comes the integration as the number of Hs, the shape of the signal (here 'd' for doublet), the size of coupling constants in Hz, and the assignment, usually related to a diagram. The integration refers to the combined area under both peaks in the doublet. If the doublet is exactly symmetrical, each peak integrates to half a proton. The combined signal, however complicated, integrates to the right number of protons.

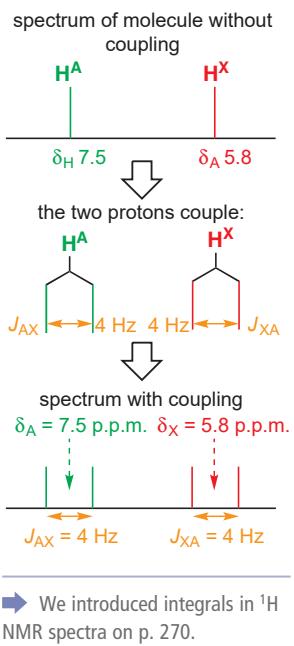
We have described these protons as A and X with a purpose in mind. A spectrum of two equal doublets is called an AX spectrum. A is always the proton you are discussing and X is another proton with a different chemical shift. The alphabet is used as a ruler: nearby protons (on the chemical shift scale—not necessarily nearby in the structure!) are called B, C, etc. and distant ones are called X, Y, etc. You will see the reason for this soon.

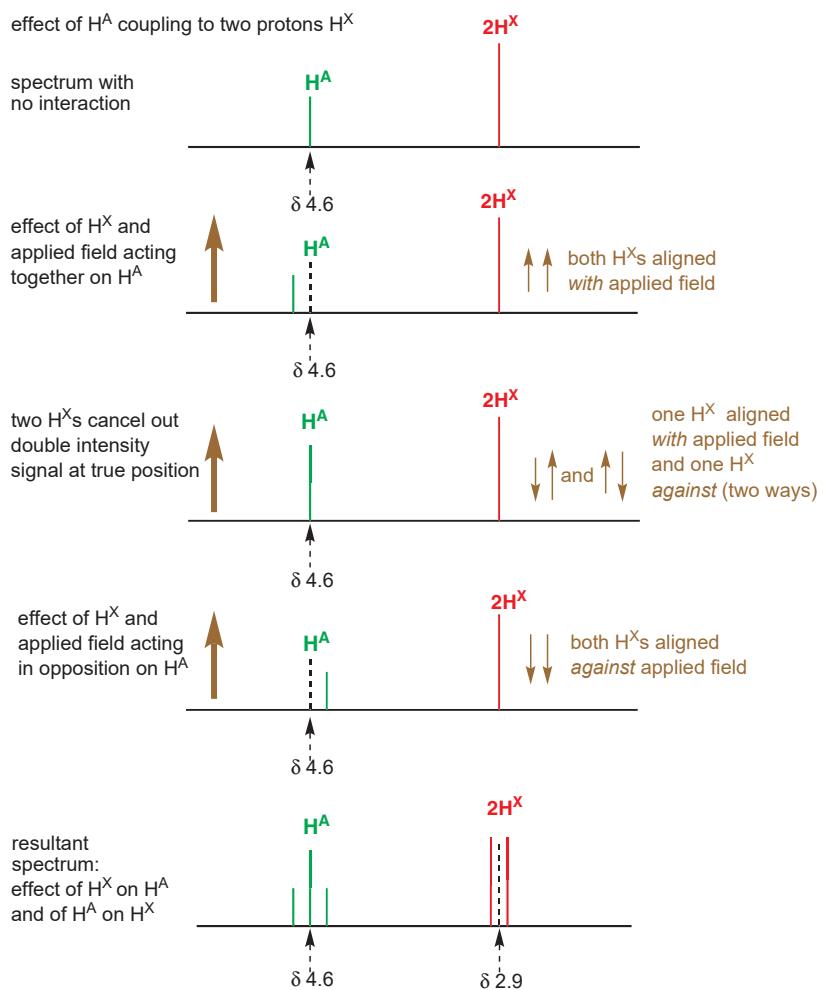
If there are more protons involved, the splitting process continues. Here is the NMR spectrum of a famous perfumery compound supposed to have the smell of 'green leaf lilac'. The compound is an acetal with five nearly identical aromatic protons at the normal benzene position (7.2–7.3 ppm) and six protons on two identical OMe groups.



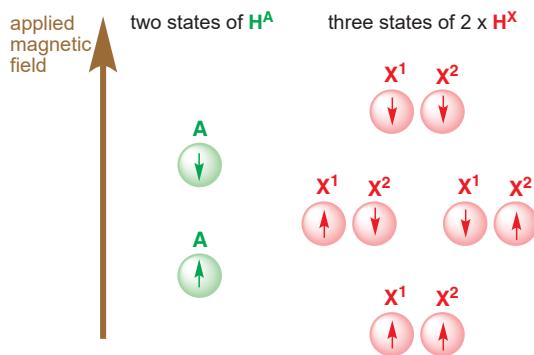
It is the remaining three protons that interest us. They appear as a 2H doublet at 2.9 ppm and a 1H triplet at 4.6 ppm. In NMR talk, triplet means three equally spaced lines in the ratio 1:2:1. The triplet arises from the three possible states of the two identical protons in the  $CH_2$  group.

If one proton  $H^A$  interacts with two protons  $H^X$ , it can experience protons  $H^X$  in three different possible states. Both protons  $H^X$  can be aligned with the magnet or both against. These states will increase or decrease the applied field just as before. But if one proton  $H^X$  is aligned with and one against the applied field, there is no net change to the field experienced by  $H^A$ . There are two arrangements for this (see diagram overleaf). We'll therefore see a signal of double intensity for  $H^A$  at the correct chemical shift, one signal at higher field and one at lower field. In other words, a 1:2:1 triplet.

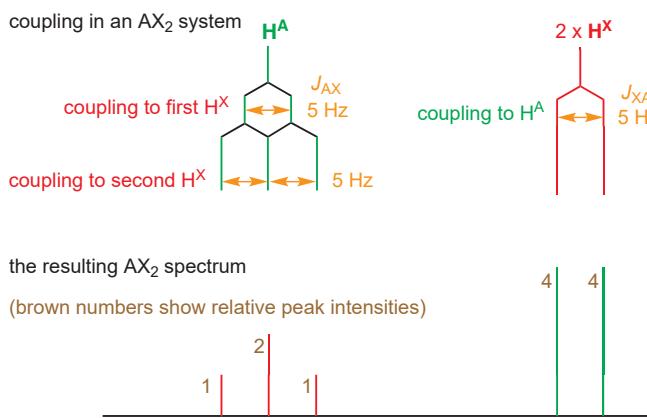




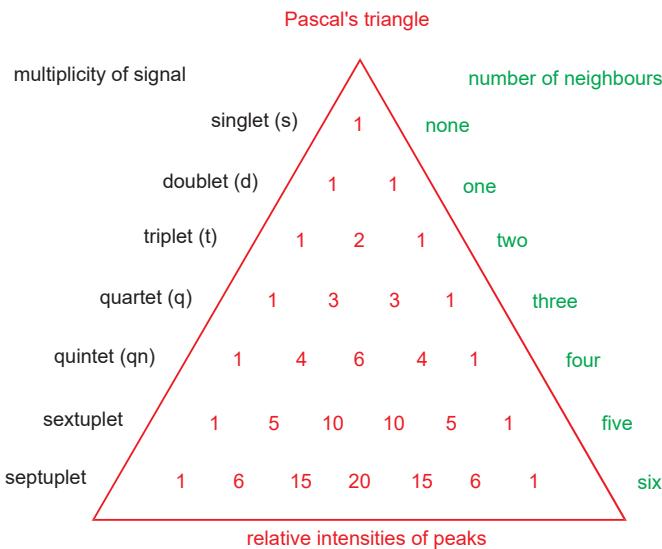
We could look at this result by our other methods too. There is one way in which both nuclei can be aligned with and one way in which both can be aligned against the applied field, but two ways in which they can be aligned one with and one against. Proton H<sup>A</sup> interacts with each of these states. The result is a 1:2:1 triplet.



Using our third way of seeing coupling to see how the triplet arises, we can just make the peaks split in successive stages:



If there are more protons involved, we continue to get more complex systems, but the intensities can all be deduced simply from Pascal's triangle, which gives the coefficients in a binomial expansion. If you are unfamiliar with this simple device, here it is.



### ■ Constructing Pascal's triangle

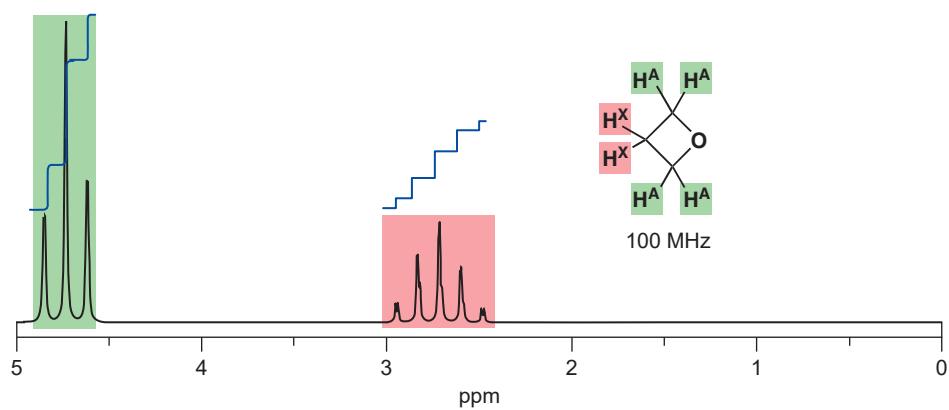
Put '1' at the top and then add an extra number in each line by adding together the numbers on either side of the new number in the line above. If there is no number on one side, that counts as a zero, so the lines always begin and end with '1'.

You can read off from the triangle what pattern you may expect when a proton is coupled to  $n$  equivalent neighbours. There are always  $n+1$  peaks with the intensities shown by the triangle. So far, you've seen 1:1 doublets (line 2 of the triangle) from coupling to 1 proton, and 1:2:1 triplets (line 3) from coupling to 2. You will often meet ethyl groups ( $\text{CH}_3\text{CH}_2\text{X}$ ), where the  $\text{CH}_2$  group couples to three identical protons and appears as a 1:3:3:1 quartet and the methyl group as a 1:2:1 triplet. In isopropyl groups,  $(\text{CH}_3)_2\text{CHX}$ , the methyl groups appear as a 6H doublet and the CH group as a septuplet.

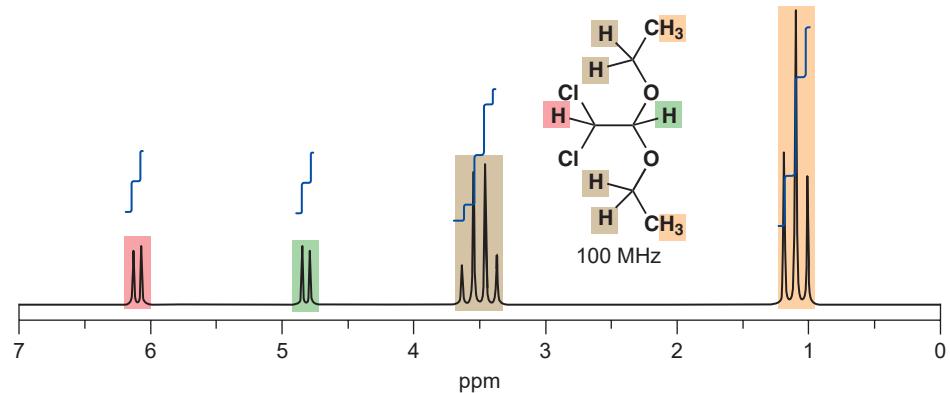
Here is a simple example: the four-membered cyclic ether oxetane. Its NMR spectrum has a 4H triplet for the two identical  $\text{CH}_2$  groups next to oxygen and a 2H quintet for the  $\text{CH}_2$  in the middle. Each proton  $\text{H}^X$  'sees' four identical neighbours ( $\text{H}^A$ ) and is split equally by them all to give a 1:4:6:4:1 quintet. Each proton  $\text{H}^A$  'sees' two identical neighbours  $\text{H}^X$  and is split into a 1:2:1 triplet. The combined integral of all the lines in the quintet together is 2 and of all the lines in the triplet is 4.

■ Identical protons do not couple with themselves

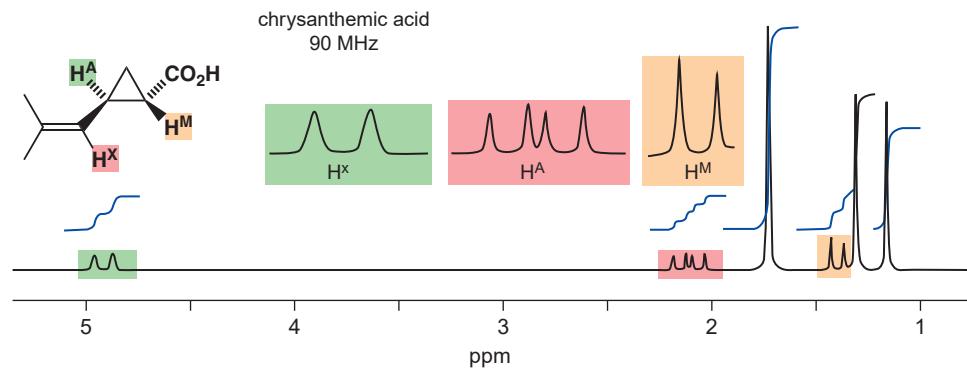
Remember, the coupling comes only from the *neighbouring* protons: it doesn't matter how many protons form the signal itself (2 for  $\text{H}^X$ , 4 for  $\text{H}^A$ )—it's how many are next door (4 next to  $\text{H}^X$ , 2 next to  $\text{H}^A$ ) that matters. The protons in each  $\text{CH}_2$  group are identical and cannot couple with each other. It's what you see that counts not what you are.



A slightly more complicated example is the diethyl acetal below. It has a simple AX pair of doublets for the two protons on the 'backbone' (red and green) and a typical ethyl group (2H quartet and 3H triplet). An ethyl group is attached to only one substituent through its  $\text{CH}_2$  group, so the chemical shift of that  $\text{CH}_2$  group tells us what it is joined to. Here the peak at 3.76 ppm can only be an OEt group. There are, of course, two identical  $\text{CH}_2$  groups in this molecule.



In all of these molecules, a proton may have had several neighbours, but all those neighbours have been the same. And therefore all the *coupling constants* have been the same. What happens when coupling constants differ? Chrysanthemic acid, the structural core of the insecticides produced by pyrethrum flowers, gives an example of the simplest situation—where a proton has two different neighbours.

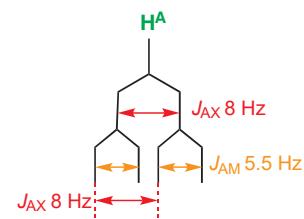
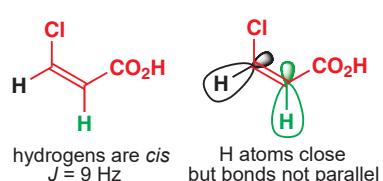
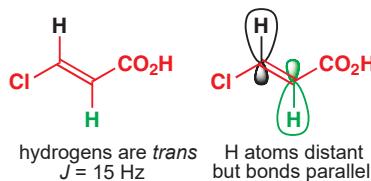


Chrysanthemic acid has a carboxylic acid, an alkene, and two methyl groups on the three-membered ring. Proton H<sup>A</sup> has two neighbours, H<sup>X</sup> and H<sup>M</sup>. The coupling constant to H<sup>X</sup> is 8 Hz, and that to H<sup>M</sup> is 5.5 Hz. We can construct the splitting pattern as shown on the right.

The result is four lines of equal intensity called a **doublet doublet** (or sometimes a **doublet of doublets**), abbreviation dd. The smaller coupling constant can be read off from the separation between lines 1 and 2 or between lines 3 and 4, while the larger coupling constant is between lines 1 and 3 or between lines 2 and 4. The separation between the middle two lines is not a coupling constant. You could view a double doublet as an imperfect triplet where the second coupling is too small to bring the central lines together: alternatively, look at a triplet as a special case of a double doublet where the two couplings are identical and the two middle lines coincide.

### Coupling is a through-bond effect

Do neighbouring nuclei interact through space or through the electrons in the bonds? We know that coupling is in fact a ‘through-bond effect’ because of the way coupling constants vary with the shape of the molecule. The most important case occurs when the protons are at either end of a double bond. If the two hydrogens are *cis*, the coupling constant *J* is typically about 10 Hz, but if they are *trans*, *J* is much larger, usually 15–18 Hz. These two chloro acids are good examples.



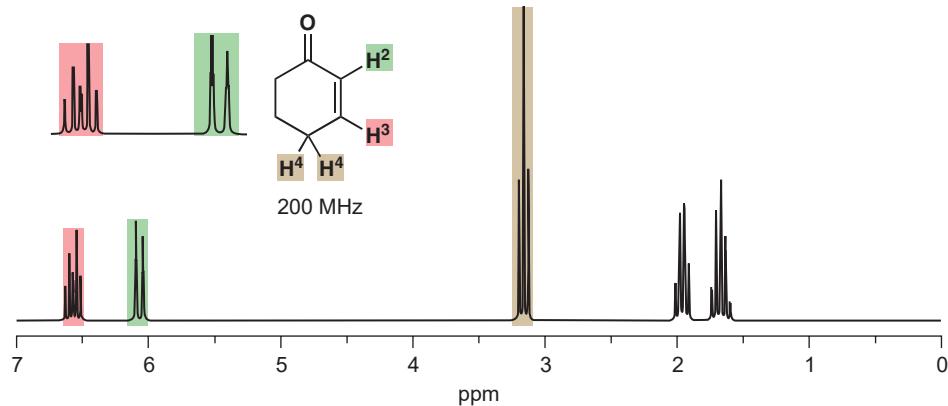
Abbreviations used for style of signal

Abbreviation	Meaning	Comments
s	singlet	
d	doublet	equal in height
t	triplet	should be 1:2:1
q	quartet	should be 1:3:3:1
dt	doublet triplet	other combinations too, such as dd, dq, tt
m	multiplet	a signal too complicated to resolve*

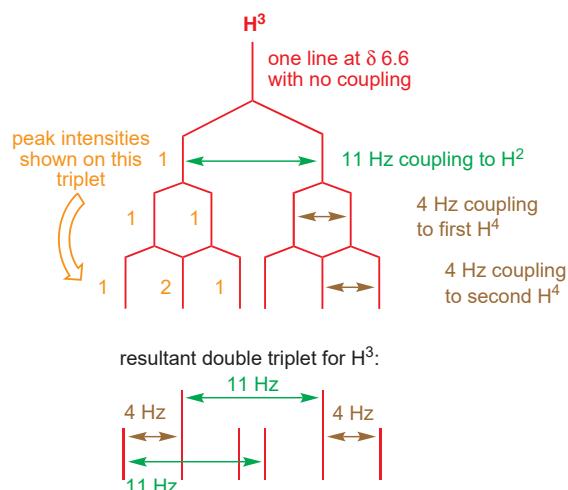
\* Either because it contains a complex coupling pattern or because the signals from different protons overlap.

If coupling were through space, the nearer *cis* hydrogens would have the larger *J*. In fact, coupling occurs *through the bonds* and the more perfect parallel alignment of the bonds in the *trans* compound provides better communication and a larger *J*.

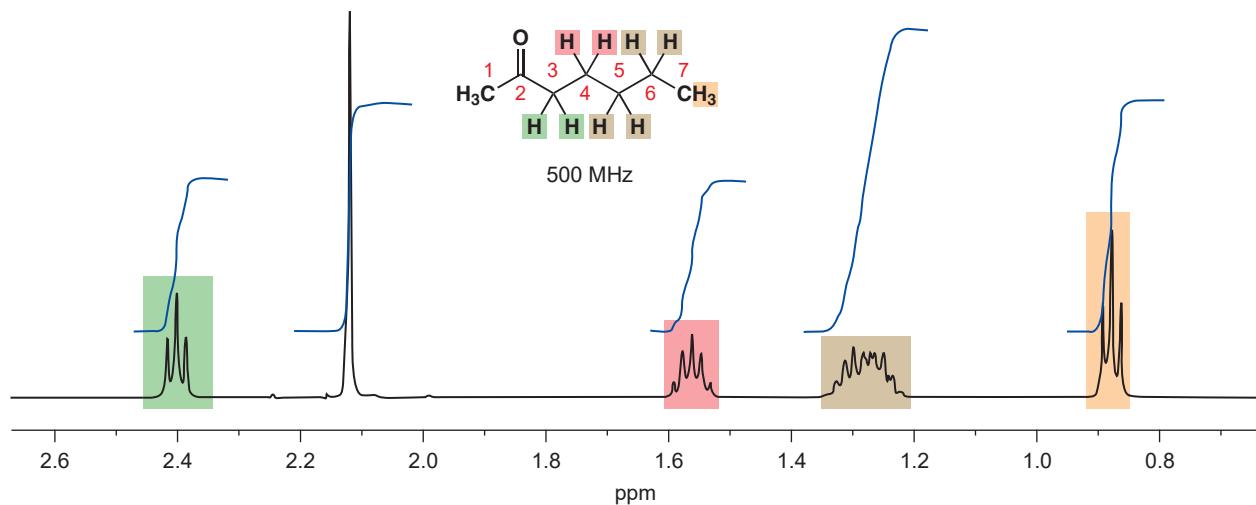
Coupling is at least as helpful as chemical shift in assigning spectra. When we said (p. 280) that the protons on cyclohexenone had the chemical shifts shown, how did we know? It was coupling that told us the answer. The proton next to the carbonyl group (H<sup>2</sup> in the diagram) has one neighbour (H<sup>3</sup>) and appears as a doublet with *J* = 11 Hz, just right for a proton on a double bond with a *cis* neighbour. The proton H<sup>3</sup> itself appears as a double triplet. Inside each triplet the separation of the lines is 4 Hz and the two triplets are 11 Hz apart.



The coupling of H<sup>3</sup> is as complex as you have seen yet, but it can be represented diagrammatically by the same approach we have taken before.



As coupling gets more and more complicated it can be hard to interpret the results, but *if you know what you are looking for* things do become easier. Here is the example of heptan-2-one. The green protons next to the carbonyl group are a 2H triplet (coupled to the two red protons) with  $J = 7$  Hz. The red protons themselves are next to four protons, and although these four protons are not identical the coupling constants are about the same: the red protons therefore appear as a 2H quintet, with a coupling constant also of 7 Hz. The brown signal is more complicated: we might call it a '4H multiplet' but in fact we know what it must be: the signals for the four brown protons on carbons 5 and 6 overlap, and must be made up of a 2H quintet (protons on C5) and a 2H sextet (protons on C6). We can see the coupling of the protons on C6 with the terminal methyl group because the methyl group (orange) is a 3H triplet (also with a 7 Hz coupling constant).



### Coupling constants depend on three factors

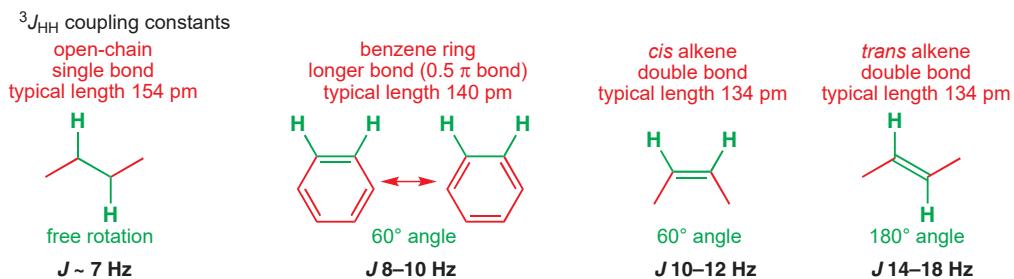
The coupling constants in cyclohexenone were different, but all the coupling constants in heptanone are about the same—around 7 Hz. Why?

#### ● Factors affecting coupling constants

- Through-bond distance between the protons.
- Angle between the two C-H bonds.
- Electronegative substituents.

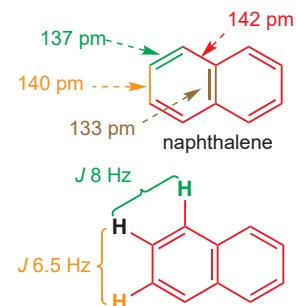
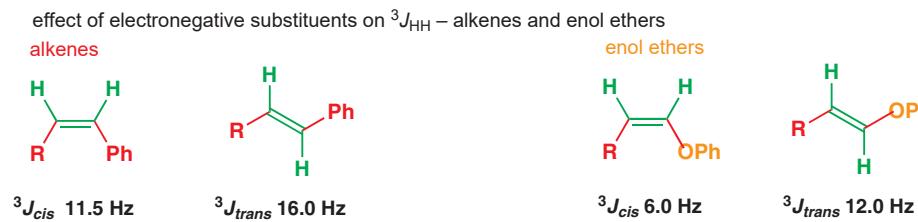
The coupling constants we have seen so far have all been between hydrogen atoms on neighbouring carbon atoms—in other words, the coupling is through three bonds ( $\text{H}-\text{C}-\text{C}-\text{H}$ ) and is designated  ${}^3J_{\text{HH}}$ . These coupling constants  ${}^3J_{\text{HH}}$  are usually about 7 Hz in an open-chain, freely rotating system such as we have in heptanone. The C–H bonds vary little in length but in cyclohexenone the C–C bond is a double bond, significantly shorter than a single bond. Couplings ( ${}^3J_{\text{HH}}$ ) across double bonds are usually larger than 7 Hz (11 Hz in cyclohexenone).  ${}^3J_{\text{HH}}$  couplings are called *vicinal couplings* because the protons concerned are on neighbouring carbon atoms.

Something else is different too: in an open-chain system we have a time average of all rotational conformations (we will look at this in the next chapter). But across a double bond there is no rotation and the angle between the two C–H bonds is fixed: they are always in the same plane. In the plane of the alkene, the C–H bonds are either at  $60^\circ$  (*cis*) or  $180^\circ$  (*trans*) to each other. Coupling constants in benzene rings are slightly less than those across *cis* alkenes because the bond is longer (bond order 1.5 rather than 2).



In naphthalenes, there are unequal bond lengths around the two rings. The bond between the two rings is the shortest, and the lengths of the others are shown. Coupling across the shorter bond (8 Hz) is significantly stronger than coupling across the longer bond (6.5 Hz).

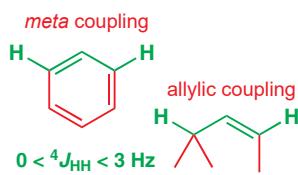
The effect of the third factor, electronegativity, is easily seen in the comparison between ordinary alkenes and alkenes with alkoxy substituents, known as enol ethers. We are going to compare two pairs of compounds with a *cis* or a *trans* double bond. One pair has a phenyl group at one end of the alkene and the other has an OPh group. For either pair, the *trans* coupling is larger than the *cis*, as you would now expect. But if you compare the two pairs, the enol ethers have much smaller coupling constants. The *trans* coupling for the enol ethers is only just larger than the *cis* coupling for the alkenes. The electronegative oxygen atom is withdrawing electrons from the C–H bond in the enol ethers and weakening communication through the bonds.



Conjugation in naphthalene was discussed in Chapter 7, p. 161.

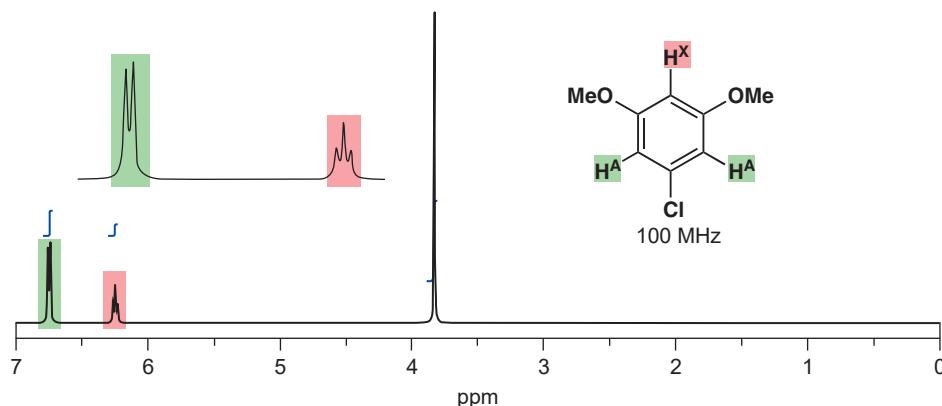
## Long-range coupling

When the through-bond distance gets longer than three bonds, coupling is not usually seen. To put it another way, four-bond coupling  ${}^4J_{\text{HH}}$  is usually zero. However, it is seen in some special cases, the most important being *meta* coupling in aromatic rings and allylic coupling in alkenes. In both, the orbitals between the two hydrogen atoms can line up in a zig-zag

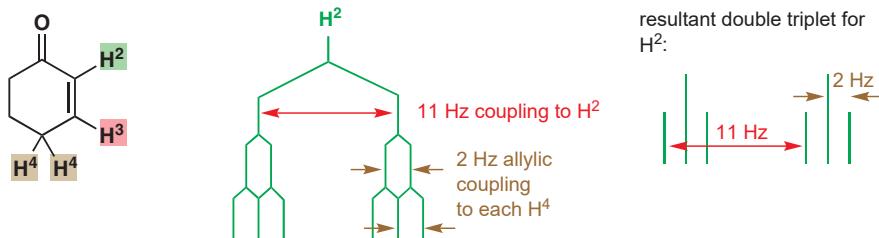


fashion to maximize interaction. This arrangement looks rather like a letter 'W' and this sort of coupling is called W-coupling. Even with this advantage, values of  $^4J_{\text{HH}}$  are usually small, about 1–3 Hz.

*Meta* coupling is very common when there is *ortho* coupling as well, but here is an example where there is no *ortho* coupling because none of the aromatic protons have immediate neighbours—the only coupling is *meta* coupling. There are two identical H<sup>A</sup>s, which have one *meta* neighbour and appear as a 2H doublet. Proton H<sup>X</sup> between the two MeO groups has two identical *meta* neighbours and so appears as a 1H triplet. The coupling is small ( $J \sim 2.5$  Hz).



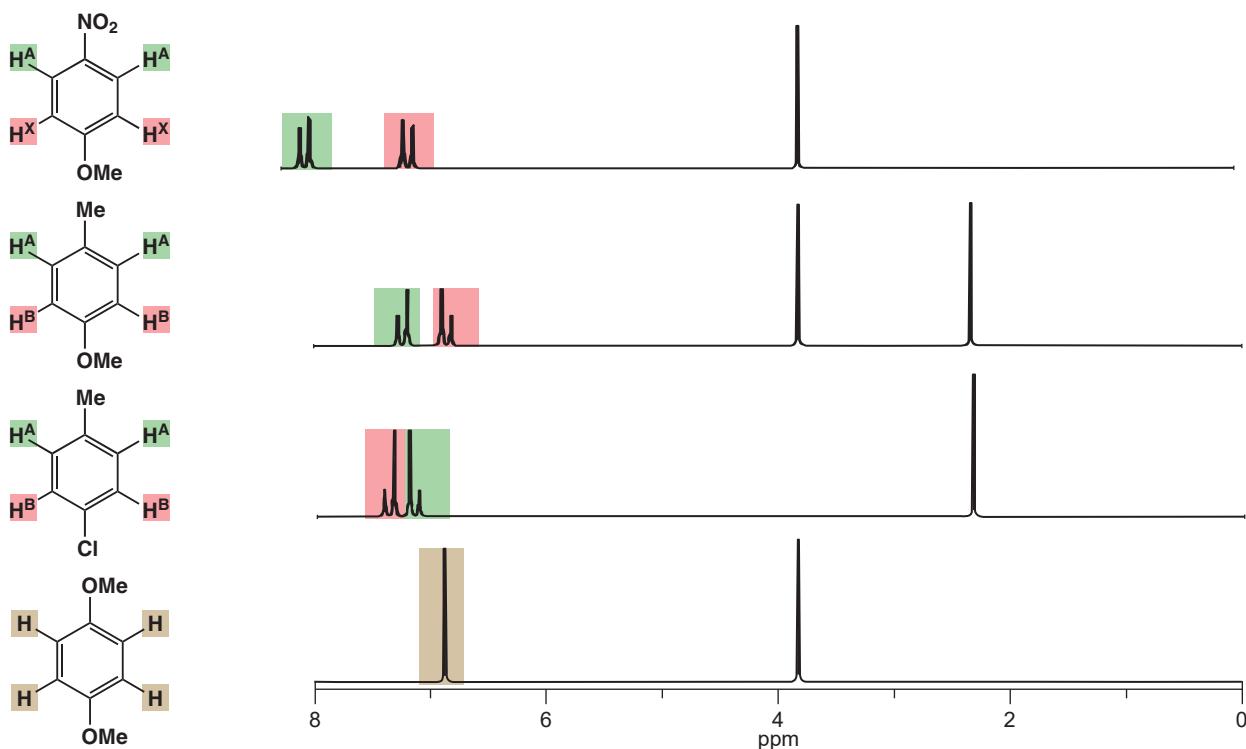
We have already seen a molecule with allylic coupling. We discussed in some detail why cyclohexenone has a double triplet for H<sup>3</sup>. But it also has a less obvious double triplet for H<sup>2</sup>. The triplet coupling is less obvious since  $J$  is small (about 2 Hz) because it is  $^4J_{\text{HH}}$ —allylic coupling to the CH<sub>2</sub> group at C4. Here is a diagram of the coupling, which you would be able to spot in an expansion of the cyclohexenone spectrum on p. 293.



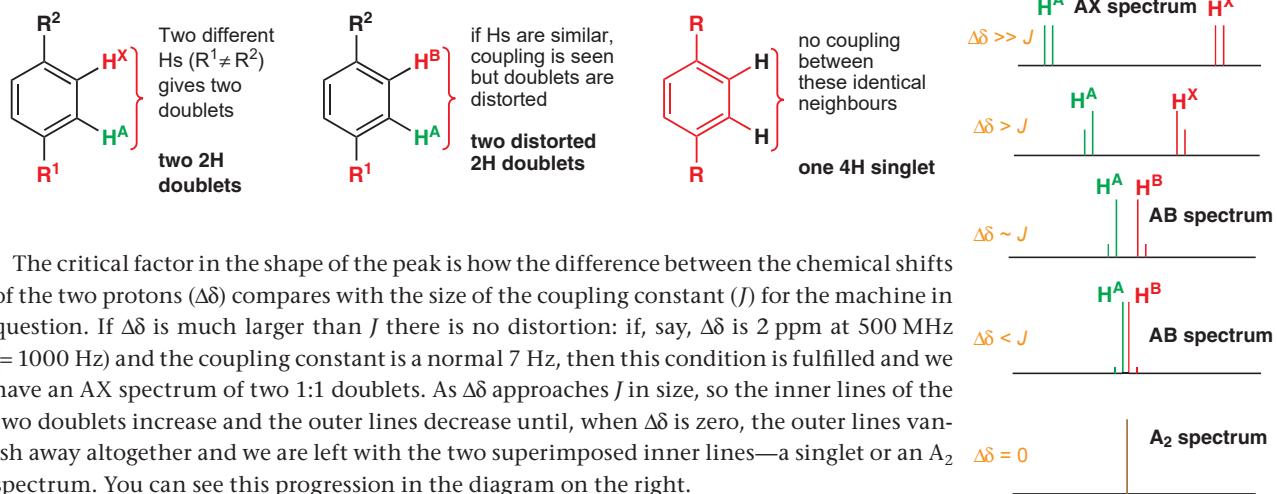
### Coupling between similar protons

Identical protons do not couple with each other. The three protons in a methyl group may couple to some other protons, but *never* couple with each other. They are an A<sub>3</sub> system. Identical neighbours do not couple either. Turn back to p. 271 and you'll see that even though each of the four protons on the *para*-disubstituted benzenes has one neighbour, they appear as one singlet because every proton is identical to its neighbour.

We have also seen how two different protons forming an AX system give two separate doublets. Now we need to see what happens to protons in between these two extremes. What happens to two similar neighbours? As two protons get closer and closer together, do the two doublets you see in the AX system suddenly collapse to the singlet of the A<sub>2</sub> system? You have probably guessed that they do not. The transition is gradual. Suppose we have two different neighbours on an aromatic ring. The spectra below show what we see. These are all 1,4-disubstituted benzene rings with different groups at the 1 and 4 positions.



You'll notice that when the two doublets are far apart, as in the first spectrum, they look like normal doublets. But as they get closer together the doublets get more and more distorted, until finally they are identical and collapse to a 4H singlet.



■ You may see this situation described as an 'AB quartet'. It isn't! A quartet is an exactly equally spaced 1:3:3:1 system arising from coupling to three identical protons, and you should avoid this misleading usage.

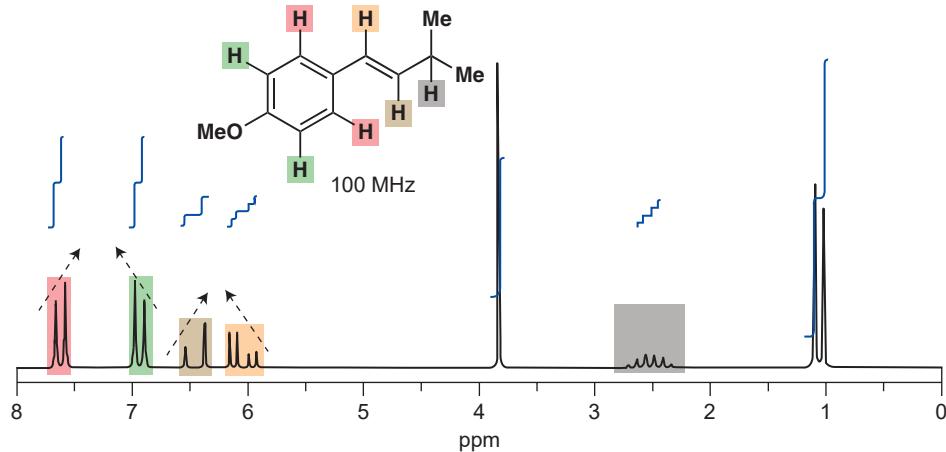
We call the last stages, where the distortion is great but the protons are still different, an AB spectrum because you cannot really talk about  $\text{H}^{\text{A}}$  without also talking about  $\text{H}^{\text{B}}$ . The two inner lines may be closer than the gap between the doublets or the four lines may all be equally spaced. Two versions of an AB spectrum are shown in the diagram—there are many more variations.

It is a generally useful tip that a distorted doublet 'points' towards the protons with which it is coupled.



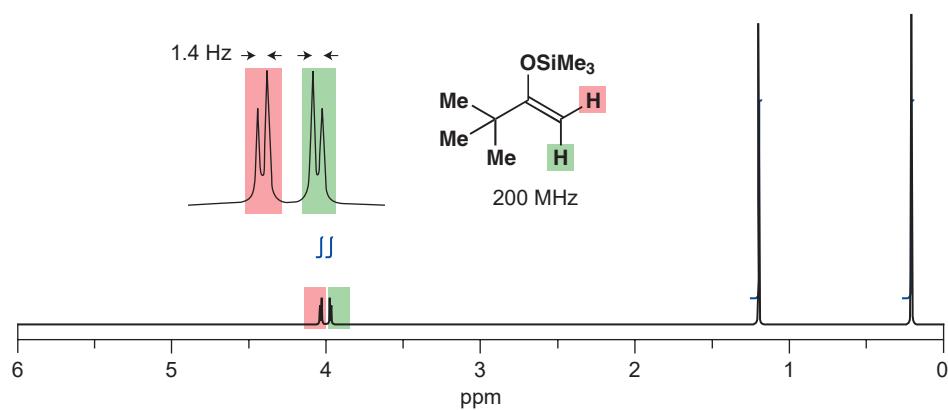
Or, to put it another way, the AB system is 'roofed' with the usual arrangement of low walls and a high middle to the roof. Look out for doublets (or any other coupled signals) of this kind.

We shall end this section with a final example illustrating *para*-disubstituted benzenes and roofing as well as an ABX system and an isopropyl group. The aromatic ring protons form a pair of distorted doublets (2H each), showing that the compound is a *para*-disubstituted benzene. Then the alkene protons form the AB part of an ABX spectrum. They are coupled to each other with a large (*trans*)  $J = 16$  Hz and one is also coupled to another distant proton. The large doublets are distorted (AB) but the small doublets within the right-hand half of the AB system are equal in height. The distant proton X is part of an *i*-Pr group and is coupled to  $\text{H}^{\text{B}}$  and the six identical methyl protons. Both Js are nearly the same so it is split by seven protons and is an octuplet. It looks like a sextuplet because the intensity ratios of the lines in an octuplet would be 1:7:21:35:35:21:7:1 (from Pascal's triangle) and it is hardly surprising that the outside lines disappear.



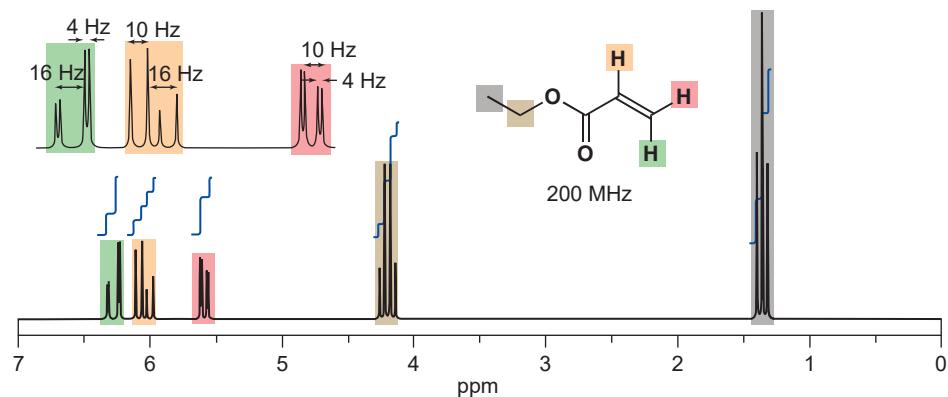
### Coupling can occur between protons on the same carbon atom

We have seen cases where protons on the same carbon atom are different: compounds with an alkene unsubstituted at one end. If these protons are different (and they are certainly near to each other), then they should couple. They do, but in this case the coupling constant is usually very small. Here is the spectrum of an example you met on p. 281.



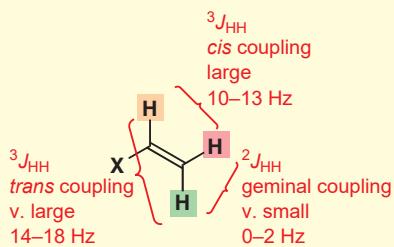
The small 1.4 Hz coupling is a  ${}^2J_{\text{HH}}$  coupling between two protons on the same carbon that are different because there is no rotation about the double bond.  ${}^2J_{\text{HH}}$  coupling is called *geminal coupling*.

This means that a monosubstituted alkene (a vinyl group) will have characteristic signals for each of the three protons on the double bond. Here is the example of ethyl acrylate (ethyl propenoate, a monomer for the formation of acrylic polymers). The spectrum looks rather complex at first, but it is easy to sort out using the coupling constants.

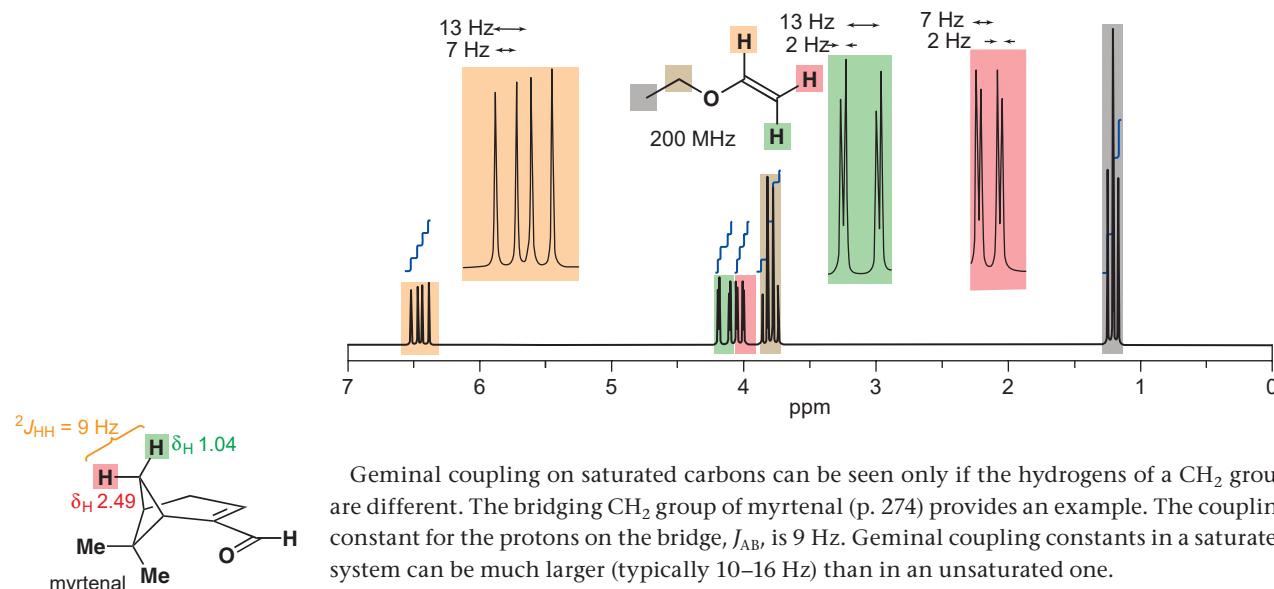


The largest  $J$  (16 Hz) is obviously between the orange and green protons (*trans* coupling), the medium  $J$  (10 Hz) is between the orange and red (*cis* coupling), and the small  $J$  (4 Hz) must be between the red and green (geminal). This assigns all the protons: red, 5.60 ppm; green, 6.40 ppm; orange, 6.11 ppm. Assignments based on coupling are more reliable than those based on chemical shift alone.

### ● Coupling constants in a vinyl group



Ethyl vinyl ether is a reagent used for the protection of alcohols. All its coupling constants are smaller than is usual for an alkene because of the electronegativity of the oxygen atom, which is now joined directly to the double bond. It is still a simple matter to assign the protons of the vinyl group because couplings of 13, 7, and 2 Hz must be *trans*, *cis*, and geminal, respectively. In addition, the orange H is on a carbon atom next to oxygen and so goes downfield while the red and green protons have extra shielding from the conjugation of the oxygen lone pairs (see p. 281).

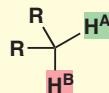


Geminal coupling on saturated carbons can be seen only if the hydrogens of a  $\text{CH}_2$  group are different. The bridging  $\text{CH}_2$  group of myrtenal (p. 274) provides an example. The coupling constant for the protons on the bridge,  $J_{\text{AB}}$ , is 9 Hz. Geminal coupling constants in a saturated system can be much larger (typically 10–16 Hz) than in an unsaturated one.

### ● Typical coupling constants

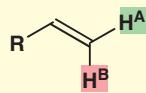
- **geminal  $^2J_{\text{HH}}$**

saturated



10–16 Hz

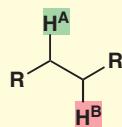
unsaturated



0–3 Hz

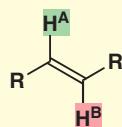
- **vicinal  $^3J_{\text{HH}}$**

saturated



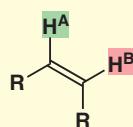
6–8 Hz

unsaturated *trans*

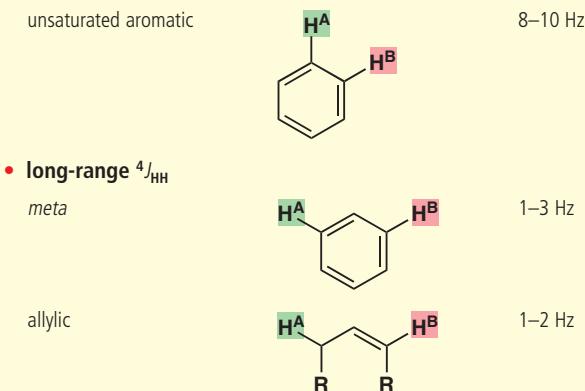


14–18 Hz

unsaturated *cis*



10–12 Hz



## To conclude

You have now met, in Chapter 3 and this chapter, all of the most important spectroscopic techniques available for working out the structure of organic molecules. We hope you can now appreciate why proton NMR is by far the most powerful of these techniques, and we hope you will be referring back to this chapter as you read the rest of the book. We shall talk about proton NMR a lot, and specifically we will come back to it in detail in Chapter 18, where we will look at using all of the spectroscopic techniques in combination, and in Chapter 31, when we look at what NMR can tell us about the shape of molecules.

## 延伸阅读

A reminder: you will find it an advantage to have one of the short books on spectroscopic analysis to hand as they give explanations, comprehensive tables of data, and problems. We recommend *Spectroscopic Methods in Organic Chemistry* by D. H. Williams and Ian Fleming, McGraw-Hill, London, 6th edn, 2007.

A simple introduction is the Oxford Primer *Introduction to Organic Spectroscopy*, L. M. Harwood and T. D. W. Claridge, OUP, Oxford, 1996. A more advanced source of practical uses of stereochemistry is the Oxford Primer *Stereoselectivity in Organic Synthesis*, Garry Procter, OUP, Oxford, 1998.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 14 立体化学

## 联系

### 基础

- 绘制有机分子 ch2
- 有机结构 ch4
- 对羰基的亲核加成 ch6
- 羰基上的亲核取代 ch10 & ch11

### 目标

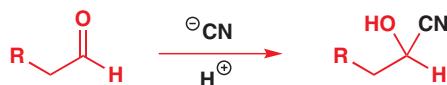
- 分子的三维形状
- 带有镜像的分子
- 带有对称性的分子
- 如何分离镜像分子
- 非对映异构体/非对映体
- 形状和生物活性
- 如何绘制立体化学

### 展望

- 饱和 C 上的亲核取代 ch15
- 构象 ch16
- 消除反应 ch18
- 控制烯烃几何结构 ch27
- 控制环状化合物的立体化学 ch32
- 非对映选择性 ch33
- 不对称合成 ch41
- 生命的化学 ch42

## 有些化合物可以以一对镜像的形式存在

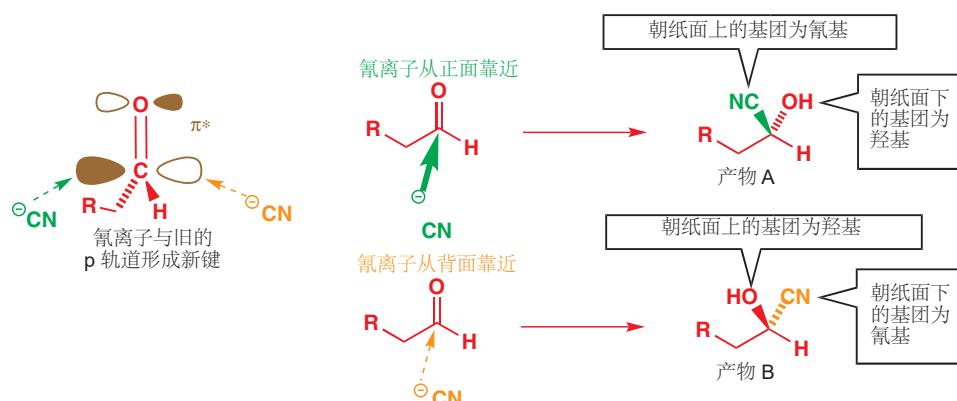
回想您在很早 (Chapter 6) 就遇到的一个反应，醛与氰离子反应，生成一个包含氨基和羟基的化合物。



这个反应生成了多少个化合物？您可能会直率地说是一个——只有一种醛、一种氰离子，和一种可能的机理。但这种分析并不完全正确。我们第一次讨论这一反应的时候忽略了一点，那就是醛的羰基有两个可被进攻的面，而这一点是当时的我们认为无关紧要的。如下所示，氰离子从这两种侧面进攻得到的产物，是截然不同的。

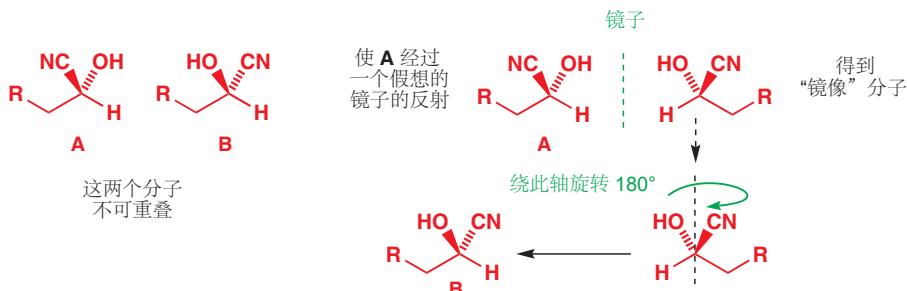
Interactive results of cyanide addition to carbonyls

■ 实楔形键朝向纸面前方，指向我们；虚楔形键朝向纸面后方，远离我们。

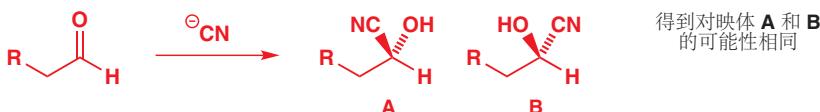


Chapter 6 (pp. 125–7) 中介绍过此反应的原理, 即氰离子进攻垂直于醛分子平面的  $\pi^*$  轨道(以和 C 原子旧的 p 轨道成键). 假如平面三角型的醛在纸平面上, 那么它有两个面都可以接受进攻, 氰离子从纸面上, 或下进攻, 很自然地会使之转变为氰基凸出, 或凹下纸平面的两种形式。

这两者是不同的化合物吗? 您可以通过搭建模型尝试, 无论如何排列, 这二者都不能完全重叠, 因此虽然它们的原子相对位置(构造)相同, 但它们的立体结构(构型)是相区别的。它们是两种不同的结构, 也是两种不同的化合物。而每一个都是另一个的镜像(mirror image): 让其中一个结构, A, 在镜子中反射, 得到的图像与 B 的结构是一样的。



对于这样的一对构造相同、构型不同, 且互为镜像的异构体, 我们称之为**对映异构体 (enantiomer, 简称对映体)**。一个不能和其镜像完全重叠的结构, 会同时存在与其构造相同的一对对映体, 这样的结构是**手性的 (chiral adj., chirality n.)**。在这个反应中, 氰离子从“正面”、“背面”进攻的可能性没有任何区别, 因此我们得到的产物是两个对映体的 50:50 混合物。



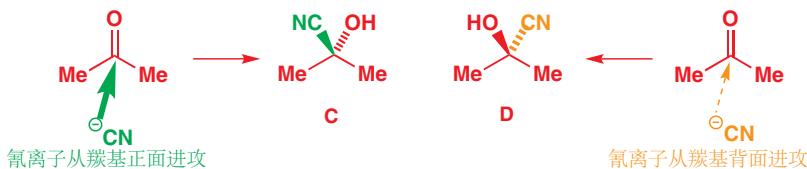
### ● 对映体和手性

- 对映体指一对互为镜像的结构, 它们的构造相同, 构型相反。
- 手性的结构不能与其镜像完全重叠。

如果说我们对这个反应稍稍变动, 改为氰离子对丙酮的加成。



同样生成了一个氰醇分子。您可能会设想: 这个反应仍然会由于进攻方向的不同而产生两种结构, 如下图 C 和 D.



然而, 与上一个反应不同的是, 第一种结构经过旋转是可以与第二种结构(其镜像)完全重叠的, 因此它们事实上是一模一样的结构。



■ 本章涉及了大量的三维空间中的操作, 而本书只能以二维平面的形式展现。在学习初期, 我们建议您通过制作分子模型参与我们的讨论。这种练习也能锻炼您的空间想象能力, 最终您将能够不依靠模型, 想象这些内容。

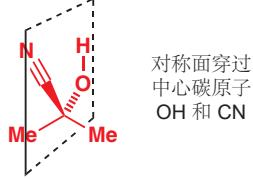
Interactive aldehyde cyanohydrin structures—chiral

Interactive acetone cyanohydrin structure—achiral

请确保您明白了这一点：**C** 和 **D** 是完全一样的分子，与互为镜像的 **A** 和 **B** 不同。真实世界中的分子可以平移和旋转，但不能反演（镜像）；而能否在真实世界中能否将两种形式完全重叠，是界定它们是否为同一结构的根本方法。仅通过第一类对称操作（实际操作）就可以完全重叠的两种形式，只是同一结构的不同画法。和自己的镜像可以完全重叠的结构是非手性的（achiral）。

● 非手性的结构可以与其镜像完全重叠。

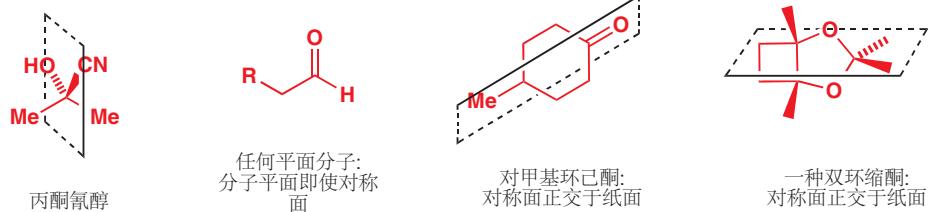
### 手性分子中不存在对称面



有些化合物可以与其镜像完全重叠，而有些不能，它们最本质的区别是什么？答案是对称性（主要是对称面），含对称面的分子都不具有手性，具有手性的分子都不含有对称面。最左侧图的丙酮氰醇有一个穿过分子的对称面，这个对称面将中心碳原子及其取代基分成了两个部分，OH 和 CN 基各自与一个甲基在一侧。另外，一切平面型分子（例如简单的醛）都不存在手性，因为分子平面同时也是一个对称面。一部分环状分子有贯穿相对的两个原子的一个对称面，如下图的对甲基环己酮结构，它的对称面贯穿甲基、羰基，以及这两个氢原子（没有画出）。最右侧的双环缩酮看起来十分复杂，但仍可发现一个将分子一分为二的对称面。这些分子都是非手性的。

Interactive molecules with a plane of symmetry

#### 含有对称面的分子



另一方面，醛氰醇分子中不含任何对称面：对于纸平面，则 OH 在一端而 CN 在另一端；对于垂直于纸平面的屏幕，则 H 在一端而 RCH<sub>2</sub> 在另一端。这个化合物没有对称面，因此它和另一结构互为对映异构体。



■ 稍后我们会介绍一个稍微不那么重要的分子对称性，即对称中心。没有对称面，而有对称中心的分子也不具有手性。

#### ● 对称面与手性

- 任何没有对称面的分子是手性的（并不严谨），存在两种互为镜像的分子（对映异构体）。
- 任何含有对称面的分子是非手性的，它们与它们的镜像为同一分子。

说到“结构”，我们并不仅仅指化学结构：以上的规则同样适用于生活用品。从我们熟悉的一些物件中找到例子也能加深我们的理解。看看您的周围，找到一个手性的物件——一把剪刀，一个螺丝钉，一辆汽车，任何写了字的东西，比如这张纸。再找找那些非手性的，有对称面的物件——一个普通的杯子，一口平底锅，一把椅子，以及大多数没有写过字的简单产品。在这其中，您身边最重要的手性的物件是您互为一对对映体的两只手。

### 手套，手和袜子

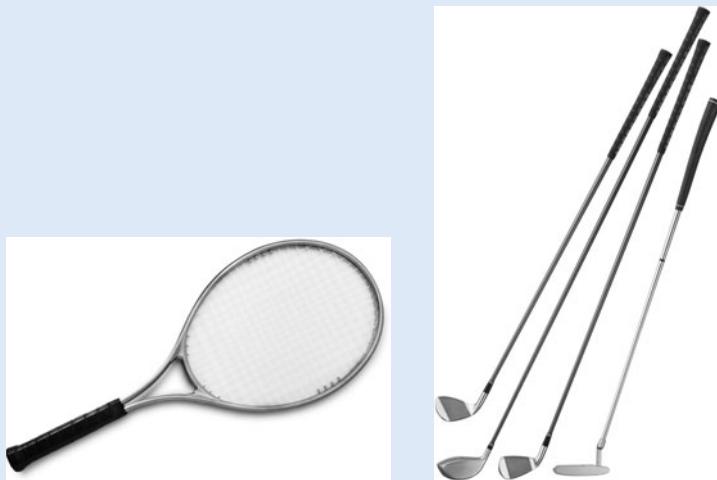


大多数手套以一套镜像的形式出现：只有左手套适合左手，只有右手套适合右手。手套，以及其中的手的这种性质，就是“手性 (chiral)”这一词的最初来源——“cheir”在希腊语中指“手”。手和手套都是右手指的，它们不含对称面，左手套也不能与其镜像（右手套）完全重叠。但袜子（通常）和前面两者不同：虽然有时候，我们很难找到两只颜色匹配的袜子，但一旦您找到了，您从来不会顾及哪只袜子对应哪只脚，这是因为袜子是非手性的。一堆袜子由两个完全相同的物品组成，每个物品都含有一个对称面。

古埃及人不太注意手的手性，它们画作中的人，甚至是法老，都经常有两只左手或者两只右手——它们似乎没有注意到这一特点。



### 网球拍和高尔夫球杆



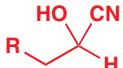
如果您是想玩高尔夫球的左利手者，那么您要么适应用右手打球，要么去找一套左手杆。如果您看过高尔夫球杆，那么您会明白，它没有对称面，因此显然是手性的；它们可以以两个对映体存在。但网球拍与之相反。左手持拍的运动员和右手持拍的运动员使用完全相同的球拍，一些运动员交替使用左右手持同一球拍。任何一款网球拍的镜像与其本身是一致的，它含有一个对称面，因而没有手性。

■ 虽然如上结论可以在大多数情况下帮您判断，但它并不完整（严谨）：我们很快会来到有关对称中心的介绍（p. 321）。

### ● 总结

- 含有对称面的结构是非手性的，可以与其镜像完全重叠，无对映体之分。
- 不含对称面的结构是手性的，不能与其镜像完全重叠，因此它们是两种不同的化合物（一对对映体）。

## 手性中心



回到氰离子和醛的反应，上文我们已经解释了其产物的手性，它以一对对映体存在。对映体显然是一类异构体，而且，它们是一对以不同方式连接相同部分而得到的化合物。对于这类仅在空间排列上不同的异构体，我们称其为**立体异构体 (stereoisomers)**，也称**构型异构体**。立体异构体间的区别不表现于原子的连接次序、连接方式上，仅表现在分子的整体形状上。

### ● 立体异构体 (构型异构体) 和构造异构体

异构体（同分异构体）描述的是每种原子数目相同，但排列方式不同的化合物。如果原子连接次序和连接方式（构造），它们被称为构造异构体（constitutional isomers）。如果连接次序和

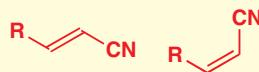
连接方式均相同（而构型不同），它们才是立体异构体。对映体是立体异构体，双键的 E、Z 构型也是立体异构体。我们稍后会遇到其他一些立体异构体的例子。



构造异构体：每种原子数目相同  
但连接次序或连接方式不同。



对映体



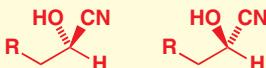
E/Z 异构体 (双键异构)

立体异构体：连接次序和连接方式相同，但在空间上排列方式不同。

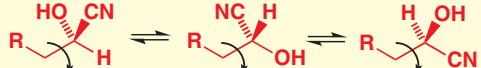
现在我们会简要地向您介绍另一组概念，即**构型 (configuration)** 和 **构象 (conformation)**，您会在 Chapter 16 中学习有关它们更多的细节。所谓的异构体即指两个真正不同的分子：它们不能在不破坏化学键的情况下相互转化，立体异构体（构型异构体）具有这一特点。构象指的是分子的空间排布形象；分子绕单键旋转就会产生另一种构象；构象的不同也是排列方式的暂时不同，任何分子都具有多种构象（本书中不将构象作为一种异构体）。类比，每个人类都有一种**构型**：手臂分别连在两个肩膀上；但每个人类都可以摆出不同的**构象**：例如手臂交叉、举起，指向某一位置，挥手等等。

### ● 构型和构象

- 分子构型的转变通常需要经过键的断裂（和重组）。
- 有不同构型的结构是不同的分子。
- 分子构象的转变意味着绕键旋转，而不是键的断裂。
- 有相同构型、不同构象的结构是易于转化的，它们不是不同的分子。



两种构型：手性分子转化为自己的  
对映体需要一根键的断裂



同一对映体的三种构象：  
由其一转化为另一个需要绕键旋转  
全部三个都是同一分子

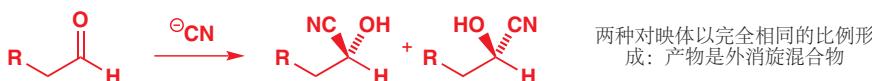
刚刚，我们判断醛氰醇具有手性，依据的是分子中没有对称面。事实上，对于分子中任意一个四面体碳原子，只要它所连的四个基团是不同的，那么这个分子自然没有对称面，因而就是手性的。例如醛氰醇中同时连有 OH, CN, RCH<sub>2</sub>, 和 H 的碳原子使氰醇有手性。对于这样的碳原子，我们称其为**手性中心 (stereogenic/chiral centre)**，有手性中心的分子就是手性的。丙酮氰醇是没有手性的，这是因为它的中心碳原子上有两个相同甲基（其他的碳原子也不是手性中心）。



- 如果一个分子中含有携带四个不同基团的碳原子，分子中就不会出现对称面，因此分子具有手性。携带四个不同基团的碳原子是手性中心。

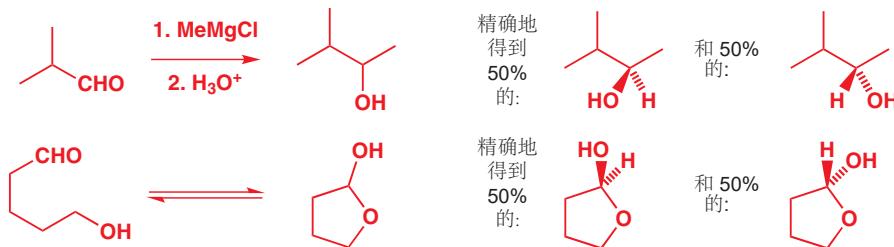
您不久后会看到包含多个手性中心的化合物不都是手性的(内消旋化合物)。

上文中我们还分析了产生醛氰醇两种对映体的原因，即氰离子进攻醛羰基的两个面。对于这两个面，氰离子没有理由更偏爱某一个，因此该反应得到的是相同比例的两种对映体的混合物。我们将一对对映体同等比例的混合物称为外消旋混合物 (racemic mixture)，意思是每个分子都有旋光性，但混合物整体的旋光性在外部消失，旋光性即手性)。



- 外消旋混合物指一对对映体以相同比例组成的混合物。这一原则十分重要：如果一个反应的原料是非手性的，而其产物却是手性的，那么该反应的产物以两种对映体的外消旋混合物存在。

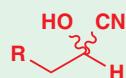
下面是更多的通过非手性原料合成手性产物的反应例子。每种情况都坚守如上原则——得到相同比例的两种对映体的混合物(外消旋混合物)。



### 自然界中的许多手性分子只以其中一种对映体存在

让我们转向一些简单，但却有手性的分子——天然的氨基酸。所有氨基酸都含一个同时携带氨基、羧基、氢原子和 R 基团(随氨基酸种类不同而不同)的碳原子。因此除非 R=H(即甘氨酸)，氨基酸都带有一个手性中心，并不含对称面。

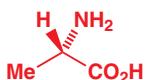
当我们不用楔形键表示分子的三维结构时，就意味着我们在同时讨论其两种对映体。另外也通常使用波浪线表示如上这种情况，即模棱两可的，两种异构体(构型)均存在的情况。不过，有的时候波浪键也会被用于表示一种单一，却未知的构型(即其中一种对映体)。



氨基酸可以在实验室中直接地合成，比如下面的图示是一种使用 Strecker 氨基酸合成法(您已在 Chapter 11 遇到)合成丙氨酸的方法：

实验室中以乙醛为原料合成外消旋丙氨酸





植物中提取的丙氨酸只有如上(两种对映体中的)一种

使用这种方法合成的丙氨酸必定是外消旋的, 因为原料是非手性的, 而产物是手性的。然而, 我们从自然资源——例如通过水解植物蛋白——得到的丙氨酸仅有左图的一种立体构型(并不是外消旋的)。类似的, 如果一份样品仅含该手性化合物一对对映体中的一种, 那么这份样品是光学纯的(enantiomerically pure, 或 optically pure)。我们通过观察 X-ray 晶体结构来判断。

### 丙氨酸的对映体

事实上, 自然界有时候也(但很少)使用丙氨酸的另一种对映体, 例如在细菌细胞壁的构建中。一些抗生素(例如万古霉素)就利用对这些“非自然的”丙氨酸的识别, 以达到破坏细菌细胞壁的目的。

### 手性和光学纯

继续学习之前, 我们需要再次强调这一对易混淆的概念。手性是针对一个分子而言的: 任何不含对称面的分子就是手性的。而外消旋与光学纯是针对一份包含手性化合物的样品的, 如果它仅包含同一种构型的对映体, 则它是光学纯的, 反之是外消旋的。任何丙氨酸都是手性的(由于分子中没有对称面), 但实验室制得的丙氨酸是外消旋的(对映体 50:50 的混合物), 而自然界中分离的丙氨酸是光学纯的。

#### ● “手性”不意味着“光学纯”。

大多数我们在自然界中找到的分子是手性的——一个复杂的分子显然不太可能含有对称面。另外, 在生命体中找到的这些手性分子还几乎都是单一的对映体, 而不是外消旋的。这一特征有深远的影响, 例如在药物的设计上, 我们稍后会提及这一方面。

### R 和 S 可以被用于描述手性中心的构型

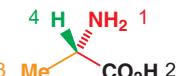
讨论立体化学时, 化学家们如何说清楚自己描述的哪一种对映体呢。当然, 画出结构图并且标明朝向纸面前和朝向直面后的基团就可以了。这对于复杂的分子是方便的。对于简单的分子, 我们同样可以用文字来叙述它们的手性。由于分子的手性是由手性碳引起的, 因此将两种立体构型的手性碳分别用 R 或 S 表示。

以从生命体中提取到的丙氨酸的构型作为例子:

1. 给手性中心上连有的取代基排序(1–4)。首先, 按照所连原子(元素)的原子序数排列, 原子序数大的序号小(优先)。丙氨酸的手性碳连有一个 N 原子(原子序数为 7), 两个 C 原子(原子序数为 6), 和一个 H 原子(原子序数为 1)。由于 N 的原子序数最大, H 的原子序数最小, 因此我们给 NH<sub>2</sub> 基标号为 1, 给氢原子标号为 4。

其次, 我们还需要确定 CO<sub>2</sub>H 和 CH<sub>3</sub> 基的顺序。对于所连原子的原子序数相同的情况, 我们将继续比较所连原子的所连原子的原子序数。在本例中, 羧基连有氧原子(原子序数为 8)而甲基仅连有氢原子(原子序数为 1)。因此 CO<sub>2</sub>H 的优先级高于 CH<sub>3</sub>, 分别标号 2 和 3。

2. 重新排列分子结构, 让最小的(次序最低的)基团远离您。在本例中, 您应当让序号为 4 的 H 远离您, 即从 H 朝向纸面内的方向看这个分子, 如右下图所示。



Interactive configuration assignment

命名烯烃的 E, Z 构型时, 同样需要使用这种次序规则排序。我们有时称其为 Cahn–Ingold–Prelog (CIP) 规则。您也可以选择使用原子量排序, 这还能解决同位素的排序问题(D 优先级高于 H)——前提是手性碳不连有极少出现的 Te 和 I 原子(观察元素周期表看看为什么)。

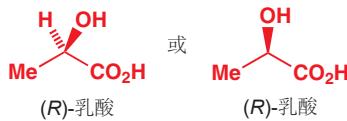


3. 观察，如果由 1 到 2, 再到 3 的旋转方向是顺时针的，那么在手性中心上标注 R；如果是逆时针的，则标注 S。

您可以形象地理解为将方向盘按次序方向转动，如果您的车会右转，那么它是 R；如果您的车会左转，那么它是 S。对于我们的分子，转动的方向由 NH<sub>2</sub> (1) 到 CO<sub>2</sub>H (2) 再到 CH<sub>3</sub> (3)，是逆时针的，因此这个对映体为 (S)-丙氨酸。

将这个过程反过来，您还需要练习从构型类型推测结构。以乳酸为例，乳酸是牛奶被细菌作用而产生的；您的肌肉在氧气供应不充分的情况下工作时也会产生，例如在您剧烈运动时。某些细菌仅产生 *(R)*-乳酸，但大多数通过发酵得到的乳酸是外消旋的；不过，肌肉中无氧呼吸产生的乳酸通常是 *S* 构型的。

请试着画出(R)-乳酸的三维结构。您可以先将这一对对映体都画出来，然后再标出构型类型。



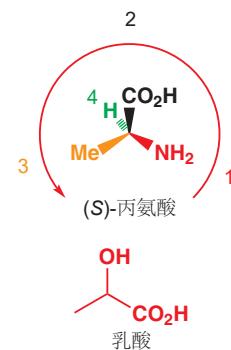
回忆一下，如果我们在实验室中使用非手性原料制备乳酸，那么得到的一定是 $(R)$ -和 $(S)$ -乳酸的外消旋混合物。生命体产生光学纯的化合物，其核心是利用酶的催化，而酶本身是光学纯的 $(S)$ -氨基酸。

两种对映体在性质上有什么不同吗？

简短的回答是：没有。<sup>\*</sup>以(S)-丙氨酸(从植物中提取的)和(R)-丙氨酸(从细菌细胞壁中发现的)为例，它们有完全相同的NMR光谱，完全相同的IR光谱，完全相同的物理性质。唯一重要的区别在于当平面偏振光通过这二者的溶液时，在(S)-丙氨酸中会向右旋转，而在(R)-丙氨酸中会向左旋转；二者的旋转幅度相同，而外消旋的丙氨酸不会旋转通过它的偏振光。

平面偏振光的旋转被称为旋光性

观察平面偏振光通过溶液的旋转，可以直接受地测定一个样品是外消旋的，还是一种对映体比另一种多的，这种方法被称为旋光法 (polarimetry). 测定旋光的仪器为旋光仪，其中，由光源发出单色光，通过盛有溶液的测量管，随后探测器可以探测到光旋转的角度，向右偏移角度为正，向左偏移为负。

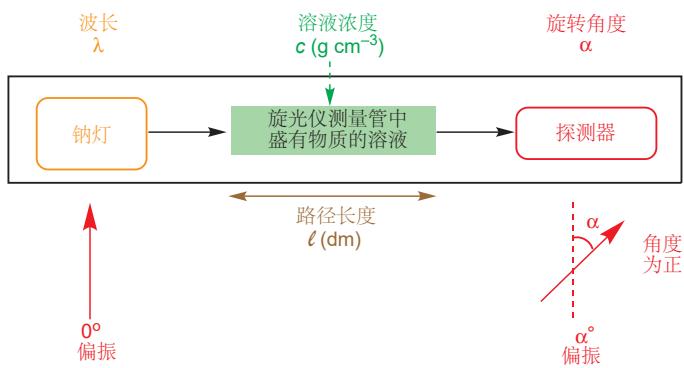


■ 还记得在 Chapter 2 (p. 21) 中我们是如何省略手性碳上的氢原子吗——四面体碳原子上的取代基占据四面体的四个顶点，因此我们自动想象氢原子填充了剩余的位置。

这同样是绘制分子的一个技巧，即将该分子手性中心所连的碳骨架画在纸平面上。如画成：



这二者都是正确的，但对于有多个手性中心的分子，第一种会更加方便。



■ 平面偏振光可以理解为所有波的振动方向都平行的一束光。将光通过偏振滤光片可以得到平面偏振光。

\* 在 Chapter 41 中我们会讨论这一问题较长、较复杂的回答。

平面偏振光通过化合物样品产生的旋转角由多种因素决定，最主要的是路径长度（光通过溶液行进了多少距离）、溶液浓度、温度、溶剂和偏振光的波长。通常，测定实验是在 20 °C 下的乙醇或氯仿中进行的，偏振光由钠灯产生，波长为 589 nm。

符号  $\alpha$  表示偏振光通过溶液旋转的角度，这个数值除以路径长度（in dm）和浓度  $c$  (in g cm<sup>-3</sup>) 得到一个新的数值，即  $[\alpha]$ ，这个数值在不同化合物的情形下是不同的。事实上  $[\alpha]$  被称作化合物的 **比旋度 (specific rotation)**。这几个单位的选择都是古怪而武断的，但它们却是普遍的，因此我们必须接受它。

$$[\alpha] = \frac{\alpha}{c}$$

大多数情况下，我们使用的是  $[\alpha]_D$  ( $D$  表示波长为 589 nm，即钠灯的“D 谱线” ) 或  $[\alpha]_{D}^{20}$  (20 °C)。于是去掉了其余的变量。



下面是一个例子。苦杏仁酸，一种简单的酸，可以从杏仁中获得它光学纯的一种对映体（左侧）。将 28 mg 样品溶解在 1 cm<sup>3</sup> 的乙醇中，并放入 10 cm 长的测量管中，旋光仪在 20 °C, 589 nm 下测量的旋转角  $\alpha$  为 -4.35° (向左旋转 4.35°)。那么这种酸的比旋度是多少呢？

首先，我们需要进行单位换算：28 mg 溶于 1 cm<sup>3</sup> 中得到溶液的浓度为 0.028 g cm<sup>-3</sup>；路径长度 10 cm 等价于 1 dm。然后计算比旋度：

$$[\alpha]_{D}^{20} = \frac{\alpha}{c} = \frac{-4.35}{0.028 \times 1} = -155.4$$

### 对映体可以用 (+) 或 (-) 描述

■ 请注意，旋转角  $\alpha$  以角度制表示；按照正确的单位计算得到的比旋度  $[\alpha]$  无量纲。

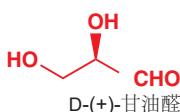
■  $[\alpha]_D$  值可以阐明一份样品中的光学纯度，换种说法是，它可以阐明两种对映体的比例。我们会在 Chapter 41 中回到这一讨论。

对于两种对映体标识的选择，可以从构型入手，也同样可以从性质入手。即我们可以将两种对映体按平面偏振光旋转的方向（比旋度的正负）标记，这种标记方法不考虑分子的微观构型。我们把会导致偏振光向右旋转（正旋转）的对映体标记为 (+)-对映体（或右旋对映体 *dextrorotatory enantiomer*）；把会导致偏振光向左旋转（负旋转）的对映体标记为 (-)-对映体（或左旋对映体 *laevorotatory enantiomer*）。偏振光的旋转方向不依赖于手性中心的 *R, S* 构型。一种 *(R)* 型手性化合物既可能是 (+)，又可能是 (-)——当然，如果它是 (+)，那么它的对映体（相同构造的 *(S)* 型化合物）必定是 (-)。举个例子，刚才提到的一种苦杏仁酸的比旋度为负，因此为 *(R)-(-)*-苦杏仁酸；而 *(S)*-丙氨酸为 *(S)-(+)*-丙氨酸。*(+)* 和 *(-)* 的标记在 X-ray 晶体学出现之前十分有用，当时的化学家并不知道他们研究的分子的微观构型是什么样的，只能通过比旋度对两种对映体加以区分。

### 对映体可以用 D 或 L 描述

X-ray 晶体学作为分析工具出现之前，化学家必须通过一系列复杂的拆分过程研究分子的详细结构和立体化学。就结构而言，他们通过将分子分解成许多组成部分，然后从已知的组成部分推导未知的分子的可能情况；就立体化学而言，他们可以测定化合物的比旋度，但不能知晓它们的具体构型。然而，通过一些列的拆分过程，也可以分析出两种化合物有相同还是相反的构型。

甘油醛是自然界最简单的手性化合物之一。因此，化学家将它作为拆分分子的目标，并用甘油醛的立体化学衡量未知分子的立体化学。甘油醛的两个对映体分别被标记为 *D*（标记右旋（*dextro*）的 *(+)*-对映体）和 *L*（标记左旋（*laevo*）的 *(-)*-对映体）。通过拆分过程，任何能与 *D-(+)*-甘油醛建立联系的分子被标记为 *D*，任何能与 *L-(-)*-甘油醛建立联系的分子被标记为 *L*。这种标记方法费时费力



(下面的图表中展示了  $(-)$ -乳酸 被标记为  $D(-)$ -乳酸 的过程)，因此在如今已经不再使用。目前，D 和 L 只用来标注那些众所周知的天然分子，以保留传统，例如 L-氨基酸 或 D-糖。D 和 L 的标记使用小号的大写字母书写。

- 记住，R/S, +/-, 和 D/L 来自对分子不同方面的观察结果。这意味着，知道一个分子是 R 构型的并不能直接推断出它的旋光性是 + 或是 -，也不能推断出它是 D 还是 L。另外，永远不要仅通过观察结构就断言分子的 D/L 或 +/- 标记。同样，不要妄图观察一个分子的结构就得出它的旋光性 + 或 -。

### D-(-)-乳酸 和 D-(+)-甘油醛 的关系研究

作为例子，我们将向您展示如何将  $(-)$ -乳酸 与 D-(+)-甘油醛 建立联系。我们不指望您记住这其中用到的反应。



注意图中有三个中间体都有“相同的”立体化学，但它们中有一个为 (R)，两个为 (S)，这是不同元素优先级的不同而导致的。这更加印证了三种标记方法无任何联系，(R) 既可以是 D，又可以是 L；即可以是 (+) 又可以是 (-)。

## 另一种立体异构体：非对映异构体

两个互为对映异构体的分子，由于一个是另一个的镜像，因此在化学性质上完全相同。但其他立体异构体之间有可能在化学性质（和物理性质）上产生区别。例如下图的两种烯烃，它们互为几何异构体 geometrical isomers (或顺反异构体 cis-trans isomers)。由于分子形状上的区别，它们的物理性质也有很大的区别。不过由于它们是平面分子，因此都没有手性。



环状化合物中还存在另一种类似的立体异构类型。下图的 4-叔丁基环己醇 中，两个取代基可以处于环的一侧，也可以分别处于环的上下两侧。同样，这两个化合物在化学和物理性质上也有显著的区别。



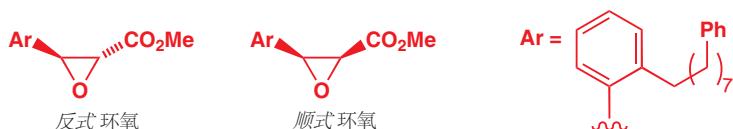
■ 我们通常并不画出全部的氢原子。如果叔丁基在三维结构中指向直面外，那么氢原子只可能指向纸面内。

并不互为镜像的一对立体异构体被称为非对映异构体 (diastereoisomers, 简称非对映体)。以上两类异构体都属于这一分类。请注意一对非对映异构体的化学和物理性质是如何不同的。

- 对映异构体间的物理和化学性质完全相同，但非对映异构体间的物理和化学性质不同。“Diastereoisomer”常被简化为“diastereomer”。

### 非对映异构体可以是手性的或非手性的

如下的一对化合物是宾夕法尼亚州的化学家在研究缓解哮喘的药物时生产的。很明显，它们同样是非对映异构体，并同样有不同的性质。生产过程会同时产生两种非对映异构体，但化学家仅需要第一种（反式的）环氧。由于这两种化合物的极性不同，因此通过层析（chromatography），这两种化合物可以相互分离。



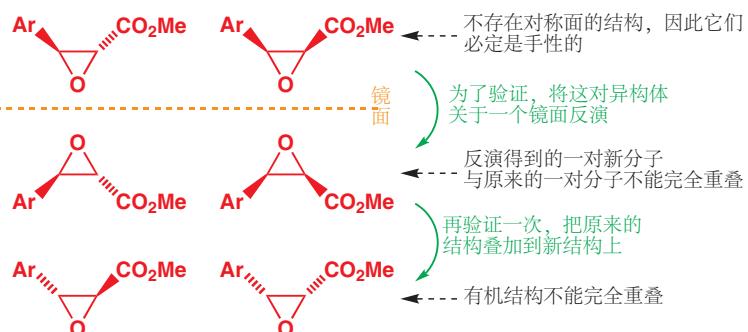
下面我们要讨论一些有关非对映异构体的复杂问题。首先来看，我们最先了解的这两对非对映异构体都是非手性的——因为它们都含有一个穿过分子的对称面。

两对非手性的非对映异构体

Interactive structures of achiral diastereoisomers

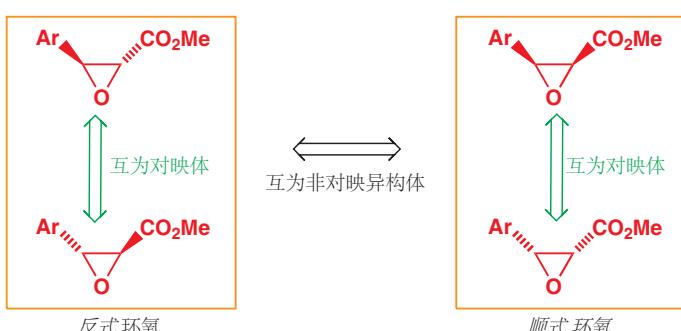


然后，我们后来了解了一对环氧化物。它们都是手性的，我们不能画出其分子中的对称面。为了验证这一点，我们可将其关于一个镜面反演，然后就会观察到镜像分子与原分子不能完全重叠。



如果一个化合物是手性的，那么它就可以以一对对映体的形式存在。而我们刚刚已经画出了这两种环氧化物的对映体。因此这种构造可以分为四种不同的构型，其中有两组非对映异构体（不互为镜像的立体异构体），每组又有两个对映异构体（互为镜像的立体异构体）。非对映异构体是顺式和反式两种环氧，它们在性质上有很大区别；对映异构体间则只能以旋光性加以区分。当您考虑一个化合物的立体化学时，应当先区分非对映异构体；然后，如果化合物有手性，再分别讨论每个非对映异构体的对映体。

Interactive structures of epoxide diastereoisomers

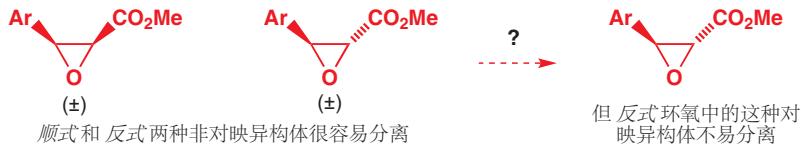


事实上，研究它们的化学家仅需要反式环氧中的一种对映体——即左上方的异构体。虽然可以通过层析法分离非对映异构体，即顺式和反式环氧；但对映体具有相同的物理和化学性质，分离它们就困难许多。实验室中由非手性的原料制备它们时，得到的必定是外消旋混合物，因此为了得到光学纯的一种化合物，化学家需要开发全新的化学方法，并使用从自然界中获得的光学纯化合物作为原料。

► 本章末尾我们会介绍分离对映体得到光学纯化合物的方法，然后我们在 Chapter 41 学习更多细节。

## 绝对立体化学和相对立体化学

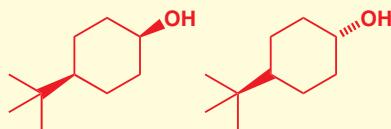
为了严谨，我们必须画出四个分子，包括非对映异构体和其对映异构体。但当我们想讨论非对映异构体间的区别，而对映异构体间只是简单的外消旋混合时，我们可以使用一种新的记号，即画出对映体中的一种，并在其旁边标出“ $\pm$ ”（表示外消旋），它表示的是“这种非对映异构体”而非“这种非对映异构体的这种对映体”。这种画法在实验上也有意义，它代表化学家可以区分两种非对映异构体，但不能仅通过化学方法分离某一种对映体。



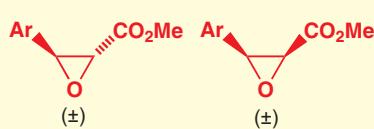
当我们强调非对映异构体间的立体化学时，我们讨论的是**相对立体化学** (*relative stereochemistry*, 也称**相对构型** “*relative configuration*”), 即分子内多个手性中心的相对位置和联系；当我们强调对映异构体间的立体化学时，我们讨论的是**绝对立体化学** (*absolute stereochemistry*, **绝对构型** “*absolute configuration*”), 即两个分子内所有手性中心都是同时反转的，但相对位置相同。

### ● 对映异构体和非对映异构体

- 对映异构体是互为镜像的一对立体异构体。一对对应异构体是相同的化合物，但它们有不同的绝对立体化学。
- 非对映异构体是不互为镜像的立体异构体。一对非对映异构体是不同的化合物，它们有不同的相对立体化学。
- 非对映异构体既可以是手性的(不含对称面)，也可以是非手性的(含对称面,这样的非对映异构体不能继续拆分为两个对映异构体)。



非手性的一对非对映异构体



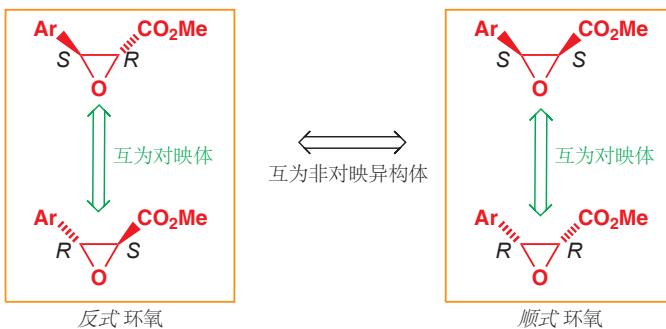
手性的一对非对映异构体

## 当立体中心有一个以上时 就会出现非对映异构体

让我们继续深入考察之前的环氧的四个立体异构体。您可能发现每个结构都包含两个立体中心。请回到 p. 312 的底部，独立给每个立体中心标出 R 或 S 标签，请不要先参看下一页的答案。

您应该这样完成 R 和 S 的安排。

► 您必须要掌握 R 和 S 的标记方法。如果您遇到了问题或者标错了，请回顾 p. 308 的内容并确保您知道原因。



● 互为非对映体、对映体的分子间的关系

- 如果一个分子是另一个分子的对映体，那么它们两个立体中心都是相反的。
- 如果一个分子是另一个分子的非对映体，那么仅有其中一个立体中心相反。

If you are asked to explain some stereochemical point in an examination, choose a cyclic example—it makes it much easier.

到目前为止，我们讨论的全部化合物都是环状的，因为环状化合物的非对映异构体比较容易考虑：立体中心上的两个取代基指向相同或相反的方向（纸面上或纸面下）就是一对非对映异构体（**顺式**或**反式**）。但链状化合物同样也可以以非对映异构体的形式存在。下面的麻黄碱和伪麻黄碱都属于安非他命类兴奋剂，它们都起到模拟肾上腺素的作用。



麻黄碱和伪麻黄碱是不互为镜像的立体异构体——麻黄碱中的其中一个立体中心翻转得到伪麻黄碱——因此它们互为非对映异构体。从立体中心的角度看分子十分有必要，这种含有两个立体中心的化合物可以以两个非对映异构体存在；而排列组合告诉我们，任何含有一个以上立体中心的化合物都可以以一个以上的非对映异构体存在。

麻黄碱和伪麻黄碱都是植物生产的光学纯产物，因此不同于前文抗哮喘药物的中间体，我们讨论的是非对映体中的一种中的对映体中的一种。肾上腺素同样是手性的，但由于它仅含一个立体中心，在自然界中它只能以对映体中的一种存在，而不能以其他的“非对映异构体”存在。



**麻黄碱和伪麻黄碱**

麻黄碱是中草药“麻黄”的提取物，它还被用做减充血的鼻喷剂（治疗鼻黏膜充血）。伪麻黄碱是减充血药速达菲（Sudafed）的有效成分。

这两种非对映体的“天然”对映体分别是（-）-麻黄碱和（+）-伪麻黄碱，但您并不能从其中获得有关结构的任何消息，但如果告诉您分别是（1R,2S）-（-）-麻黄碱和（1S,2S）-（+）-伪麻黄碱，您就可以

推断出相应的结构了。

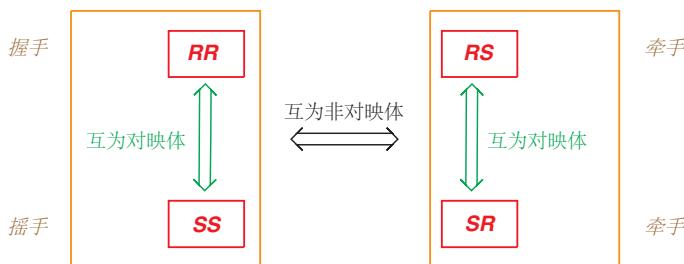
下面是  $(1R,2S)$ -(-)-麻黄碱,  $(1S,2S)$ -(+)-伪麻黄碱, 以及它们的“非天然”对映体(需要在实验室中合成得到),  $(1S,2R)$ -(-)-麻黄碱和 $(1R,2R)$ -(-)-伪麻黄碱的一些性质。

	$(1R,2S)$ -(-)- 麻黄碱	$(1S,2R)$ -(+)- 麻黄碱	$(1S,2S)$ -(+)- 伪麻黄碱	$(1R,2R)$ -(-)- 伪麻黄碱
mp	40–40.5 °C	40–40.5 °C	117–118 °C	117–118 °C
$[\alpha]_D^{20}$	-6.3	+6.3	+52	-52

■ 回忆一下, (+) 和 (-) 反映的是特征的旋光性的信息, 而 R 和 S 由观察化合物的结构直接得到。两种对映体间两个信息均相反, 但它们之间没有简单的联系。

- 两种非对映异构体是不同的化合物, 有不同的名称和不同的性质; 而一对对应异构体具有相同的性质, 仅仅在旋光方向上相反。

我们可以通过考虑您与他人的握手, 来说明同一化合物中含有两个手性中心的情况。显然, 只有双方使用同一侧的手时, 握手的过程才是成功的! 按照习惯, 您通常使用右手; 当然, 用左手握同样是可能的; 这两种握手的总体模式是相同的: 右手与右手握手, 左手与左手握手, 这二者是一对对映体, 区别仅仅在于它们互为镜像。然而, 如果您不小心使用右手握了别人的左手, 这时握着的手包含一只左手和一只右手; 这时并不是握手, 而是牵手。两种牵手的过程和两种握手的过程的互动效果是截然不同的, 我们可以说它们是非对映异构体。我们用可能是 R 或 S 构型的两个手性中心代表我们的两只手。



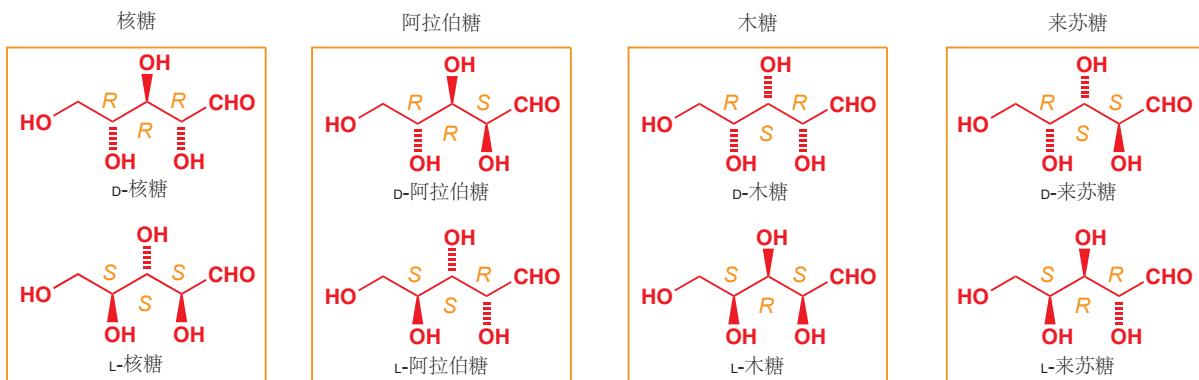
那么有两个以上立体中心的化合物呢? 糖家族提供了很多例子。核糖是一种含有三个立体中心的五碳糖, 下图所示的是核糖的一种对映体, 在任何生命体的新陈代谢中都是必须的, 习惯称之为 D-核糖。D-核糖的三个立体中心全部为 R 构型。为了方便起见, 我们考虑开链形式的核糖, 但它们通常以第二张图所示的环状形式存在。



在理论上，我们只需知道有几个立体中心，就可以通过 Rs 和 Ss 的排列组合，知道该分子有多少个“立体异构体”，本情境中为 8 ( $= 2^3$ )。

RRR	RRS	RSR	RSS
SSS	SSR	SRS	SRR

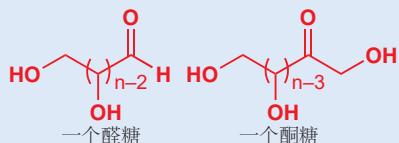
但这种算法模糊了非对映异构体和对应异构体间的区别。观察这八种情况，同一列的两个构型是一对对映体（全部三个中心都翻转），而四列之间则是非对映异构体。三个立体中心实际是产生了四种非对映异构体，每种非对映异构体包含一对对映体。在这个  $C_5$  醛糖的例子中，每个非对映异构体都是一种不同的糖（有不同的名字）。下面的图表绘制了上面八种情况的结构，上方的是 (D) 构型的，而下方的是 (L) 的。



■ 您不需要记住这些糖的名字。

### 糖类的结构

糖类的实验式为  $C_nH_{2n}O_n$ ，由碳链构成，其中一个糖是羰基的一部分，其他碳连有 OH 基团。如果羰基在碳链的末端（换句话说，是一个醛），我们叫它醛糖（aldose）；如果羰基不在碳链末端，我们叫它酮糖（ketose）。我们将会在 Chapter 42 中详细讨论。碳原子的总数  $n$  为 3-8：醛糖含有  $n - 2$  个立体中心，酮糖含有  $n - 3$  个立体中心。事实上，大多数糖是以开链形式和环状形式的平衡混合物存在的 (Chapter 6)。

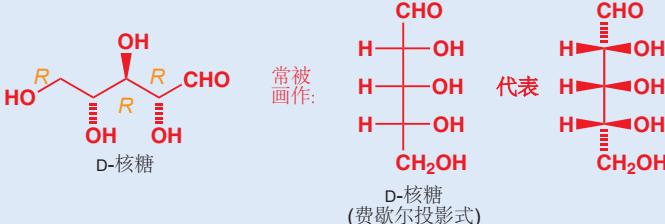


■ 这是一种过于简单化的算法，它默认了所有的非对映异构体均有手性，对于对称的分子无效，因此在使用时需要谨慎。

您可能已经发现，一个结构的立体中心的数目和立体异构体的数目之间，存在一个简单的数学关系式。通常情况下，一个包含  $n$  个立体中心的结构有  $2^n$  个立体异构体（包括它本身）。这些立体异构体包含  $2^{n-1}$  个非对映异构体，每个非对映异构体包含一对对映体。

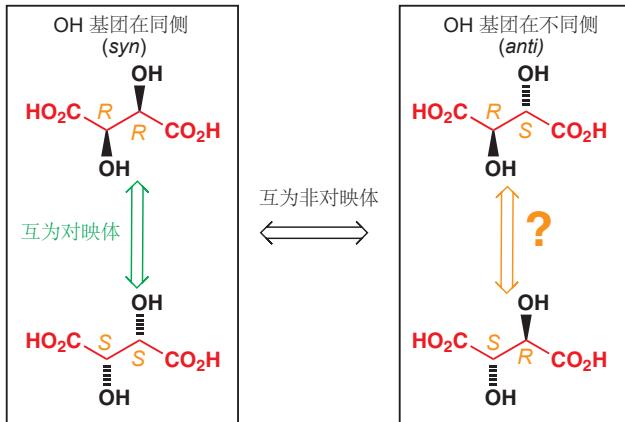
### 费歇尔投影式

糖类的立体化学常常通过费歇尔投影式 (Fischer projections) 表示。首先竖直的直线表示碳原子，然后整个分子随之扭曲，使得取代基都朝向纸面前方，即朝向我们的方向。费歇尔投影是和真正的分子差异十分大，因此您可能永远不需要使用它们。但您仍会在一些旧书中遇到它们，因此您至少需要掌握如何识别它们。您只需要记住，连在中间主干上的所有分支，实质上都是粗楔形键（朝向纸面前方），而中间主干处于纸平面上。通过想象将主干扭曲成锯齿状，您就会得到熟悉的糖分子。



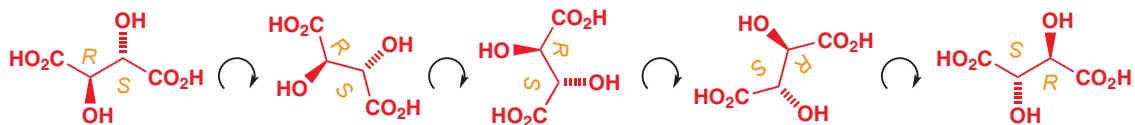
## 非“通常情况下”——含多个立体中心的非手性化合物

有时，分子的对称性会导致一些立体异构体的简并，或者说“抵消”——立体异构体的数目并没有您期待的那么多。以酒石酸为例，这种酒石酸的立体异构体存在于葡萄中；它的盐，酒石酸氢钾，可以在葡萄酒的底部析出形成晶体。它有两个立体中心，因此您会期待它有  $2^2 = 4$  个立体异构体：两个非对映异构体，每个含有一对对映体。



Interactive stereoisomers of tartaric acid

左边的一对结构显然就是一对对映体，但当您仔细看右边的一对结构时，您会发现它们其实是一模一样的结构，而不是对映体。您只需要将上方的结构在纸平面上旋转 180° 即可证明这一点。



Interactive display of meso form of tartaric acid

(1R,2S)-酒石酸 和 (1S,2R)-酒石酸 不是一对对映体，而是完全相同的。这是因为虽然它们具有手性中心，但它们是非手性的。将 (1R,2S)-酒石酸 的一侧绕中心的键旋转 180° 后，您会发现该分子具有一个对称面，因此它必定是非手性的。由于分子含有一个对称面，而且 R 是 S 的镜像，因此构型为 R,S 非对映异构体不能是手性的。



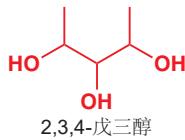
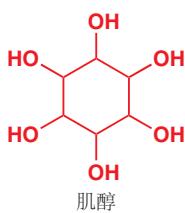
■ These two structures are the same molecule drawn in two different conformations—to get from one to the other just rotate half of the molecule about the central bond.

- 含有手性中心，但是非手性的化合物被称为内消旋化合物 (*meso compounds*)。这表示该分子中含有一个对称面，两个手性中心分布在对称面两侧并分别具有 R 和 S 的立体化学。

因此酒石酸可以以两个非对映异构体存在，其中一个包含两对对映体，另一个是非手性的（内消旋化合物）。值得注意的是，“含有  $n$  个立体中心的化合物含有  $2^{n-1}$  个非对映异构体”的公式仍然成立，仅是“含有  $2^n$  个‘立体异构体’”的公式不成立了。一般来说，相比于直接计算“立体异构体”的数目；更安全的方法是先计算非对映异构体，再人工判断哪个非对映异构体有手性，即具有一对对映体。

### 内消旋的握手

我们也可以将握手与非对映体间的类比也推广到内消旋化合物。想象一对双胞胎兄弟握手，我们可以区分它们分别都握左手，或都握右手时的情形，因为这二者是一对对映体。但当他们牵手的时候（一人的左手握另一人的右手），我们就无法区分是左手拉右手还是右手拉左手了，因为兄弟二人本身就无法区分——这就是内消旋的牵手！



■ *syn* (顺式) 和 *anti* (反式): 它们反映取代基在碳链、碳环的同侧(顺式)或异侧(反式)。它们只能用于参考图表。

	手性的非对映体		非手性的非对映体
	(+)-酒石酸	(-)-酒石酸	内消旋-酒石酸
$[\alpha]_D^{20}$	+12	-12	0
m.p.	168–170 °C	168–170 °C	146–148 °C

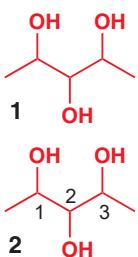
### 肌醇的内消旋非对映体

注意到，内消旋的非对映体在其分子整体上具有一定程度的对称性。肌醇有六个立体中心，其中一种非对映体是一种重要的生长因子。或许考察它有多少个立体异构体是有挑战性的——事实上除了一种非对映体外，其余的都是内消旋的。

### 化合物立体化学的研究方法

当您想讨论一个化合物的立体化学时，我们建议您先识别非对映异构体，然后再逐一考察它们是否有手性。请不要直接计算“立体异构体”的数目——一直截了当地认为一个含有两个立体中心的化合物就是含有四个“立体异构体”。分清主次是根本要求，就像是当您说两个人要结婚了的时候，不要说“四只手结婚了”一样。

让我们通过一个简单的例子，直线型的 2,3,4-三羟基戊五或 2,3,4-戊三醇来巩固研究一个化合物立体化学的基本方法。下面是您需要做的事：



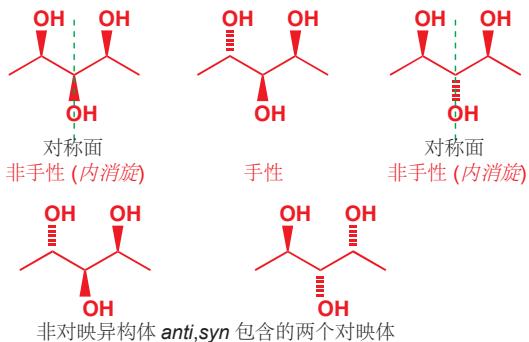
1. 在纸上画出化合物的结构，其中碳链表示为锯齿形，如图 1.



2. 识别全部手性中心，如图 2.



3. 判断非对映异构体的数目。每对手性中心上的两个取代基可以在同侧(*syn*)或是在异侧(*anti*)，写出每个非对映异构体的构型类型会对您有所帮助。本例有三个非对映异构体：三个OH基团可以都在同侧，也可以是两侧的OHs与中间的在异侧，还可以是一侧的与其余的在异侧。我们称第一种为 *syn,syn*，因为两对手性中心(1 & 2, 和 2 & 3)都将各自的两个OHs排列在同一侧(顺式)。



4. 通过检查是否存在对称面，确定非对映异构体是否有手性。本例中，只有穿过中心的平面可能成为对称面。

5. 画出手性的非对映异构体的对映体，即将其全部立体中心上的构型翻转。纸平面就是为我们准备的镜面，做分子关于纸平面的镜像，得到的就是对映体，全部“朝上”的基团都“朝下”，反之亦然。

6. 得出最终结论。最普通的表述是，本例中有四个“立体异构体”。更有价值的表述是，本例中有三个非对映异构体，即 *syn,syn*, *syn,anti*, 和 *anti,anti*；其中 *syn,syn* 和 *anti,anti* 是非手性的(内消旋)，而 *syn,anti* 是手性的，并包含两个对映体。

## 费斯特酸 (Feist's acid) 的奥秘

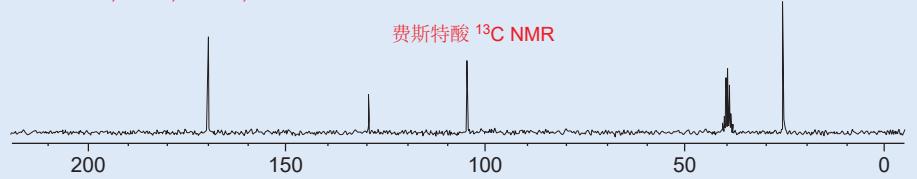
现在的我们无法理解在光谱法诞生之前求解结构的困难性。一个著名的例子是“费斯特酸”，1893年由费斯特(Feist)通过一个看似简单的反应合成并发现。不包含光谱法的早期研究指向两种可能的结构，这二者都是建立在一个三元环的基础上的。三元环的出现给了这个化合物很多名声，因为不饱和的三元环是十分稀少的。最受人喜爱的是第一种环丙烯式结构。

对于该物质结构的争论即使到1950年代第一台NMR光谱仪出现时仍在继续。虽然红外观察支持了环丙烯式的结构，但原始的40MHz仪器显示，该分子没有甲基，并且双键连有两个质子。这一研究佐证了第二种环外亚甲基式的结构。

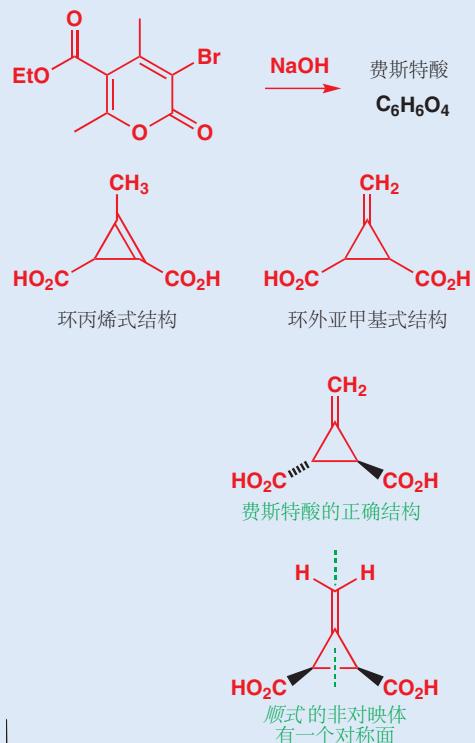
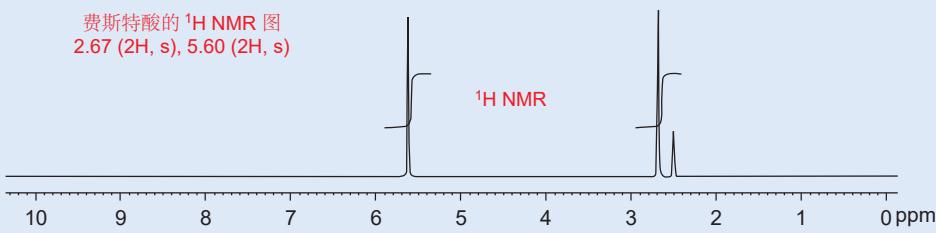
这一结构含有两个手性中心，那么会有多少非对映异构体呢？答案很简单：由于费斯特酸是手性的，因此(环上的两个羧基)必然是反式构型(顺式构型有一个对称面)，因此它以一对对映体的形式存在。另外，虽然费斯特酸没有对称面，但它有对称轴，学完后面您会知道，对称轴和手性是可以共存的。

现代的NMR光谱的方法大大简化了推断流程。氢谱：仅有两个 $\text{CO}_2\text{H}$ 上的两个质子会与溶剂DMSO中的交换；而双键上的两个质子等价(5.60 ppm)，环上两个羧基上的质子也等价，与预期的强场相符(2.67 ppm)。碳谱共四个：一个 $\text{C}=\text{O}$ 碳的信号在170 ppm处，双键两侧碳的信号介于100和150 ppm之间，环上另两个等价碳的信号在25.45 ppm处。

费斯特酸的 $^{13}\text{C}$  NMR图  
170.3, 129.8, 105.05, 25.45



费斯特酸的 $^1\text{H}$  NMR图  
2.67 (2H, s), 5.60 (2H, s)

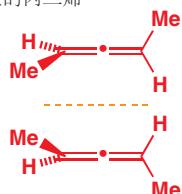


Interactive possible structures for Feist's acid

## 没有立体中心的手性化合物

有一少部分手性化合物并没有立体中心。例如右侧展示的丙二烯，它没有手性中心，但它不能与其镜像完全重叠，因此它也是手性的：这种化合物存在两种对映体。一些联芳类化合物(biaryl compounds)也与之相似，例如下面所示的双膦(bisphosphine)结构，被称为BINAP，由于围绕绿色的联芳键的旋转受到阻碍，因此也以两个独立的对映体存在。所谓的阻碍在于，如果您沿着这跟键向下看这个分子，您会看到两个环所在的平面实际上是互相正交的，整个分子与丙二烯一样处于90°扭曲的状态。像这样的，由于单键的旋转受阻导致的手性/对映体，我们称之为阻转异构体(atropisomers，来自希腊语‘不会旋转’)。

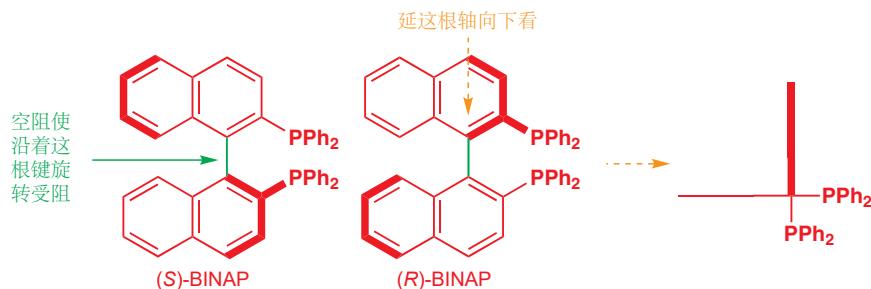
一种手性的丙二烯



Interactive chiral compounds without stereogenic centres—allene

► 我们会在 Chapter 41 中继续了解 BINAP。

Interactive chiral compounds without stereogenic centres—BINAP

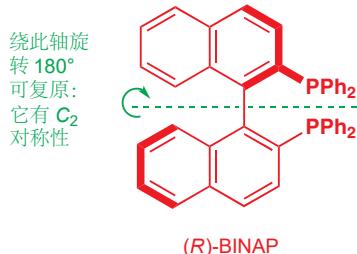


以上两个例子都依赖于  $\pi$  体系的刚性，如下简单的不饱和体系也同样是手性的。由于中心碳原子是四面体构型，因此两个环必须是正交的。由此，虽然分子中没有立体中心，但分子中也同样没有对称面。像这种，包含两个环通过单个 C 原子连接起来的化合物称为螺环化合物 (spiro compounds)。对于螺环化合物，虽然您一眼看过去它们都很对称，但它们常常是手性的；当您想研究它们的立体化学时，请从对称面出发仔细考察。

Interactive chiral compounds without stereogenic centres—spiro amide



## 对称轴与对称中心



Interactive BINAP showing  $C_2$  axis of symmetry

■ 下标 2 代表“二重”对称轴。化学中也包含其他重数的对称轴，但在一般的有机物中它们却十分稀少。

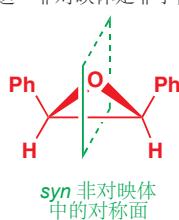
Interactive epoxide diastereoisomers showing plane of symmetry

■ 我们之前曾提醒过您，这种表述是不完整的 (pp. 304 和 312)：现在我们将要完善它。

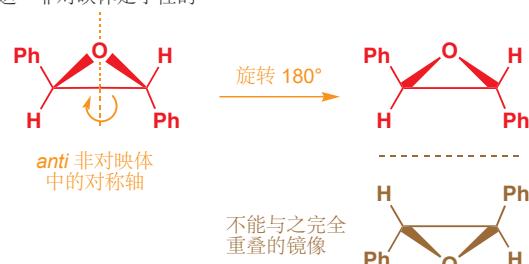
您可能会纳闷为什么刚刚这三个化合物 (连同 p. 319 文字框中的费斯特酸) 是手性的，因为它们看上去是如此的“有对称性”。事实上，它们含有的唯一对称元素是对称轴，而对称轴恰恰是唯一的不对分子的手性产生影响的对称元素。如果一个分子可以绕一轴旋转 180° 后能复原回原分子。那么称它有二次对称性 (twofold axial symmetry)，或  $C_2$  对称性。只要不含对称面或对称中心，那么无论化合物有没有对称轴，它都是手性的。

除去上节举的例子外， $C_2$  对称性在日常分子中也是很普遍的。下面是一个拥有两种非对映异构体的化合物的例子。一种 (我们称其为 syn 非对映体——由于两个苯环在同一侧) 包含对称面——因此它是非手性的 (尽管整个分子非手性，但它含有手性中心，我们可以叫它内消旋非对映体)；另一分子仅有对称轴作为对称元素，因此它是手性的。橘色展示了其  $C_2$  对称轴，绕此轴旋转 180° 可以得到相同的结构。但关于一个镜面做它的镜像则不能与之重合。

这一非对映体是非手性的



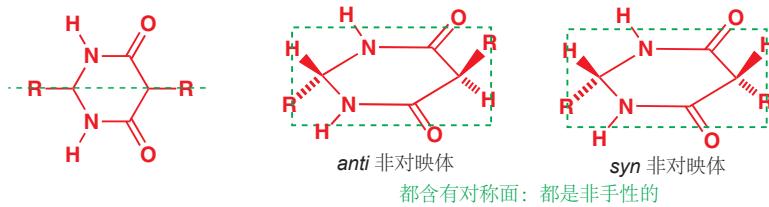
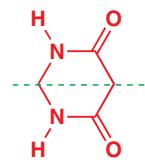
这一非对映体是手性的



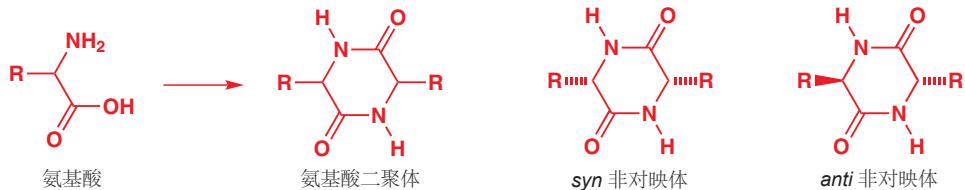
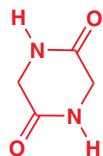
到目前为止，我们一直在使用对称面作为衡量一个分子是否具有手性的特征：我们已经说过多此，如果一个分子没有对称面，那么它就具有手性。但现在我将向您介绍另一个与分子手性不兼

兼容的对称元素类型。如果一个分子含有对称中心，那么它也是非手性的。现在我们将解释如何注意到分子的对称中心。

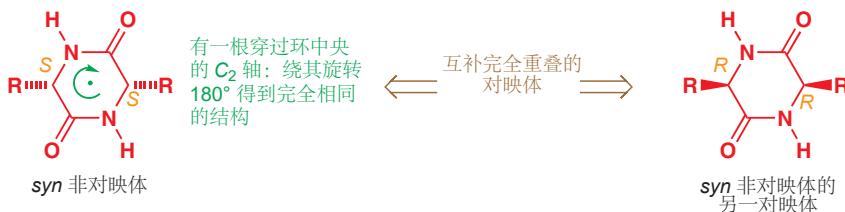
右侧的二酰胺骨架具有两个对称面，一个是纸平面，另一个是与纸平面垂直的，穿过两个饱和碳原子的平面（图中绿色标出的）。如果我们在这个结构中加入两个 R 取代基，我们可以得到两个非对映异构体，R 基分别在环平面的同侧 (*syn*) 或异侧 (*anti*)。虽然纸平面不再是一个对称面，但由于原先的另一对称面在此时仍然将两个取代基平分，因此它仍然是非手性的。到目前为止还没有新知识。



现在，请考虑右侧的一个二酰胺。这次纸平面仍然是一个对称面，但垂直的另一对称面却不存在了。这种杂环被称为“二酮哌嗪”，它可以由一种氨基酸二聚得到：右侧的二酮哌嗪是由甘氨酸二聚得到的。对于有取代的氨基酸，例如  $R \neq H$  时下图所示的情况，又会产生两种非对映异构体，*syn* 和 *anti*。这二者的对称性是不同的，其中 *syn* 异构体是手性的，而 *anti* 异构体是非手性的。

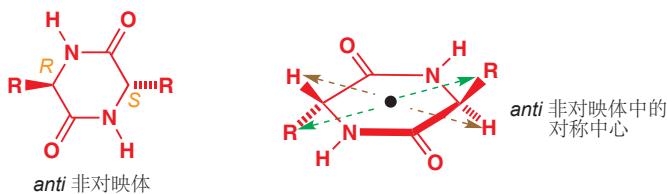


对于手性的 *syn* 非对映体，它不含任何对称面，但您可以找到一个穿过环中央的  $C_2$  对称轴。当然，对称轴是与手性相兼容的。在这个化合物中，两个手性中心都是 *S* 构型，而它的对映体则都是 *R* 构型。



Interactive diamides showing centre of symmetry

非手性的 *anti* 非对映体，既不含对称面，也不含对称轴，但它含一个对称中心（下一页图中黑点标出的）。这意味着，当从该中心出发，沿一个方向能遇到一个事物，例如一个 R 基团时；仍从该中心出发，沿相反的方向也同样能得到相同的事物（绿色箭头）。同样的道理也适用于棕色箭头，还使用与环本身。在 *syn* 异构体中不存在这种对称中心，因为这里的绿色、棕色箭头，在该分子中均连接的是一侧的 R 和另一侧的 H。因为对称中心的存在，*anti* 异构体能与其镜像完全重叠，并因此是非手性的。



● 从对称面、对称中心、对称轴的角度看手性

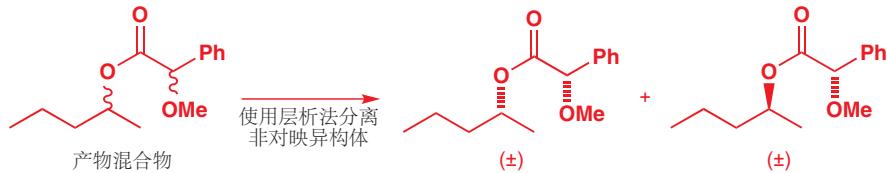
- 任何含有对称面或对称中心的分子是非手性的。
- 如果不含对称面或对称中心，含有对称轴的分子仍是手性的。对称轴是唯一与手性相兼容的对称元素。

## 对映体拆分

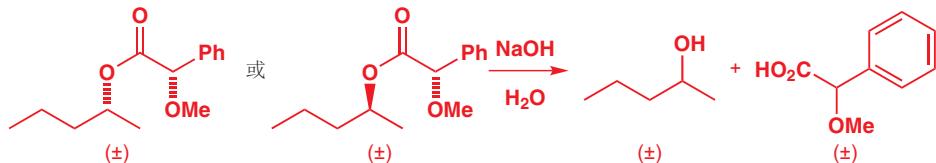
本章的早期内容谈到过，自然界产生的分子大多是手性的，而且自然界通常仅生产单一一对映体。我们已经讨论过氨基酸、糖类、麻黄碱、伪麻黄碱和酒石酸——自然资源经过分离得到的这些化合物均为单一对映体。而另一方面，在实验室中使用非手性原料合成的手性化合物，注定是外消旋混合物。那么如果不从自然资源中提取，化学家是如何分离得到单一对映体的化合物的呢？我们将在 Chapter 41 更详细地讨论这一话题，而现在我们将以一种简单的方式考察：使用自然界中的光学纯化合物，帮助我们分离自己的外消旋混合物。这一过程称为拆分。现在，请您想象一下在普通的酸催化酯化机理下 (Chapter 10)，手性但外消旋的醇和羧酸，生成酯的过程。



产物有两个手性中心，因此我们预计它会产生两种非对映异构体，每种非对映异构体都是各自的一对对映体的外消旋混合物。而非对映异构体间有不同的物理性质，可以使用例如层析法等手段分离。

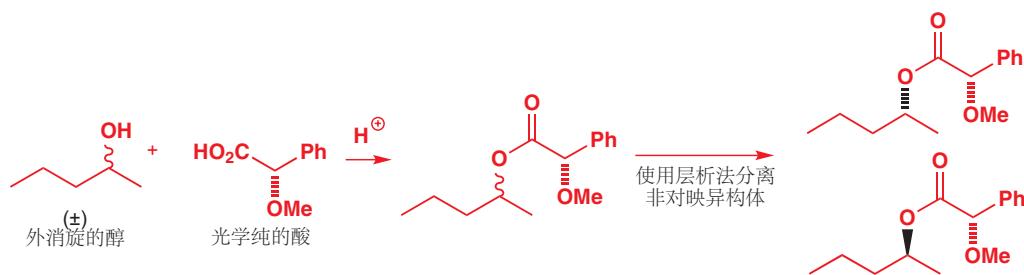


然后我们可以进行逆酯化过程，水解这两种非对映异构体中的任意一个，则可以重新得到外消旋的醇和外消旋的酸。

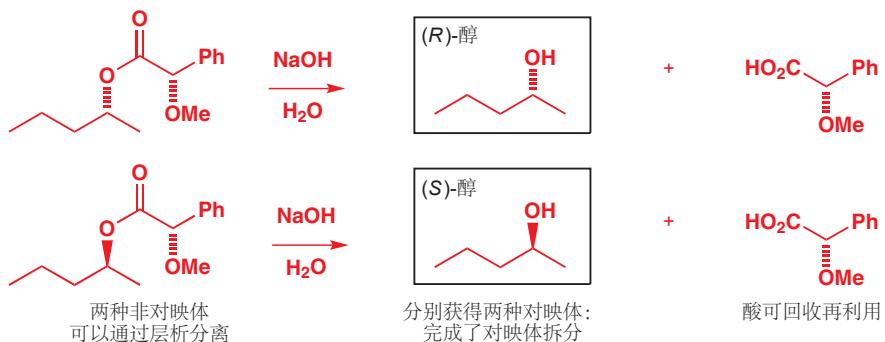


■ 回忆：(±) 代表以外消旋混合物存在：于是我们可以舍弃绝对立体化学，仅展示相对立体化学。

如果我们用光学纯的羧酸重复这一反应，例如用您在 p. 310 看到的杏仁提取物，(R)-苦杏仁酸。产物同样是两种非对映体，但与之前不同的是，这两种非对映体都是光学纯的。注意下图中最右侧的产物结构，它的立体化学是绝对立体化学。



现在，如果我们将每种非对映体分离后分别水解，那么我们就完成了一件非凡的事情：我们将起始的外消旋醇，分离为了两种单一的对映体。



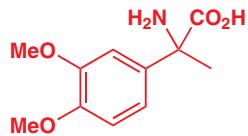
一对对映体的分离被称为**拆分 (resolution)**。拆分过程需要利用一种已经达到光学纯的化合物（旋光性拆分剂 optically active resolving agent）：大自然给我们提供了这样的便利；拆分过程几乎总是在使用从自然界中分离的化合物。

### 大自然的手性

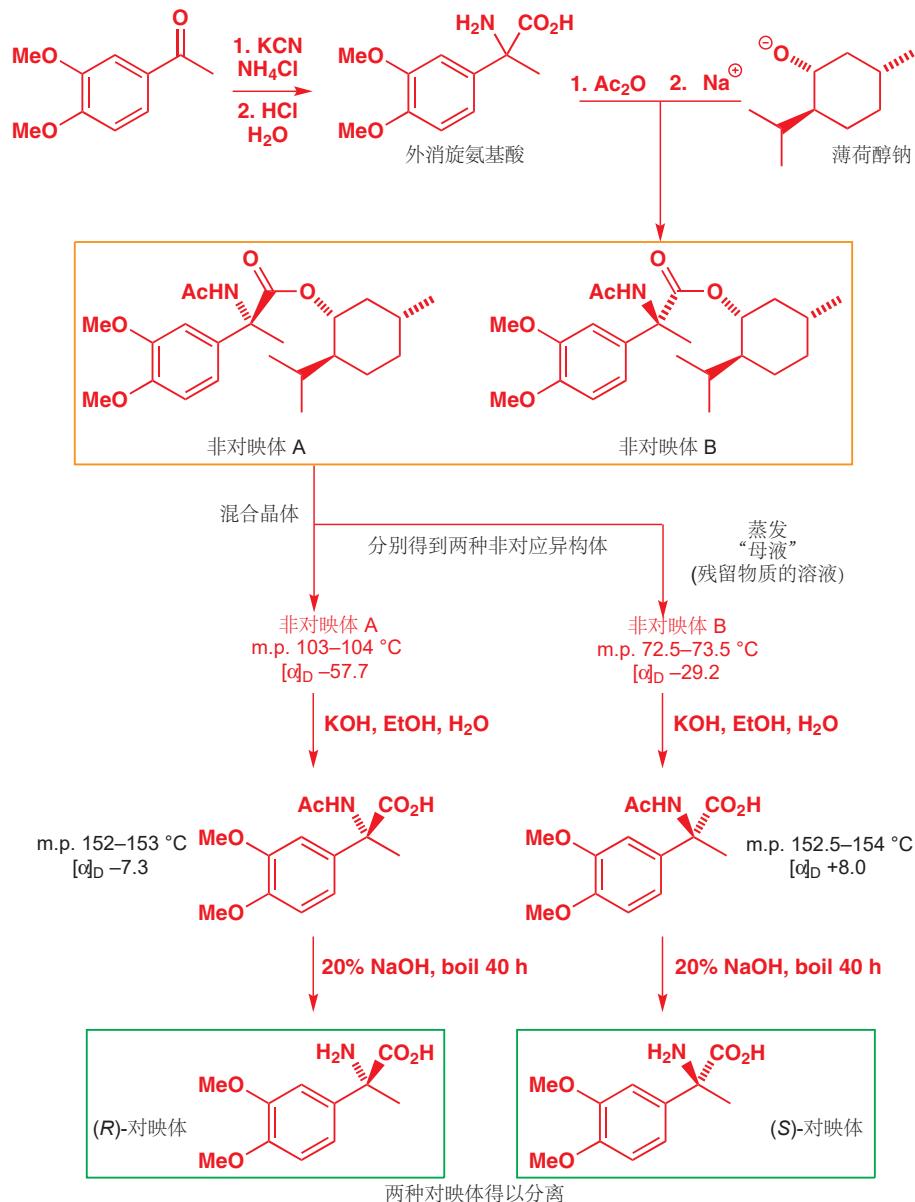
为什么大自然对于那些重要的生化物质的使用，仅钟情于一种对映体。当您了解了不对称性是如何第一次进入分子世界的，或者了解了 L-氨基酸 和 D-糖 相比其另一对映体更具有的优势是什么时，这个问题可能变得简单。例如，如果有大量非对映异构体的存在，外消旋的氨基酸样品可能会产生十分复杂的蛋白质。有关起源问题，有人认为生命产生于单手性的石英晶体的表面，它为生命体所需的光学纯分子提供了不对称的环境；又有人认为这种不对称性最初起源于伽马射线释放的电子的自旋不对称性；还有人考虑到，光学纯的生命系统比外消旋的更加简单，也许是偶然的机会让 L-氨基酸 和 D-糖 胜出了。

现在让我们考察一个真实的例子。研究氨基酸在脑功能中的作用的化学家，需要分离右侧的氨基酸的两种非对映体。通过您在 Chapter 11 学过的 Strecker 合成法，可以得到外消旋混合物。然后他们用乙酸酐处理，得到混合酸酐，再用从自然界中获取的光学纯的薄荷醇钠，得到两个非对映的酯。

在这两种非对映体中，其中一种比另一种更易结晶（即有更高的熔点），化学家可以通过逐渐结晶它们的混合物，得到前者；然后蒸发剩余的溶液（“母液”），进而得到后者。



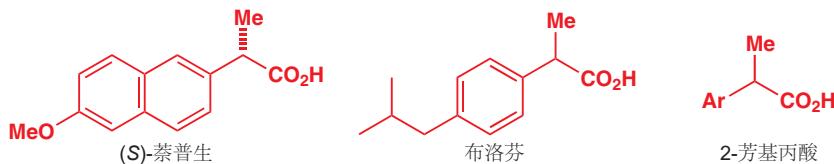
然后将两种非对映酯分别溶于 KOH 溶液煮沸，使之水解。两个体系分别得到了两种对映体，从其产物（几乎）相反的旋光度和相似的熔点可以证明这一结论。最后，对酰胺进行更剧烈的水解（用 20% 的 NaOH 煮沸 40 小时），可以得到生物研究中需要的氨基酸（见 p. 322 底部）。



### 通过非对映盐拆分

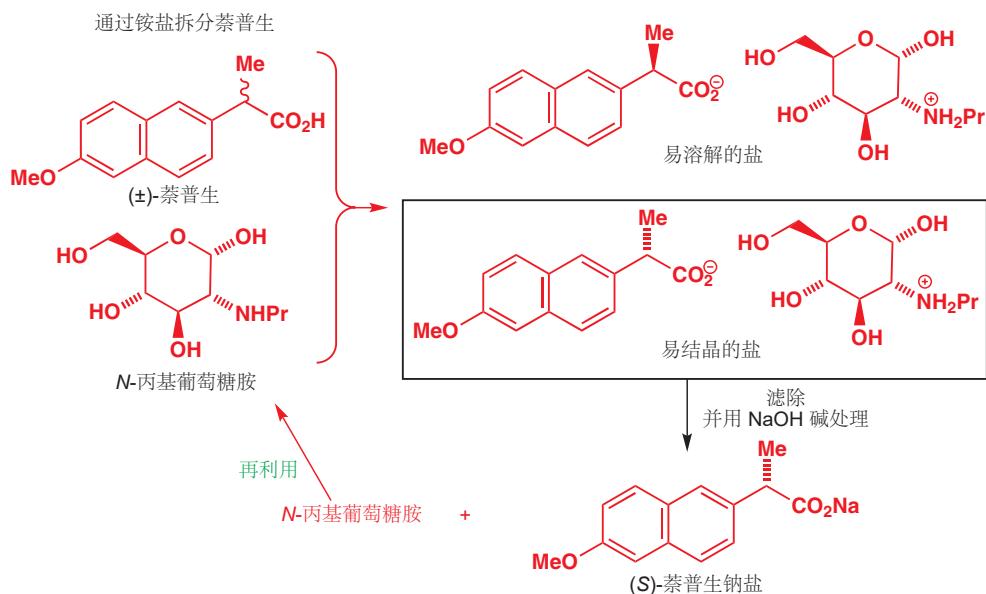
对映体拆分的关键点是我们必须将两个立体中心联系起来：可分离的非对映异构体是由不可分离的对映体产出的。在上两个例子中，两个立体中心被联系到了一个共价化合物中，即酯中。而离子化合物也可以很好地完成这项工作——事实上，如果使用离子化合物，还有拆分后便于回收的优点。

一个重要的例子是萘普生对映体的拆分。萘普生是非甾体抗炎药 (NSAIDs, 2-芳基丙酸) 中的一员。由博姿公司 (Boots) 开发的布洛芬 (商品名为诺洛芬 Nurofen) 的止痛药也属于这一类。



萘普生和布洛芬都是手性的，它们也都是仅有 (S) 对映体有止痛，或抗炎作用。布洛芬在人体内会外消旋化 racemize (见 Chapter 20)，因此分离它的对映体没有什么意义。但萘普生的对映体则会在发售前被美国制药公司 Syntex 所拆分。

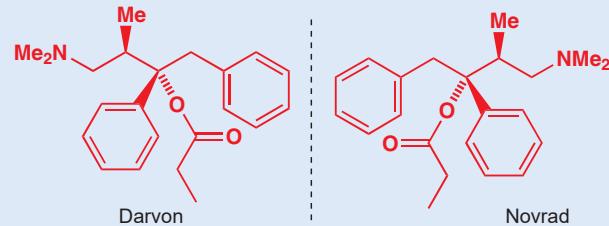
由于萘普生是一个羧酸，因此他们选择使用一种光学纯的胺产出羧酸盐，他们发现最有效的试剂是葡萄糖衍生物。羧酸与胺的反应产生了 (S)-萘普生铵盐 和 (R)-萘普生铵盐，后者更易溶解，因此在逐渐结晶时留在了溶液中。将晶体滤出，用碱洗涤后可重新得到胺 (回收再利用)，并得到想要的 (S)-萘普生 的钠盐。这次拆分过程所用的胺类是不寻常的，因为我们通常使用简单的胺类；但为了找到合适的拆分试剂，化学家需要经过多次尝试。



### 手性药物

您可能会纳闷，对映体总是有相同的性质，而萘普生却需要在上架前拆分对映体。虽然萘普生的两个对映体确实在实验室中具有相同的性质，但当它们进入一个生命系统后，它们就会与生命系统中原有的其他手性分子 (光学纯的) 相互作用，于是就自然产生了区别。比方说一对手套，它们有相同的重量，用相同的材料制成，也有相同的颜色——在这些方面它们是相同的；但如果试图将它们戴在一只手上 (外在的手性环境)，却只有其中一只手套是合适的。

药物与受体的结合十分接近手套与手的结合这一类比。药物受体，几乎都是由纯 L-氨基酸 形成的光学纯的蛋白质。因此药物的一种对映体往往比另一种对映体与之相互作用的效果好得多，或者干脆以完全不同的方式相互作用，因此手性药物的两种对映体在药理效果上往往完全不同。对于萘普生来说，(S)-对映体 要比 (R)-对映体 高效 28 倍。另一方面，布洛芬仍然以外消旋体 (racemate) 的形式出售，因为这种化合物在血循环中会外消旋化。

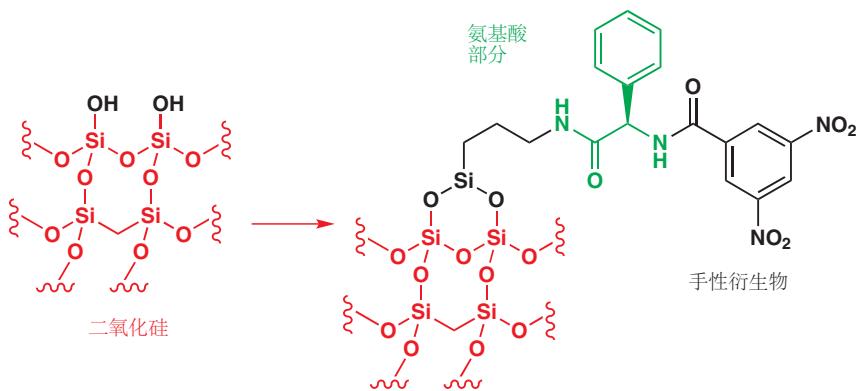


有时候，一种药物的两种对映体可能具有完全不同的治疗性质。例如止痛药 Darvon，它的对映体 Novrad 却是一种止咳药。注意高于它们结构之上的对映体关系！在 Chapter 41 中，我们会详细讨论两种对映体具有完全不同生物效果的情况。

### 通过手性原料的层析拆分

■ 二氧化硅,  $\text{SiO}_2$ , 是硅原子和氧原子组成的大分子体系。它的表面分布着游离OH基团, 可以与手性衍生试剂相结合。

比离子键还弱的相互作用甚至也能用于分离对映体。层析分离法依赖固定相 stationary phase (通常是二氧化硅) 和流动相 mobile phase (流经固定相的溶剂, 称为洗脱剂 eluent) 间的亲核性差异, 例如氢键, 或范德华相互作用。如果固定性通过与一个光学纯化合物 (通常是一个氨基酸衍生物) 结合从而具有手性, 层析法就可以用于分离对映体了。

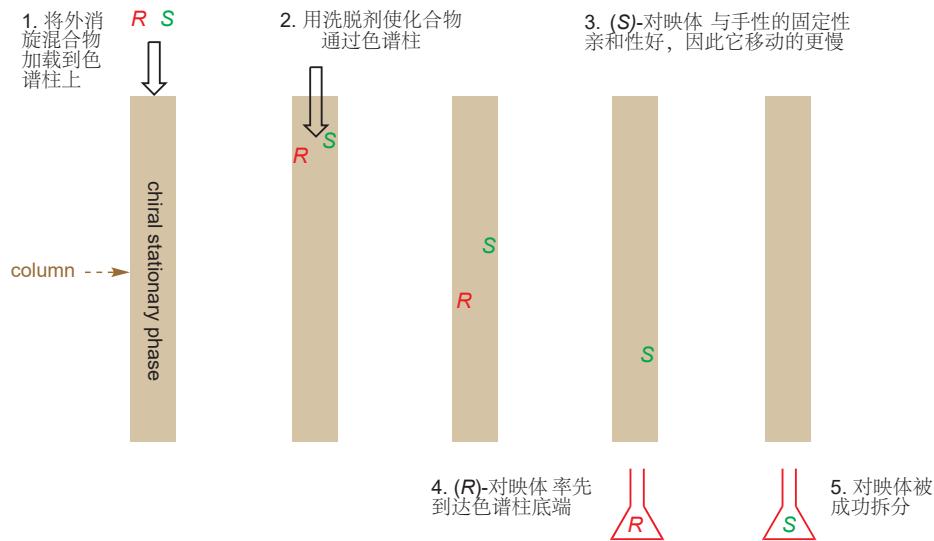


当待拆分的化合物没有合适的官能团，用于制造经典的拆分过程所需的衍生物（酯或盐）时，手性固定相的层析法就显得尤为重要。例如，一种镇静剂安定（地西泮）的类似物的两种对映体，就因为有完全不同的生物活性而必须被拆分。

#### 一种安定的类似物



为了进一步研究这些化合物的性质，获得光学纯的两种对映体是必须的工作。将外消旋混合物的溶液加载到与手性的氨基酸衍生物成键后的二氧化硅（固定相）色谱柱上，然后使用洗脱剂洗涤；这时，由于  $(R)$ - $(-)$ -对映体对固定相的亲和性很差，因此率先被从色谱柱上洗脱（elute）下来，而  $(S)$ - $(+)$ -对映体则最后被洗脱下来。



一个分子的两种对映体或许是相同的化合物，但它们仍在有限的情境下表现出不同。例如它们与生物系统以不同的方式作用；当与另一光学纯的（单一对映体的）化合物反应时，则会得到性质差距较大的两种盐或化合物。实质上，除非将其放入手性的环境中，一对对映体的性质都是完全相同的。在 Chapter 41 中我们会看到使用手性的化合物直接制备单一对映体的情形，而接下来我们将开始讨论三种立体化学在其中起决定作用的反应类型：取代反应，消除反应和加成反应。

■ 您可以这样考虑手性层析法。考虑下列情形，您要帮助一位在战争中失去左腿的退休朋友找鞋（仅需右鞋）。一爿本地鞋店会把他们多余的鞋捐给您，既有左鞋又有右鞋，都适合他的尺码（同时也适合您的）。当您开始挑选右鞋时，突然停电了。您该怎么做？您会将每一双鞋中在右脚上试一下，如果它合您的脚，就将其留下；如果发现穿反了，则将它丢掉。

这就是手性固定性的层析做所的事情。固定相就像很多只伸出来的“右脚”（用于吸附的光学纯手性分子），流过的外消旋混合物是各种“鞋”；只有“右鞋”可以被很好的媳妇，而“左鞋”就会继续向下流到色谱柱的下端。

## 延伸阅读

有很多关于立体化学的书。最详尽的大概是：E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley Interscience, Chichester, 1994。在此阶段，详尽的内容可能不适合您。Oxford Primer *Organic Stereochemistry*, M. J. T. Robinson, OUP, Oxford, 2001 中有更加易懂的介绍。

Feist 酸正确结构的首次发表：M. G. Ettinger, *J. Am. Chem. Soc.*, 1952, 74, 5805 还有一篇很有趣的补充文章，给出了其 NMR 光谱：W. E. von Doering and H. D. Roth, *Tetrahedron*, 1970, 26, 2825。

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 15

## 饱和碳上的亲核取代

### 联系

#### → 基础

- 在羰基上的亲核进攻 ch6 & ch9
- 羰基上的取代反应 ch10
- 羰基氧原子的取代反应 ch11
- 反应机理 ch12
- $^1\text{H}$  NMR ch13
- 立体化学 ch14

#### 目标

- 在饱和碳原子上的亲核进攻，导致取代反应
- 饱和碳原子上的取代反应与  $\text{C}=\text{O}$  上的取代反应的不同
- 亲核取代反应的两种机理
- 取代反应的中间体和过渡态
- 取代反应如何影响立体化学
- 什么样的亲核试剂可以取代，什么样的离去基团可以被取代
- 可以通过取代反应制取的分子，和它们可以由什么制取

#### → 展望

- 消除反应 ch17
- 芳香化合物作为亲核试剂的取代反应 ch21
- 烯醇盐作为亲核试剂的取代反应 ch25
- 逆合成分析 ch28
- 参与、重排和碎片化反应 ch36

### 亲核取代的机理

Chapter 10...



本章...

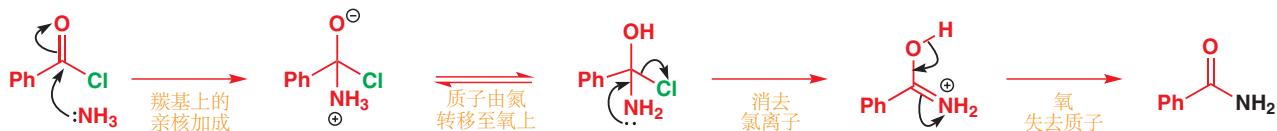


取代反应是一个基团被另一个集团取代的过程。您在 Chapter 10 中遇到过如左图所示的反应，反应中  $\text{Cl}$  被  $\text{NH}_2$  基团所取代，因此它是一个取代反应。当时您还学过，我们管反应中的氨 ( $\text{NH}_3$ ) 叫做亲核试剂 (nucleophile)，管氯离子叫做离去基团 (leaving group)。在 Chapter 10 中，亲核取代通常发生在羰基的三角型 ( $\text{sp}^2$ ) 碳上。

而在本章中，我们将要了解的是左图的第二种反应。这同样是取代反应，因为  $\text{Cl}$  被  $\text{PhS}^-$  基团取代。不同的是，这个反应发生在  $\text{CH}_2$  基的四面体型 ( $\text{sp}^3$ )，或者说饱和的碳原子上。从表面上看，这两个反应好像是相同的，但它们在机理上有相当大的区别；它们对好的试剂的要求也是不同的——这也是为什么我们将亲核试剂从  $\text{NH}_3$  换成了  $\text{PhS}^-$ ：氨在第二个反应中生成  $\text{PhCH}_2\text{NH}_2$  的过程不会有好的产率。

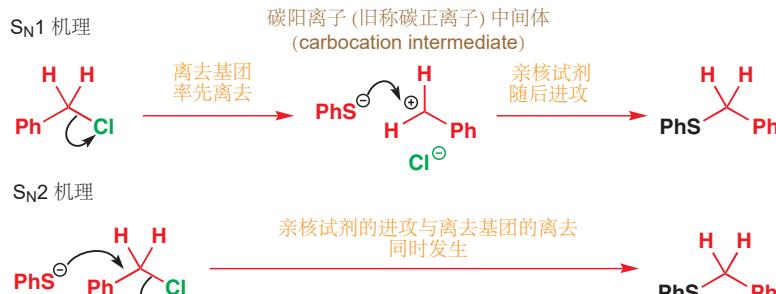
让我们来看一看为什么这两个取代反应的机理必须是不同的。下面是第一个反应的机理。

## 羰基上的亲核取代机理



在第一步中，亲核试剂进攻  $C=O \pi$  键。十分明显，这一步在饱和碳原子上不可能发生。电子无法加入  $\pi$  键，因为  $CH_2$  基已经饱和了；事实上，亲核试剂根本无法在离去基团离去之前先加上去（就像羰基的反应一样），因为这样会得到一个不可能的五键碳原子。

相反，另两种新的机理是可能的。其一是离去基团先自己离去，然后亲核试剂再加成到原来的位置上；其二是加成和离去两步在同时发生。我们常称第一种可能性为  $S_N1$  机理，第二种为  $S_N2$  机理，第二种机理展示了中性分子如何在接受电子的同时失去另一对电子。您接下来会发现，对于这个分子，苄基氯，这两种机理都是可行的。



Interactive mechanism for amide formation

Interactive mechanisms for  $S_N1$  and  $S_N2$

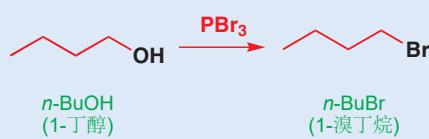
## 为什么了解这两种取代机理很重要？

如果我们知道一个化合物以哪种机理反应，我们就会知道用哪种条件可以得到高产率。例如，醇中的 OH 被 Br 取代的反应是一个十分常见的亲核取代反应；而您会发现，取决于醇的结构，叔丁醇与伯醇使用了两种完全不同的反应条件。叔醇与 HBr 迅速反应得到叔丁基溴；而另一方面，伯醇与 HBr 仅缓慢地反应，常常通过  $PBr_3$  使其转化为溴代烃。原因在于，前者是  $S_N1$  反应的例子，而后者是  $S_N2$  反应的例子：在本章的结尾，您会对如何预测机理，和选择合适的反应条件有一个清晰的描绘。

## 叔丁醇的取代反应



## 伯醇的取代反应



对于 则是二级反应  
(速率与  $[R-Br]$  和  $[OH^-]$  均有关系)

对于 则是一级反应  
(速率仅取决于  $[R-Br]$ ，而与  $[OH^-]$  无关)

 $S_N1$  和  $S_N2$  机理的动力学证据

在我们继续深入前，我们要更详细地看看这两种反应，因为它们允许我们解释和预测取代反应的很多方面。动力学证据让化学家确信，饱和碳原子的亲核取代有两种不同的机理：反应速率，例如右边氢氧根取代溴离子的反应速率。

这一理论主要由 Hughes 和 Ingold 在 1930s 发现：有些亲核取代反应是一级反应（即速率仅取决于

Edward David Hughes (1906–63) 和英果尔德 (Sir Christopher Ingold, 1893–1970) 在 1930s 年间在伦敦大学工作。他们首创了当今有机化学家认为理所当然的很多机理性想法。

■ 在 Chapter 12 中有更多关于机理与反应速率之间关系的描述。方括号表示浓度，比例系数  $k$  被称为速率常数。

■ 请注意如何书写这个符号，S 和 N 均为大写字母，其中 N 是下标。

于卤代烃单分子的浓度，与亲核试剂的浓度无关)，还有一些是二级反应（速率与卤代烃、亲核试剂的浓度都有关系）。我们如何解释这一现象？p. 329 中我们称为“ $S_N2$ ”的机理仅包含一步，下面是正丁基溴被氢氧根取代的一步  $S_N2$  机理。



由于仅有一步，那么它同时也是快步 (rate-determining step)。整个反应的速率都取决于快步的速率，运动学理论告诉我们，一个反应的速率与其反应物的浓度成比例：

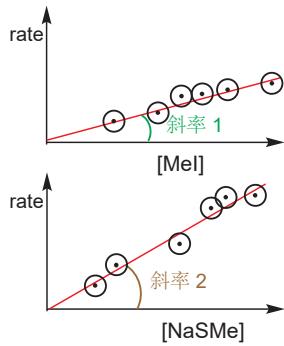
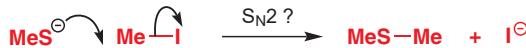
$$\text{rate} = k[n\text{-BuBr}][\text{HO}^-]$$

如果机理是正确的，那么反应速率将仅简单地与  $[n\text{-BuBr}]$  和  $[\text{HO}^-]$  成线性比例关系。事实也是如此，Ingold 测量了反应速率，并发现它们确实与这两种反应物的浓度都成正比——换句话说，这个反应是二级反应。因此该反应是二级亲核取代反应 (Substitution, Nucleophilic, 2nd order)，简写作  $S_N2$ 。速率方程如下所示， $k_2$  为二级反应速率常数。

$$\text{rate} = k_2[n\text{-BuBr}][\text{HO}^-]$$

### $S_N2$ 速率方程的意义

这个方程之所以有用，是在于两个地方。其一是，它验证了  $S_N2$  机理；让我们用另一个例子来说明这一点：NaSMe (一个离子盐——亲核试剂是阴离子  $\text{MeS}^-$ ) 与 MeI 生成  $\text{Me}_2\text{S}$  和二甲硫醚的反应。



为了研究速率方程，我们首先要控制 NaSMe 的浓度恒定，并在一系列实验中改变 MeI 的浓度，观察速率的变化。另一组实验则是保持 MeI 浓度恒定，改变 MeSNa，观察速率的变化。如果反应确实是  $S_N2$ ，那么我们在两种情况下都得到线性关系：第一张图展示了一组典型数据。

第一张图告诉我们，速率与  $[\text{MeI}]$  成正比，即  $\text{rate} = k_a[\text{MeI}]$ ；而第二张图告诉我们速率与  $[\text{MeSNa}]$  成正比，即  $\text{rate} = k_b[\text{MeSNa}]$ 。但为什么它们的斜率不同？仔细考察这两个速率方程您就会发现我们将每组实验中，控制恒定的那个反应物的浓度混入了速率常数中。正确的速率方程是：

$$\text{rate} = k_2[\text{MeSNa}][\text{MeI}]$$

如果  $[\text{MeSNa}]$  恒定，则方程变为

$$\text{rate} = k_a [\text{MeI}], \text{ 其中 } k_a = k_2[\text{MeSNa}]$$

如果  $[\text{MeI}]$  恒定，则方程变为

$$\text{rate} = k_b [\text{MeSNa}], \text{ 其中 } k_b = k_2[\text{MeI}]$$

如果您仔细观察左图，就会发现两个变量分别恒定时简化得到的方程斜率不同，因为

$$\text{斜率 } 1 = k_a = k_2[\text{MeSNa}], \text{ 而斜率 } 2 = k_b = k_2[\text{MeI}]$$

我们可以很容易地从这些结论中得到这真正的速率常数  $k_2$ ，因为我们知道第一个实验中控制的  $[\text{MeSNa}]$  的数值，和第二个实验中控制的  $[\text{MeI}]$  的数值。两个实验中得到的  $k_2$  应当相等。这个反

应的机理确实是  $S_N2$ : 亲核试剂  $\text{MeS}^-$  进攻, 伴随着离去基团  $\text{I}^-$  的离去。

$S_N2$  速率方程的第二个有用之处在于, 它证实了,  $S_N2$  反应的效果同时取决于**亲核试剂和碳亲电试剂**。因此我们可以通过改变其中任何一个, 来使反应进行得更好 (加速反应, 或增加产率)。例如, 如果我想用氧亲核试剂取代  $\text{MeI}$  中的  $\text{I}^-$ , 那么我们会考虑下表中的任何一种。

$S_N2$  反应的氧亲核试剂

氧亲核试剂	共轭酸的 $pK_a$	$S_N2$ 反应速率
$\text{HO}^-$	15.7 ( $\text{H}_2\text{O}$ )	快
$\text{RCO}_2^-$	大约 5 ( $\text{RCO}_2\text{H}$ )	适中
$\text{H}_2\text{O}$	-1.7 ( $\text{H}_3\text{O}^+$ )	慢
$\text{RSO}_2\text{O}^-$	0 ( $\text{RSO}_2\text{OH}$ )	慢

→ 见 Chapter 8 对  $pK_a$  值的讨论。

氢氧根有碱性, 和好的亲核性是同一原因造成的 (主要由于负离子状态不稳定, 因此活泼)。碱性可以看作是对质子的亲核性, 与对碳原子的亲核性必定是有一定联系的。因此如果我们想让反应加速, 我们就应该用  $\text{NaOH}$ , 而不是例如  $\text{Na}_2\text{SO}_4$  做亲核试剂。因为即使在相同浓度下,  $\text{HO}^-$  作为亲核试剂的速率常数  $k_2$  也远大于  $\text{SO}_4^{2-}$  做亲核试剂的速率常数  $k_2$ 。

但这不是我们唯一可做选择的地方。亲电碳的反应性和结构也对反应效果产生影响。如果我们想让在甲基上的取代速率更快, 我们虽然不能改变碳链结构, 但我们可以改变离去基团。下表展示了使用不同的甲基卤与  $\text{NaOH}$  反应的情况。使反应快速进行的最佳选择 ( $k_2$  的最大值) 是  $\text{MeI}$  与  $\text{NaOH}$  得到甲醇。



您在 Chapter 10 中曾看到, 亲核试剂对羧基的进攻与碱性的联系十分密切。但对饱和碳原子的进攻与碱性的关系与其不同, 但我们可以知道, 仍有一些联系。

■ 我们会在稍后更详细地讨论亲核性和离去基团的离去性。

$S_N2$  反应的卤素离去基

$\text{MeX}$ 中的卤素 $X$	共轭酸 $\text{HX}$ 的 $pK_a$	与 $\text{NaOH}$ 的反应速率
F	+3	确实非常慢
Cl	-7	适中
Br	-9	快
I	-10	非常快

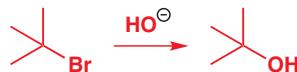
### ● $S_N2$ 反应的速率取决于:

- 亲核试剂
- 碳骨架结构
- 离去基团

当然, 通常还有温度和溶剂因素。

### $S_N1$ 速率方程的意义

如果将正丁基溴换成叔丁基溴, 那么我们可以得到如右图所示的取代反应。动力学结果表明, 这个反应是一级反应: 它的速率仅取决于  $\text{tert-BuBr}$  的浓度——而与所加入的氢氧根的浓度无关: 速率方程为



$$\text{rate} = k_1[t\text{-BuBr}]$$

原因在于，这个反应分两步进行：第一步中溴离子离去，生成一个碳阳离子；然后氢氧根才去进攻，生成醇。

$S_N1$  机理： $t\text{-BuBr}$  与氢氧根离子的反应

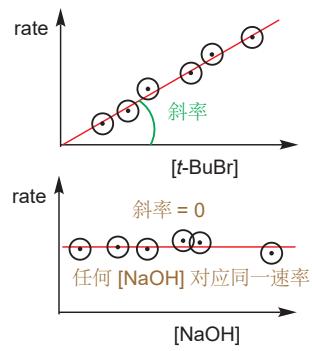


在  $S_N1$  机理中，碳阳离子的生成是决速步。这很有道理：碳阳离子是不稳定的物种，因此由稳定的中性有机分子生成碳阳离子是很缓慢的；一旦碳阳离子生成，它就会立刻反应，不管亲核试剂是什么。因此， $t\text{-BuBr}$  消失的速率仅是缓慢的第一步的速率：亲核试剂氢氧根并没有参加这一步，因此也不含出现在速率方程中，更不会影响反应速率。如果这个观点对您来说不好理解，那么想象一下，一簇人群正在通过几个闸机 (turnstiles) 离开火车站或者球赛场，无论他们能走多快，能跑多快，或者之后坐的出租车能开多快，但仅有闸机开合的速度可以决定火车站或球赛场的散场速率。

再重复一遍，速率方程让我们方便地判断反应是  $S_N1$  还是  $S_N2$ 。之前我们画了  $S_N2$  机理速率随浓度变化的图，我们也可以画出  $S_N1$  的变化图，如左侧所示。一张图是  $[NaOH]$  恒定时速率随  $[t\text{-BuBr}]$  的变化规律，另一张图是  $[t\text{-BuBr}]$  恒定时速率随  $[NaOH]$  的变化规律。

图一的斜率是简单的一级速率常数，因为  $\text{rate} = k_1[t\text{-BuBr}]$ ；但图二的斜率为零。这是由于决速步不含  $NaOH$ ，因此添加再多也不会加速反应。这个反应的表现是一级动力学的（速率仅与一种物质的浓度成正比），因此该机理被称作  $S_N1$ ，即一级亲核取代 (Substitution, Nucleophilic, 1st order)。

这种观察十分有价值。亲核试剂并没有出现在速率方程中，这意味着它的浓度在反应速率上是无关紧要的——它的反应性同样无关紧要！如果我们为了完成这个反应而打开一瓶  $NaOH$ ，那我们完全是在浪费时间——用水就能办到同样的事。前面提到过的所有强亲核试剂与  $t\text{-BuBr}$  反应的速率都是相同的（虽然与  $MeI$  反应的速率天差地别）。实际上， $S_N1$  取代反应通常使用亲核性较弱的、无碱性的亲核试剂，这是最好的，目的是为了避免与消除反应的竞争，我们会在 Chapter 17 详细讨论。



#### ● $S_N1$ 反应的速率取决于：

- 碳骨架结构
- 离去基团

当然，通常还有温度和溶剂因素。

不取决于亲核试剂。

## 如何判断给定有机物会采取的机理 ( $S_N1$ 或 $S_N2$ )

综上所述，饱和 C 上的亲核取代反应会遵循两种机理中的一种反应，这两种机理对亲核试剂的性质的依赖程度完全不同。能够预测每个此类的反应所遵循的机理是十分重要的，与其通过动力学实验探究，我们可以给您一些关于哪类情况适用哪类机理的简单观点。影响反应采用哪种机理的因素

会帮我们解释为什么这种机理会被适用。

最重要的因素是碳骨架的结构。一个泛论是，能够形成相对稳定的碳阳离子的化合物倾向于采取  $S_N1$  机理，而其他的化合物别无选择，不得不采取  $S_N2$  机理。您马上就会看到，最稳定的碳阳离子通常是带正电的碳上所连取代基最多的一个，因此反应中心上的取代基越多，越容易采取  $S_N1$  机理。

恰巧，使碳阳离子稳定的结构因素通常也会减缓  $S_N2$  反应的速率。反应中心取代基多的化合物在  $S_N1$  中表现很好，同时也在  $S_N2$  反应中表现得很不好，这是因为亲核试剂必须通过拥挤的取代基抵达反应中心。 $S_N2$  反应的底物最好在反应中心上仅有氢原子——甲基代物在  $S_N2$  机理中反应迅速。最简单的结构变化产生的影响，可以总结为下表 (R 是一个简单的烷基，例如甲基、乙基)。

### ● $S_N1$ 还是 $S_N2$ ?

简单的结构和对  $S_N1$  或  $S_N2$  机理的选择

结构 类型	$Me-X$	伯碳	仲碳	叔碳
$S_N1$ 反应?	不	不	适中	非常好
$S_N2$ 反应?	好	好	适中	不

无阻碍地进攻  
很容易生成碳阳离子

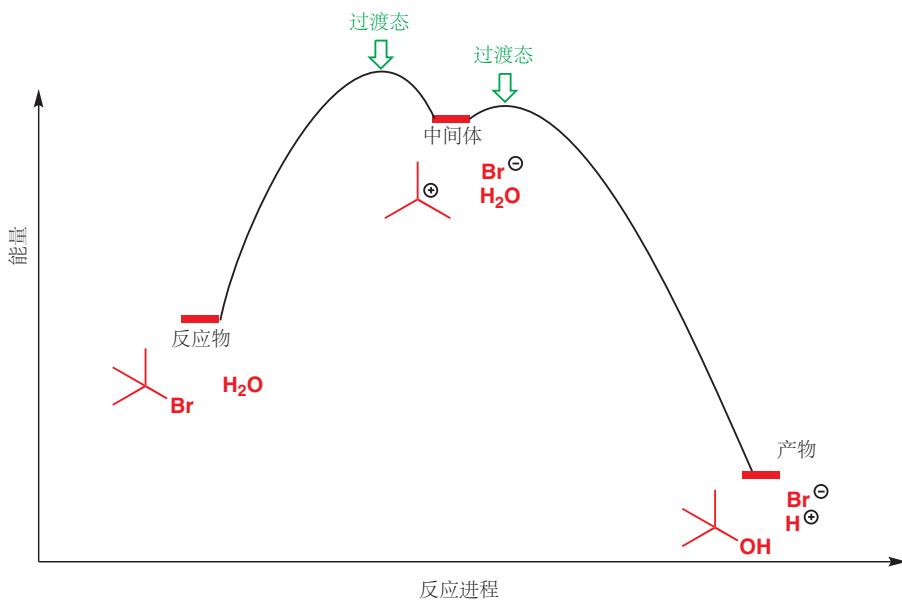
唯一值得怀疑的是仲烷基取代五，因为这两种机理它们都可以采用，然而在每一种机理中反应都不是特别好。当您面对一个新的亲核取代反应时，您首先要问的问题是“亲电碳是甲基碳，伯碳，仲碳还是叔碳？”这会让您对那个反应的研究有一个好的开始，这也是为什么我们在 Chapter 2 中向您介绍这些重要的术语。

在本章的后面，我们将更详细地探讨这两种机理的差异，和倾向于按各自反应的结构，但一切内容都建立在上面的表格上。

## 细看 $S_N1$ 反应

在上面关于  $S_N1$  反应的讨论中，我们提到，叔丁基溴通过先离去溴离子，得到一个合理的中间体，叔丁基碳阳离子。而我们现在需要解释碳阳离子如何存在，以及为什么叔丁基碳阳离子相比于例如正丁基碳阳离子等等其他的碳阳离子稳定很多。

在 Chapter 12 中，我们介绍了用反应能量变化图跟踪反应进程的思路，包括从反应物、产物、过渡态、中间体的能量相对关系。叔丁基溴与水发生  $S_N1$  反应的反应能量变化图如下页所示：



碳阳离子在图中被表示为一个中间体——一个寿命有限的物种，原因我们稍后讨论。因为我们知道，反应的第一步，即碳阳离子的生成是缓慢的，因此过渡态的能量很高。过渡态的能量，决定了反应速率，同时也与碳阳离子中间体的稳定性密切相关；正是由于这个原因，决定一个  $S_N1$  反应效果的最重要因素，是可能作为中间体生成的碳阳离子的稳定性。

### 碳阳离子的形状和稳定性

我们在 Chapter 4 (p. 103) 讨论了甲基阳离子的平面型形状，而叔丁基阳离子也与其相似：中心碳原子是六电子构型的，来自三根  $\sigma$  键，因此它还含有一个空的 p 轨道。任何碳阳离子都表现为平面型中心碳，和其上的一个空 p 轨道。用下列方式思考：只有填充了电子的轨道会对分子的能量产生影响，因此如果一个原子不得不有一个空轨道（碳阳离子通常有的），那么空轨道最好在能量上尽可能高，这样充满轨道的能量就随之变得最低了。p 轨道的能量高于 s 轨道（也高于  $sp$ ,  $sp^2$ , 和  $sp^3$  杂化轨道），因此碳阳离子通常让一个 p 轨道空置。

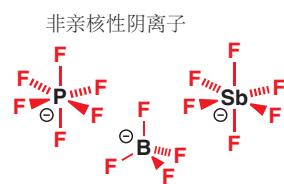
#### 碳阳离子稳定性

叔丁基阳离子比其他碳阳离子稳定很多很多，但仍不足以让您将它们存在一个瓶子里并摆在架子上！碳阳离子稳定与否的概念在理解  $S_N1$  反应时很重要，但您要知道这些比较都是相对的：最稳定的碳阳离子也是活泼的缺电子物种。



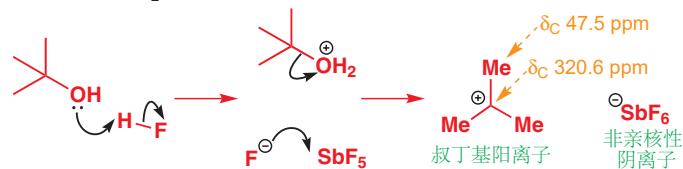
叔丁基阳离子足够稳定，以至于可以被观察到。George Olah 曾对此进行研究，并于 1994 年获诺贝尔化学奖。这个实验所面临的挑战是，碳阳离子是十分活泼的亲电试剂，解决这个问题，Olah 的想法是使用没有亲核试剂的溶液。而任何阳离子都需要相对应的阴离子来平衡电荷，因此他使用了由卤素包裹住中心原子的阴离子，它们有负电荷，但很稳定，不会作为亲核试剂。例如  $BF_4^-$ ,  $PF_6^-$ , 和  $SbF_6^-$ 。第一种是小体积的四面体型，后两者是大体积的八面体型。

在这些阴离子中，负电荷不等于一对孤电子（例如  $BH_4^-$  中负电荷所表示的），并且它们中也没有高能的充满轨道，可以作为亲核试剂。使用非亲核性溶剂，液态  $SO_2$  在低温下观察，Olah 能够将醇转化为碳阳离子与这些负离子的盐。下面是叔丁醇与  $SbF_5$ , HF 在液态  $SO_2$  中的变化。酸使羟基质子化



化，进而离去水分子；这时 SbF<sub>5</sub> 紧紧抓住氟离子，使其不能充当亲核试剂。碳阳离子现在孤立无援。

Olah 在液态 SO<sub>2</sub> 中制备叔丁基阳离子



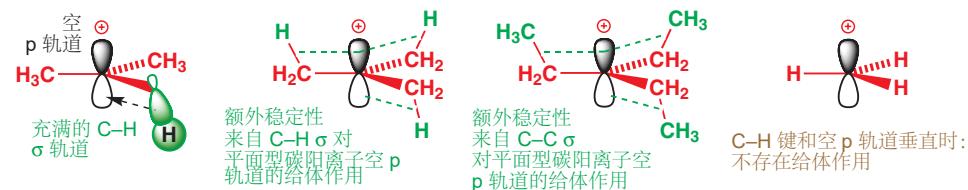
叔丁基阳离子的质子 NMR 表明，三个甲基只有一个在 4.15 ppm 处的信号，与 C-Me 基的低磁场相距很远。则远低于此信号。<sup>13</sup>C 光谱也显示了在 47.5 ppm 处的低磁场 Me 信号，但证实阳离子形成的关键证据在于中心碳原子的位移达到了惊人的 320.6 ppm，比任何您之前见过的物种都低磁场。这个碳去屏蔽性很强——它带正电，极度缺电子。

从 Olah 的工作中，我们知道叔丁基阳离子在 NMR 中的样子，那么我们可以通过 NMR 证实它是取代反应中的中间体吗？如果我们在 NMR 管中混合 *t*-BuBr 和 NaOH，并让它们在 NMR 仪中反应，我们不会观察到属于碳阳离子的信号。这没有证明任何问题。我们不能指望一个活泼的中间体以明显的浓度出现。原因很简单。如果碳阳离子不稳定，它就会迅速与周围的任何亲核试剂发生反应，溶液中则不会出现任何可观浓度的碳阳离子。碳阳离子生成的速率会比反应掉的速率慢很多。

## 烷基取代使碳阳离子稳定

Olah 发现，他可以测出叔丁基阳离子的光谱，但他一直无法在溶液中测出甲基阳离子。为什么中心碳上取代基的增多会使碳阳离子稳定呢？

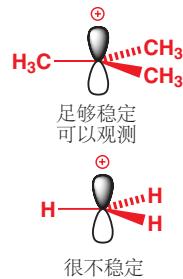
任何带电荷的有机中间体都天生不稳定。碳阳离子也仅仅在有一些额外的稳定性的帮助下，才会生成。额外的稳定性可以来源于  $\sigma$  键对空 p 轨道的给体作用 ( $\sigma$ -共轭,  $\sigma$ -conjugation)，这种作用较微弱。在叔丁基阳离子中，这种作用同一时间存在三个：C-H 键指向上方还是下方并不产生影响；在任何时间，每个甲基中必定有一个 C-H 键平行于空 p 轨道的一个瓣。第一张图使用轨道图表示了其中一个重叠，第二、三张用虚线表示了同时存在的三个重叠。



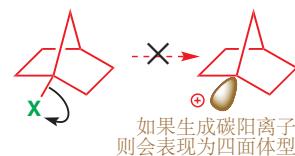
C-H 键对空轨道的给体作用并没有什么特别的：C-C 键同样可以，其他一些键还会做用地更好（例如 C-Si）。但它们必定都属于一类——如果直接连氢原子，则既没有孤对电子，也没有  $\sigma$  键可以稳定碳阳离子。

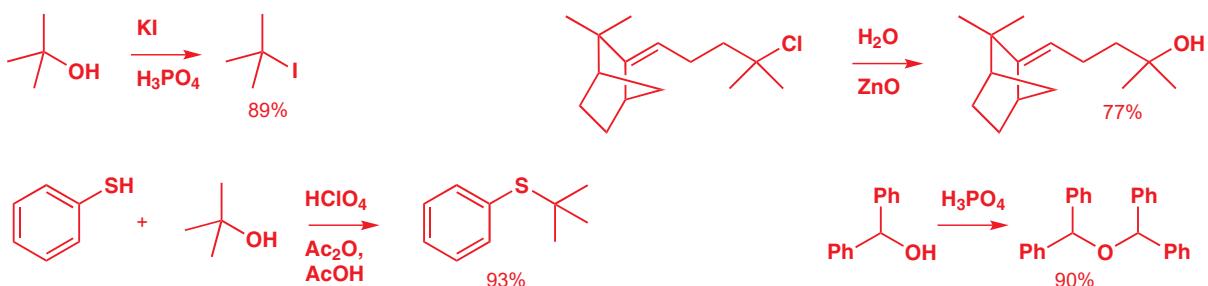
碳阳离子的平面型是非常重要的结构特征，如果叔碳阳离子不能形成平面型，那么它也不会形成。一个经典的例子是右侧的结构，它不能与亲核试剂通过 S<sub>N</sub>1 或 S<sub>N</sub>2 机理反应。它不能通过 S<sub>N</sub>1 反应是因为不能生成平面型的碳阳离子；不能通过 S<sub>N</sub>2 反应是因为亲核试剂不能从正确的方向接近碳原子。

一般来说，简单的叔碳取代会以 S<sub>N</sub>1 机理有效地发生。在有好的离去基团，例如卤素的情况下，取代反应可以在中性条件下进行；离去基团较差，例如反应物是醇类或是醚类的时候，则需要酸催化。下面给出了 S<sub>N</sub>1 反应可以很好地发生的几种不同情形。



Interactive display of stability and structure of carbocations





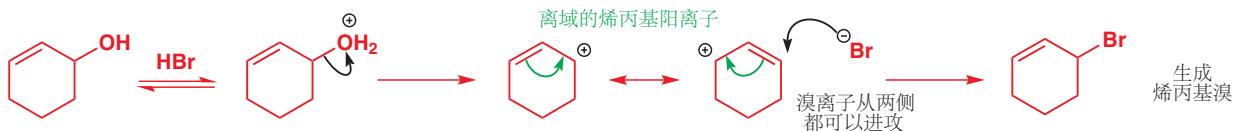
### 相邻的 C=C π 体系使碳阳离子稳定：烯丙基阳离子和苄基阳离子

我们在 Chapter 7 中讨论过了烯丙基阳离子的共轭作用。

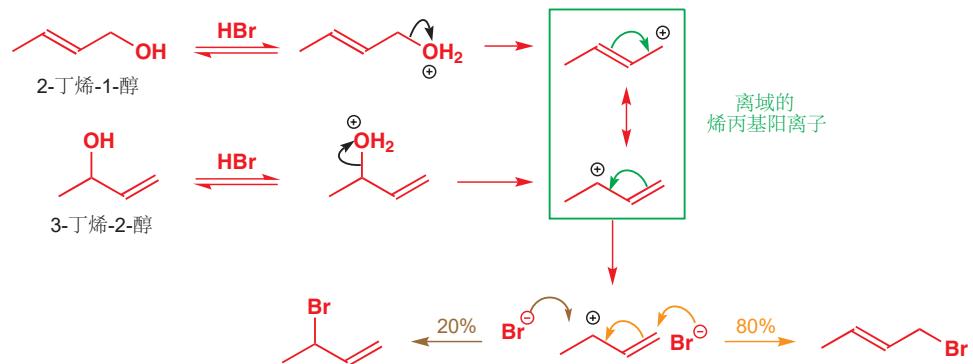
叔碳阳离子比伯碳阳离子要更稳定，但当空 p 轨道与相邻的  $\pi$  键或孤对电子产生名副其实的共轭时，则会提供更强大的稳定性。烯丙基阳离子含有一个充满的轨道，这个轨道上的两个电子离域在三个原子之间，而正电荷离域在两端的碳原子上。这个轨道是会被亲核试剂进攻的轨道，弯曲箭头告诉我们相同的事情。



烯丙基亲电试剂会很好地以  $S_N1$  机理反应，因为烯丙基阳离子相对稳定。下面是一个与您目前看到的大多数反应相反方向进行的例子——我们开始于醇，并得到溴代物。环己烯醇和 HBr 的反应中给出了烯丙基阳离子的溴化物。

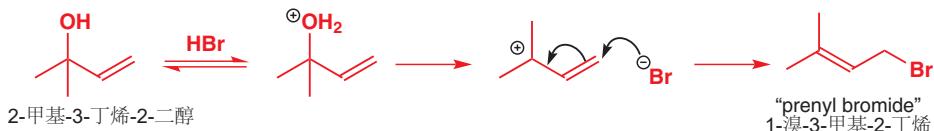


在这个情形中，只生成了一种化合物，因为进攻烯丙基阳离子的两端都给出相同的产物。但当烯丙基阳离子是不对称的时候，就会得到烦人的混合产物。下面两种丁烯醇与 HBr 反应的效果是相同的，因为它们会经历相同的离域的烯丙基阳离子中间体。

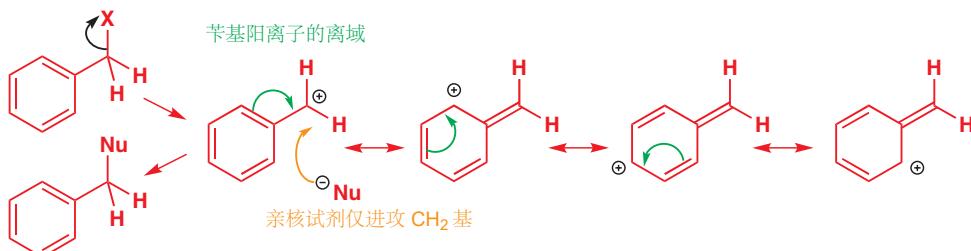


当这个阳离子与 Br<sup>-</sup> 反应时，大约 80% 进攻一侧，而 20% 进攻另一侧，得到两种丁烯基溴的混合物。这种**区域选择性 regioselectivity**（亲核试剂进攻位置的选择性）来源于空间位阻：在烯丙基体系中阻碍小的地方进攻快，在阻碍大的地方进攻慢。

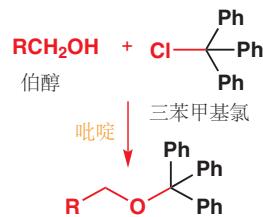
这种选择性的分析是模棱两可的，但有时却很有用。叔丙烯基醇 2-甲基-3-丁烯-2-二醇 很容易通过 S<sub>N</sub>1 机理的反应制备，因为制备反应所经过的碳阳离子既是叔的，又是烯丙基的。烯丙基碳阳离子中间体是不对称的，溴仅进攻取代少的一端得到“prenyl bromide”。



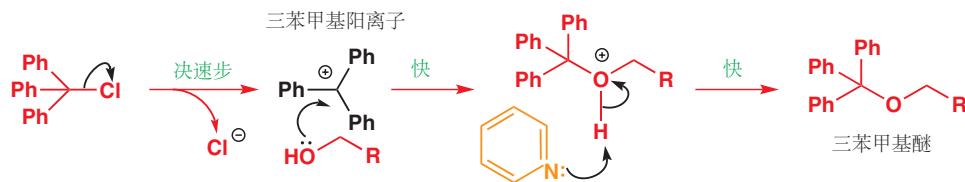
苄基阳离子与烯丙基阳离子一样稳定，但并不能像烯丙基阳离子一样得到混合产物。虽然正电荷被离域到整个苯环上，尤其是在下图所示的三个位置，但苄基阳离子通常还是会在侧链上反应，这样可以保护芳香性。



当三个苯环用于稳定同一个正电荷时，所得到的碳阳离子，即三苯甲基阳离子 (triphenylmethyl cation, 简写作 “the trityl cation” )，就会异常稳定。三苯甲基氯被用于通过 S<sub>N</sub>1 反应与伯醇制备醚。您会发现在这个反应中，必定被用作溶剂。吡啶 (一个弱碱：它的共轭酸的 pK<sub>a</sub> 为 5.5——见 Chapter 8) 并不足以去掉伯醇的质子 (pK<sub>a</sub> 大约 15)，因此没有足够强的碱性生成 RCH<sub>2</sub>O<sup>-</sup> 作为亲核试剂，并没有影响 S<sub>N</sub>1 反应的发生。相反，TrCl 会先电离成三苯甲基阳离子，然后捕获伯醇，并生成锌离子，这时吡啶就有能力从锌盐上移去质子了。吡啶并不是反应的催化剂；它的作用在于除去生成的 HCl，使体系不会随着反应进行而逐渐变酸。吡啶也是被用于离子反应的一种方便的有机极性溶剂。



■ 符号 Tr 代表 Ph<sub>3</sub>C 基。



下一页的表格展示了在 50% 的乙醇水溶液中取代的烯丙基氯、苄基氯和简单氯代烃的溶剂解 (i.e. 溶剂充当亲核试剂的反应) 速率。这些数值可以帮助您建立一个对不同种类化合物之间相对反应性的印象。这些速率大多反映的是 S<sub>N</sub>1 的，但其中有一些是伯醇，有 S<sub>N</sub>2 反应性。

50% 乙醇水溶液, 44.6 °C 下氯代烃的溶剂解速率

化合物	相对速率	注释
	0.07	伯氯代物: 很可能仅发生 S_N2
	0.12	仲氯代物: 可以发生 S_N1 但不是很好
	2100	叔氯代物: 在 S_N1 上表现很好
	1.0	伯烯丙基氯: S_N1 是好的
	91	其中一端是仲碳的烯丙基氯
	130000	其中一端是叔碳的烯丙基氯: 与简单叔氯代物的 2100 进行对比
	7700	伯碳, 但既是烯丙基阳离子也是苯基阳离子

### 相邻的孤对电子使碳阳离子稳定

被称为甲基氯甲基醚的卤代烷,  $\text{MeOCH}_2\text{Cl}$ , 可以很好地与醇反应生成酯。作为一个伯卤代烷, 您会想这个反应是遵循  $\text{S}_{\text{N}}2$  机理的, 但事实上它有  $\text{S}_{\text{N}}1$  的特征反应性。通常来说, 它倾向于  $\text{S}_{\text{N}}1$  机理的原因, 在于它有生成稳定碳阳离子的能力。在相邻的氧的孤对电子的帮助下, 可以脱去氯离子, 我们可以将所生成的阳离子画成锌离子, 也可以将其画成碳阳离子。

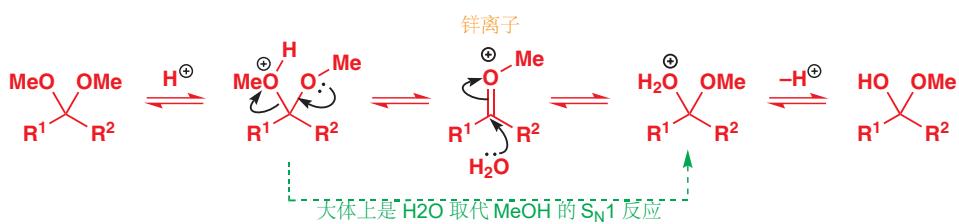


### 甲氧基甲基阳离子



Olah 也曾使用上述方法在溶液中自缚甲氧基甲基阳离子。虽然这个阳离子既可画作锌离子, 又可以画作伯碳阳离子, 但锌离子的结构更贴近真实。将这个阳离子的质子 NMR 光谱与异丙醇的对比 (我们可以做的最适合的对比) 显示  $\text{CH}_2$  基上的质子在 9.9 ppm 处共振, 而不是真正的碳阳离子的 13.0 ppm 处。

回想 Chapter 11, 您会回忆起缩醛水解的第一步反应与之相似, 水代替烷氧基得到半缩醛。我们在 Chapter 11 中考虑这个反应的机理时, 没有考虑关注第一步反应所属的分类。它其实是一种  $\text{S}_{\text{N}}1$  取代反应: 质子化的缩醛分解产生锌离子。如果您将这一步与刚才氯醚的反应对比, 就会发现它们在机理上十分相似。



Interactive mechanism for acetal hydrolysis

### 常见错误

请不要试图走捷径，水直接通过  $S_N2$  反应取代甲醇的机理是错误的。



在此如此拥挤的碳上不会发生  $S_N2$  机理。然而，主要原因在于，由于  $MeO$  上孤对电子对碳阳离子中间体的稳定作用， $S_N1$  机理已经十分有效了， $S_N2$  机理并没有机会实施。

同一个碳原子上，一个负电性基团作为亲核试剂，通过  $S_N1$  机理取代另一个负电性基团的例子十分常见。您应该在一个碳原子上连有两个，例如 O, N, S, Cl, 或 Br 的基团时注意这个问题。很好的离去基团（例如卤素）不需要酸催化，稍微差些的离去基团（N, O, S）则需要酸。



对于氮的例子，请回顾 Chapter 11 中亚胺离子的生成。

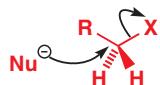
下面较完整地梳理了一般会通过  $S_N1$  机理（而非  $S_N2$ ）发生反应的结构种类。

### $S_N1$ 反应中作为中间体的稳定碳阳离子

碳阳离子类型	例子 1	例子 2
简单烷烃	叔（好） 叔丁基阳离子 $Me_3C^+ = Me-\overset{Me}{\underset{Me}{\overset{\oplus}{C}}}-$	仲（不是很好） 异丙基阳离子 $Me_2CH^+ = H-\overset{Me}{\underset{Me}{\overset{\oplus}{C}}}-$
共轭	烯丙基阳离子 	苄基阳离子 
杂原子	氧（锌离子） 	氮（亚胺离子） 

## 细看 $S_N2$ 反应

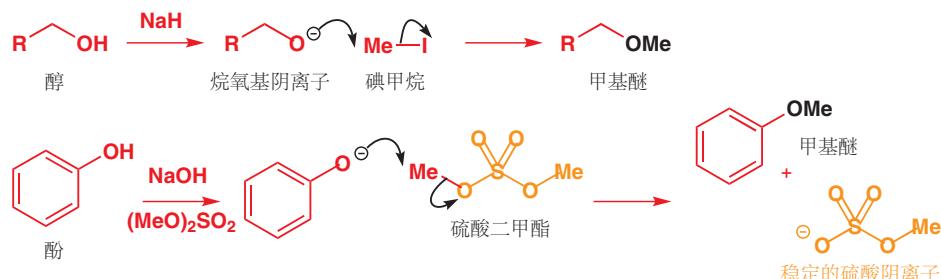
注意到我们说的是“简单的烷基化合物”：当然，伯烯丙基，伯苯基和 RO 或 R<sub>2</sub>N 取代的伯碳也可能通过  $S_N1$  反应！



亲核试剂通过  $S_N2$  反应利落地进攻甲基化合物 ( $R=H$ ) 和伯烷基化合物 ( $R=\text{烷基}$ )

简单的烷基化合物中，甲基碳和伯碳通常通过  $S_N2$  机理反应，从不通过  $S_N1$  机理反应。一部分是因为碳阳离子的不稳定性，一部分是因为氢原子的空阻小，使亲核试剂很容易穿过。

醚类通常可以通过烷氧基阴离子和一个烷基卤代物的反应制备。如果是甲基卤代物，那么我们可以肯定地说，反应会通过  $S_N2$  机理进行。我们还需要一个强碱，例如此处的 NaH，用来生成烷氧基阴离子 (alkoxide ion)，因为醇的酸性很弱 ( $pK_a$  大约 16)。碘甲烷是一种合适的亲电试剂。

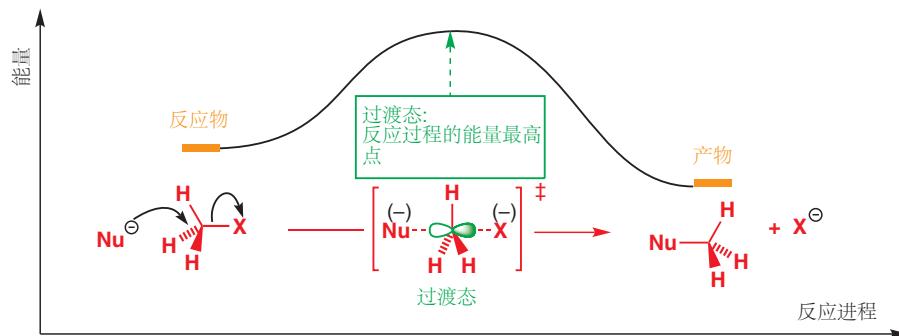


对于酸性较强的苯酚 ( $pK_a$  大约 10)，NaOH 就足以作为生成烷氧基阴离子的碱。硫酸二甲酯 (dimethyl sulfate) 常被用作亲电试剂。使用强碱，来让醇成为更好的亲核试剂是十分值得的，因为 p. 331 关于  $S_N2$  反应的速率方程的描述告诉我们：亲核试剂的能力和浓度对于反应的速率是会产生影响的。

### $S_N2$ 反应的过渡态

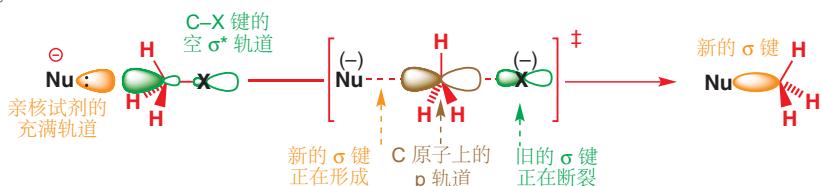
我们在 Chapter 12 中介绍了过渡态 (transition state) 和中间体 (intermediate) 的术语。

有关这一机理，我们还可以从过渡态予以讨论，亲核试剂、甲基和离去基团都在过渡态中出现。过渡态是反应过程的能量最高点。在  $S_N2$  反应中，它会是亲核试剂将要形成的新键还未完全形成，而离去基团的旧键还未完全断裂的时刻。如下所示：



过渡态中的虚线表示半键 partial bonds (即 C–Nu 键断裂一半，而 C–X 键形成一半)，而括号中的电荷表示部分电荷 partial charges (本情形中两个基团都带半个单位负电荷)。过渡态通常画在方括号中，并用符号  $\ddagger$  即标记。

轨道也可以作为一种理解方式。亲核试剂必定有孤对电子，正是孤对电子与 C–X 键的  $\sigma^*$  轨道相互作用。

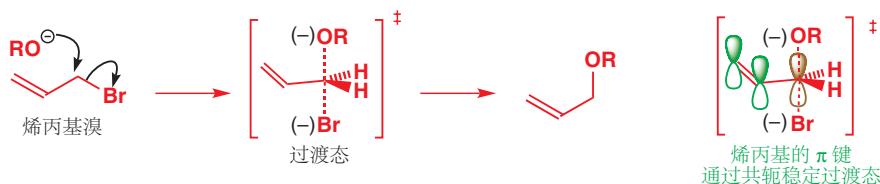


在过渡态中，中心碳原子有一个 p 轨道在旧键、新键之间共享一对电子。这两幅图都表明，S<sub>N</sub>2 反应的过渡态在中间有一个近似平面的碳原子，亲核试剂和离去基团分别排列在其两侧，成角 180°。这幅图可以帮助我们解释对 S<sub>N</sub>2 反应的观察得到的两个重要结论——第一是可以有效反应的结构种类，第二是反应的立体化学。

### 相邻的 C=C 或 C=O π 体系可以提高 S<sub>N</sub>2 反应的速率

我们认可：甲基和伯碳化合物通过 S<sub>N</sub>2 机理反应良好，而仲碳化合物则只是勉强能通过 S<sub>N</sub>2 反应。但同样有一些重要的结构特征会促进 S<sub>N</sub>2 机理的发生。烯丙基和苄基化合物的出现会促进 S<sub>N</sub>1 机理，然而它们也可以促进 S<sub>N</sub>2 机理。

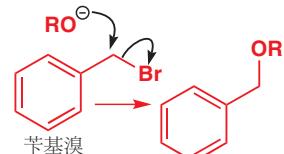
烯丙基溴可以很好地与醇盐反应生成醚，此过程是一个典型的 S<sub>N</sub>2 机理，如下所示。观察反应过渡态可以发现，烯丙基化合物通过 S<sub>N</sub>2 反应十分迅速的原因是邻位双键的 π 体系通过共轭对过渡态的稳定作用。反应中心的 p 轨道（图中以棕色表示，和 p. 340 中棕色表示的轨道相同）通过两个电子成两根半键——它是缺电子的，因此相邻的 π 体系所提供的额外的电子密度，会对过渡态有稳定作用，并且加快反应速率。



Interactive S<sub>N</sub>2 mechanism at allylic and benzylic centres

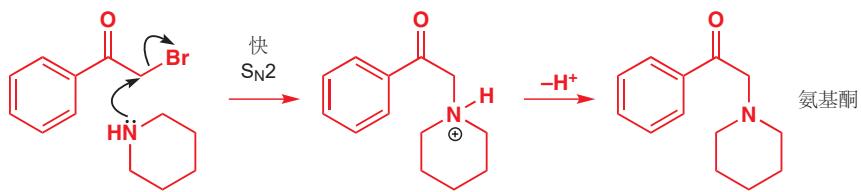
苄基的作用与其大同小异，苯环的 π 体系会通过与 p 轨道的共轭稳定过渡态。苄基溴可以很好地与醇盐反应生成苄醇。

在所有的 S<sub>N</sub>2 反应中，离去基团与羰基相邻的情况反应速率最快。对于 α-溴代羰基化合物，如图中的两个相邻的碳原子都是强的亲电位点；都有低能的空轨道——C=O 的  $\pi^*$  和 C-Br 的  $\sigma^*$ （这两个碳原子亲电性的具体体现）。它们可以结合生成一个新的 LUMO ( $\pi^* + \sigma^*$ )，它在能量上比两个轨道都要更低，而亲核试剂则会进攻这个轨道的系数最大的位点，如下图橘色。



这两个反键轨道之间相互作用的效果是：由于另一个基团的存在，每个基团的亲电性都有所增强——C=O 的存在使 C-Br 键更加活泼，而 Br 使 C=O 更加活泼。事实上，亲核试剂确实可能会进攻羰基，但这种情况可逆的，而对溴的进攻则是不可逆的。

这类反应有很多例子，例如胺就可以很好地反应，而氨基酮 (aminoketone) 产物也被广泛地应用于药物合成。



### 结构对 $S_N2$ 反应的定量影响

一些真实数据可能会帮助您理解。以下是烷基氯与  $KI$  中  $50^\circ C$  丙酮中反应的反应速率，大致反映了我们刚刚分析的  $S_N2$  反应方式。它们都是将  $n\text{-BuCl}$  看作“典型的伯卤代物”(为 0) 而从得到的相对速率。您不应该过分注意它们确切的数值，而是应该从趋势上考察，并注意大的变化——最差到最好的变化是从 0.02 到 100,000，大约是十的八次。



### 烷基氯与碘离子发生取代反应的相对速率

烷基氯	相对速率	注释
$\text{Me}-\text{Cl}$	200	空阻最小的烷基氯
	0.02	仲烷基氯；由于空阻比较慢
	79	过渡态中的共轭加速烯丙基氯反应
	200	苄基氯比烯丙基稍稍活泼：苯环提供的 $\pi$ 共轭稍好于孤立双键提供的
	920	氧原子孤对电子通过共轭加速反应(这是一个 $S_N1$ 反应)
	100,000	羰基提供的共轭比简单的烯烃或苯环都要有效； $\alpha$ -卤代羰基化合物是最活泼的烷基卤

## $S_N1$ 与 $S_N2$ 之间的对比

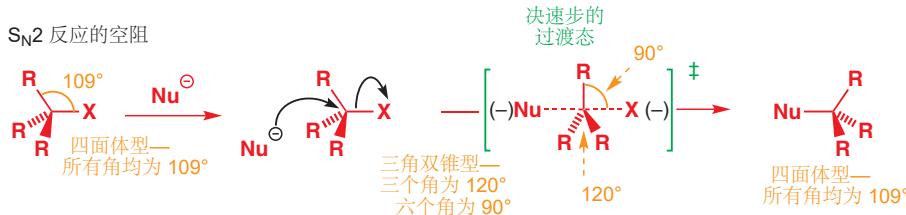
目前为止，这两种重要的取代机理的关键特征都呈现在您面前了；阅读到此处时，您应当对  $S_N1$  和  $S_N2$  反应过程的动力学，过渡态和中间产物的性质，以及电子因素、空间因素有所把握。

本节，我们将继续更详细地探讨这两种机理中的重要差异，要么是因为某种差异会导致不同的结果产生，要么是因为它会让遵循两种机理发生反应的反应性变化。

### 空间因素

我们已经指出，反应中心上的烷基取代基越多，就越倾向于通过  $S_N1$  而非  $S_N2$  机理反应，有两点原因：首先是碳阳离子随着碳级数的增大而稳定，随之更倾向于  $S_N1$ ；其次是因为  $S_N2$  反应的决速步涉及亲核试剂对中心碳的进攻，而取代基越多，则由于空间原因亲核试剂越难靠近。让我们更详细地讨论这两个反应中最缓慢的一步的过渡态，来考察空间是如何影响它们的。

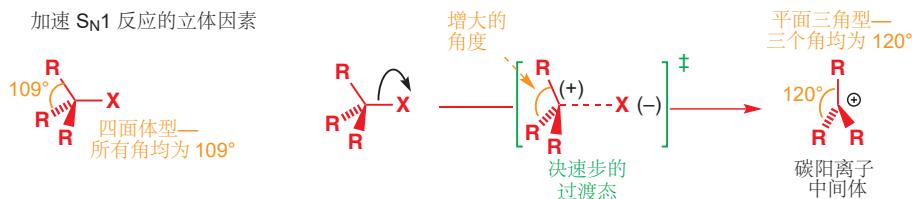
在 S<sub>N</sub>2 的过渡态中，被进攻的碳原子接受新的取代基，并（短暂地）处于五配位。取代基之间的键角由四面体角减少为 90°。



在起始物中，所有的四个角均为 109°。而在过渡态（使用  $\ddagger$  标记的方括号中的）中则有三个角是 120°，另六个角是 90°，拥挤程度显著增加。取代基 R 的体积越大，拥挤的严重程度就越大，而过渡态的能量也随之越高。比较如下三种结构发生反应的效果，我们可以很轻易地看出空阻的影响。

- 甲基: CH<sub>3</sub>-X: 很快的 S<sub>N</sub>2 反应
- 伯碳: RCH<sub>2</sub>-X: 较快的 S<sub>N</sub>2 反应
- 仲碳: R<sub>2</sub>CH-X: 较慢的 S<sub>N</sub>2 反应

S<sub>N</sub>1 反应的情况则恰恰相反。这类反应的决速步是离去基团的离去，其过渡态如下图所示——有相比于起始物更长、更脆弱、更极化的 C-X 键。起始物中的四个键角仍是四面体角 109°，而中间体阳离子中的三个键角是 120° ——更大的角度，意味着拥挤程度的缓解，因此过渡态会向阳离子的方向转变。正是由于过渡态中的 R 基团间的距离比起始物中的远，因此 R 基团越大，过渡态和起始物间的活化能则会越低。烷基取代加快 S<sub>N</sub>1 反应的原因，是碳阳离子的稳定性，和拥挤程度的缓解所共同导致的。



## 立体化学

请回到 p. 340 重新考察 S<sub>N</sub>2 反应的过程图，您会发现，亲核试剂总会从离去基团的反位（正好相对的位置）进攻碳原子。然后，仔细观察受进攻的这个碳原子，在反应前后，它的所有取代基都发生了由内而外的翻转，就像大风中的雨伞一样。如果这个受进攻的碳是一个立体中心（Chapter 14），那么反应的发生会导致构型翻转（inversion of configuration）。而在 S<sub>N</sub>1 反应中，这件事则完全不同，我们会通过一个简单的例子说明这种差别。

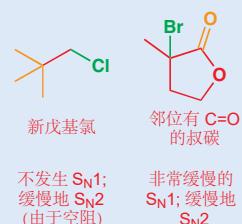


由正旋光性的仲丁醇（2-丁醇，一种二级醇）出发，可以按 p. 338 叙述的方法得到二级碳阳离子。然后用水淬灭（quench）碳阳离子，就会得到得到无光活性的醇。在这一过程中，水分子必然会以

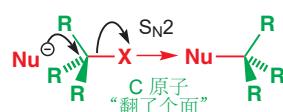
虽然叔碳化合物由于空间阻碍，根本无法通过 S<sub>N</sub>2 机理发生反应；但事实上它们通过 S<sub>N</sub>1 反应的速度是其他一切通过 S<sub>N</sub>2 反应的化合物，甚至是甲基化合物，所不能望其项背的。您可以参考 p. 338 的数据。

有一些叔碳化合物也可以缓慢地，勉强发生 S<sub>N</sub>2 反应；例如如果邻位有吸电子的羰基，那么 S<sub>N</sub>1 反应的发生会被组织，而与之对应的 S<sub>N</sub>2 反应则略有优势。

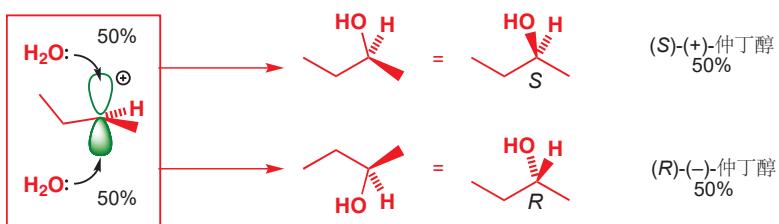
另一类特例，由于其他原因而导致空间位阻增大的伯烷基卤，既不能通过 S<sub>N</sub>1 反应（因为是伯碳），也不能通过 S<sub>N</sub>2 反应（因为空阻）——“新戊基卤化物”就因此不具反应性。



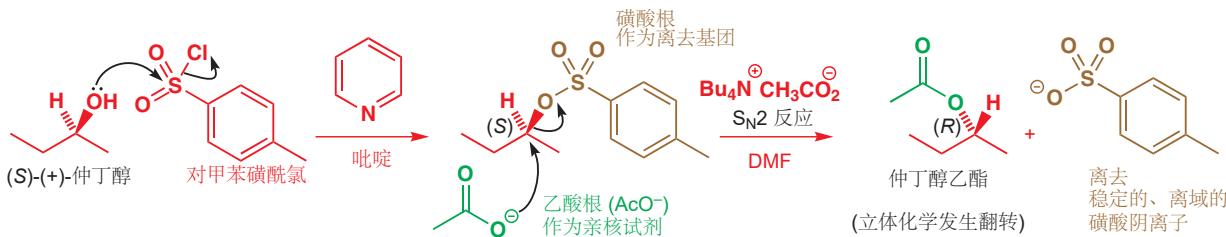
注意到 S<sub>N</sub>1 反应过渡态的结构很接近于碳阳离子的结构，在 p. 334 的能量分布图上它们也是离得很近的。当我们说到碳阳离子的稳定性对 S<sub>N</sub>1 反应速率的影响时，就意味着我们其实是在说即将生成碳阳离子的过渡态的稳定性。然而，由于它们的结构十分相似，您完全可以假设它们的空间因素、电子因素都是相似的。



相同的可能性进攻平面型碳阳离子的两个面：因此其产物是 50:50 的 (S)-仲丁醇与 (R)-仲丁醇的混合物，即外消旋。



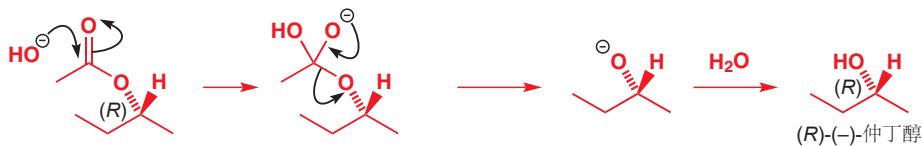
或者，我们还可以将羟基做成一个好的离去基团，使仲丁醇发生  $S_N2$  反应。几页后我们会向您介绍我们将要用的离去基团，即一个磺酸酯，的具体内容；但现在您只需要接受以下观点：在吡啶中，磺酰氯可以通过对 OH 的亲核取代得到如下图棕色所示的磺酸酯；在手性碳原子上没有任何键的形成和断裂，也就是说该手性碳仍是 (S) 立体化学。



于是，醋酸根离子就可以通过  $S_N2$  反应进攻。我们将醋酸根以季铵盐 (tetra-alkyl ammonium salt) 的形式溶解在 DMF 中，有效地避免了溶剂化，增强了其作为亲核试剂的反应活性，这在作为  $S_N2$  反应的试剂时是十分有用的。而磺酸根阴离子是一个极好的离去基团——因为负电荷离域在三个氧原子上。

► 旋光性的描述在 p. 309.

产物仲丁醇乙酯是有光活性的，我们可以测量其旋光度。但就目前来说，这是毫无意义的，因为我们无法通过旋光度的正负判断构型，除非我们知道其中一种仲丁醇乙酯纯品的旋光度。在理论上，我们期待它是 (R) 立体化学的，以下方法可以轻易地证实这一结论。我们将酯水解，重新得到醇。醇是我们的起始原料，因此我们知道醇旋光度的正负与其构型的对应关系；而且我们也知道酯水解 (Chapter 10) 发生在羰基碳上，对我们要研究的手性中心的立体化学无影响。



现在事情解决了。得到的仲丁醇样品与我们的起始样品的旋光度正好互为相反数。它是光学纯的 (−)-(R)-仲丁醇，因此反应过程经历了构型翻转。我们知道构型翻转并不发生在硫酸酯的形成、乙酯的水解，这些在手性中心上没有键的形成或断裂的步骤上。因此它发生在  $S_N2$  反应的过程本身。

●  $S_N2$  反应会导致被进攻的碳原子构型翻转，而  $S_N1$  反应通常得到外消旋产物。

### 溶剂效应

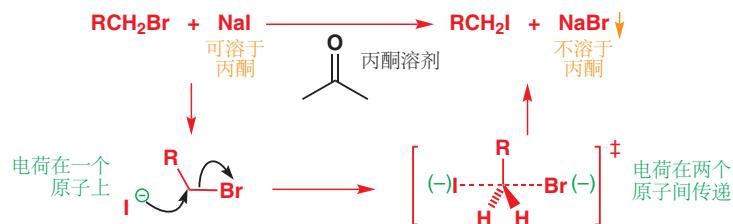
► Chapter 12 叙述了不同种类的溶剂。

为什么刚刚的  $S_N2$  反应在 DMF 中进行？您会发现， $S_N2$  反应通常发生于非质子，极性较小的溶剂中；而  $S_N1$  反应则典型地发生在质子偶极溶剂中。 $S_N2$  反应的一个常用溶剂是丙酮——弱极性

足以用来溶解离子性试剂，而极性又比不上醋酸，S<sub>N</sub>1 反应的常用溶剂。

S<sub>N</sub>1 反应需要极性溶剂的原因十分明显：其决速步包含离子的生成（通常是离去基团阴离子，和碳阳离子/阳离子），因此作为可以溶剂化这些离子的极性溶剂，当然有增快反应速率的作用。更准确地讲，反应的过渡态比反应物更加极化（之前的图中括号中的电荷），因此会被极性溶剂所稳定。因此水或者羧酸 (RCO<sub>2</sub>H) 是理想的。

然而 S<sub>N</sub>2 反应为什么需要弱极性溶剂的原因，就不那么明显了。最寻常的 S<sub>N</sub>2 反应需要一个阴离子作为亲核试剂，而其过渡态则比反应物更不极化（电荷由定域在一个原子上，到在两个原子间传递）。下面是一个例子：烷基溴被取代为烷基碘。由于丙酮不能溶剂化碘离子，因此使得它的反应活性很高，而过渡态对溶剂化的需求很少，所以总体上反应速度加快。



这个反应还利用了碘化钠、溴化钠在丙酮中的溶解度区别，使生成物溴化钠从溶液中沉淀出来，以防止溴离子竞争亲核试剂的地位。

DMF 和 DMSO，都是我们在 Chapter 12 讨论过的非质子极性溶剂 (p. 255)，它们也是 S<sub>N</sub>2 反应很好的溶剂，因为它们可以很好地溶解离子化合物，但却不能很好地溶解阴离子，进而使阴离子更加活泼。选择 Bu<sub>4</sub>N<sup>+</sup> 的原因则是因为它是一个大的、非配位阳离子。

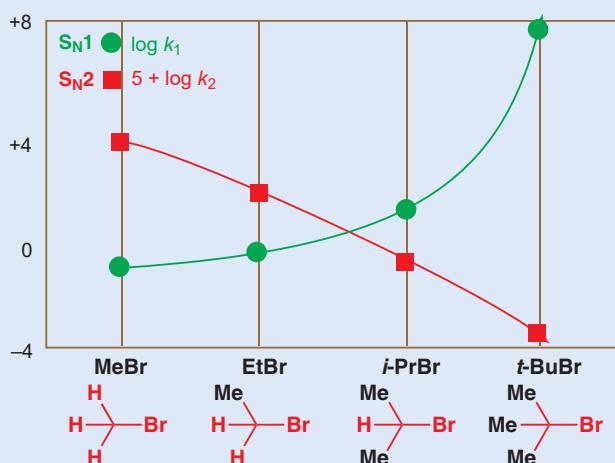
### 量化 S<sub>N</sub>1 和 S<sub>N</sub>2 反应的速率

下面的数据说明了结构对 S<sub>N</sub>1 和 S<sub>N</sub>2 反应速率的影响。图中绿色曲线显示了一个 S<sub>N</sub>1 反应的速率 ( $k_1$ )：100 °C 下甲酸中烷基溴转化为烷基甲酯的反应。甲酸是一个极性溶剂，也是一个弱亲核试剂，十分有利于 S<sub>N</sub>1 反应。红色曲线显示了 25 °C 的丙酮中 Br<sup>-</sup> 被放射性的 <sup>82</sup>Br<sup>-</sup> 取代的速率。丙酮溶剂和亲核试剂 Br<sup>-</sup> 都有利于 S<sub>N</sub>2。其速率 ( $k_2$ ) 需要乘以 10<sup>5</sup> 才能使对应的曲线被画在同一幅图中。



两条曲线都以对数标尺绘制，真实速率的 log<sub>10</sub> 被画在 y 轴上，x 轴没有真实含义，仅给出四种简单结构：MeBr, MeCH<sub>2</sub>Br, Me<sub>2</sub>CHBr, 和 Me<sub>3</sub>CBr 所对应的四个点。

简单烷基溴的 S<sub>N</sub>1 和 S<sub>N</sub>2 反应速率



下表也总结了这几个值，相对速率是伯卤， $i\text{-PrBr}$  作为 1.0 得出的相对值。

简单烷基溴的  $S_{\text{N}}1$  和  $S_{\text{N}}2$  反应速率、

烷基溴类型	$\text{CH}_3\text{Br}$ 甲基	$\text{CH}_3\text{CH}_2\text{Br}$ 伯碳	$(\text{CH}_3)_2\text{CHBr}$ 仲碳	$(\text{CH}_3)_3\text{CBr}$ 叔碳
$k_1 (\text{s}^{-1})$	0.6	1.0	26	$10^8$
$10^5 k_2 (\text{M}^{-1} \text{dm}^{-3} \text{s}^{-1})$	13,000	170	6	0.0003
相对的 $k_1$	$2 \times 10^{-2}$	$4 \times 10^{-2}$	1	$4 \times 10^6$
相对的 $k_2$	$6 \times 10^3$	30	1	$5 \times 10^{-5}$

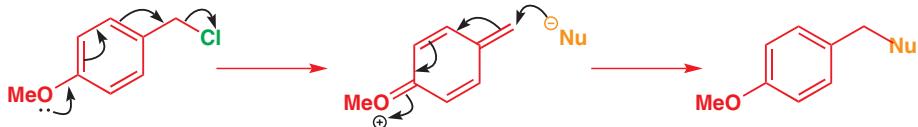
尽管某种情况下会较多地发生  $S_{\text{N}}1$  反应，另一种情况下会较多地发生  $S_{\text{N}}2$  反应，但当然，我们无法阻止分子“错误地”发生反应！ $\text{MeBr}$  和  $\text{MeCH}_2\text{Br}$  有“ $S_{\text{N}}1$ ”反应发生，事实上是由于弱亲核试剂  $\text{HCO}_2\text{H}$  对溴离子  $S_{\text{N}}2$  取代稍缓导致的，而  $t\text{-BuBr}$  发生“ $S_{\text{N}}2$ ”也许是由于丙酮减缓了  $t\text{-BuBr}$  的电离。

## 电子因素

上文中我们提到过，相邻的  $\pi$  体系会通过稳定过渡态增加  $S_{\text{N}}2$  反应的速率，也会通过稳定碳阳离子增加  $S_{\text{N}}1$  反应的速率。 $\text{G-C}$ （富电子）和  $\text{G-O}$ （缺电子）两种  $\pi$  体系都对  $S_{\text{N}}2$  反应的速率产生影响，但仅有  $\text{C=C}$  的  $\pi$  体系对  $S_{\text{N}}1$  反应的速率产生影响。事实上，相邻  $\text{C=O}$  的存在还会显著地减慢烷基卤的  $S_{\text{N}}1$  反应速率，因为羰基的吸电子效应会显著地使碳阳离子不稳定。

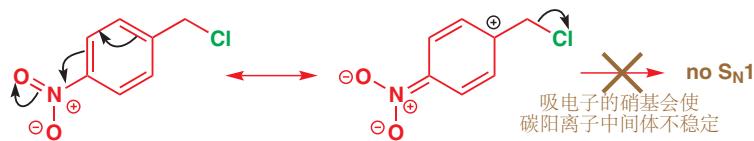
在一个将两种机理平衡地很好的物种上添加吸电子基或给电子基，就会使其倾向于其中一种机理。例如，苄基化合物不论  $S_{\text{N}}1$  还是  $S_{\text{N}}2$  都能反应地很好，溶剂的更换就可能会使其反应从一个机理切换至另一个。而如果在合适位置上放置给电子基团，则可以使其倾向于  $S_{\text{N}}1$  机理。**4-甲氧基苄基氯** 就因此按  $S_{\text{N}}1$  机理反应；下图是甲氧基帮助氯离子离去，并稳定阳离子的过程。

给电子物种喜欢  $S_{\text{N}}1$  机理



另一方面，如果将甲氧基换做一个吸电子基团，例如一个硝基，那么苄基化合物发生  $S_{\text{N}}1$  反应的速率就会减慢，进而  $S_{\text{N}}2$  机理占据上风。

吸电子物种不喜欢  $S_{\text{N}}1$  机理



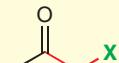
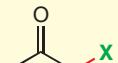
相反，它以  $S_{\text{N}}2$  机理反应



对苄基氯的速率测量验证了这一影响。我们可以使用甲醇作溶剂（甲醇是弱的亲核试剂，也是极性溶剂：都不利于  $S_{\text{N}}2$ ），从而强迫它们都按  $S_{\text{N}}1$  机理反应。将二者的速率与苄氯， $\text{PhCH}_2\text{Cl}$  其自身对比：4-甲氧基苄基氯与甲醇的反应比苄氯快 2500 倍，而 4-硝基苄基氯则慢 3000 倍。

### ● 结构变化与亲核取代机理的总结

现在，我们可以梳理一下前面几页我们讨论过的，结构对于两种机理的影响。下表列出了结构类型，以及定性的速率比较。

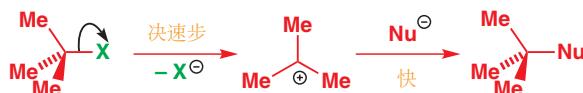
亲电试剂	Me-X	R-CH <sub>2</sub> -X	R-CH(X)-CH <sub>3</sub>	R <sub>2</sub> CH-X	R <sub>3</sub> C-X
	甲基	伯碳	仲碳	叔碳	“新戊基”
S <sub>N</sub> 1 机理？	差	差	一般	极好	差
S <sub>N</sub> 2 机理？	极好	好	一般	差	差
亲电试剂					
	烯丙基	苄基	$\alpha$ -烷氧基 (孤对电子)	$\alpha$ -羰基	$\alpha$ -羰基 并且是叔碳
S <sub>N</sub> 1 机理？	好	好	好	差	差
S <sub>N</sub> 2 机理？	好	好	还行，但 S <sub>N</sub> 1 更好	极好	可行

我们已经考虑了基本碳骨架和溶剂对 S<sub>N</sub>1 和 S<sub>N</sub>2 反应的重要影响，而现在话题将转向最后的两种结构因素：亲核试剂和离去基团。我们首先要应对离去基团的问题，因为它在不论 S<sub>N</sub>1 还是 S<sub>N</sub>2 反应中都发挥着重要作用。

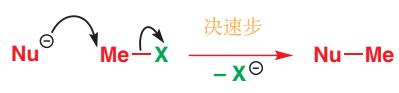
## S<sub>N</sub>1 和 S<sub>N</sub>2 反应中的离去基团

离去基团对于不论 S<sub>N</sub>1 还是 S<sub>N</sub>2 反应都是重要的，因为这两种机理的决速步都包含离去基团的离去。

### S<sub>N</sub>1 反应中的离去基团



### S<sub>N</sub>2 反应中的离去基团



到目前为止，您见到的反应基本上都是以卤离子或者水（醇的质子化产生）做离去基团。卤素和氧原子是十分重要的离去原子。现在我们将要找到影响离去基团好坏的因素，并建立理论。离去基团的好坏取决于它的离去性；但作为一个化学家，我们当然也要让反应物不那么不稳定，因此离去基团也要有适当的持久性。

### 卤离子作为离去基团

当卤素作为离去基团时，有两个发挥作用的因素：C–卤键的强度和卤素阴离子的稳定性。C–X 键的强度可以很容易地测量（键能），但我们如何测量离子的稳定性呢？一个您在 Chapter 8 遇到过的方法，是使用 HX 酸的  $pK_a$ ， $pK_a$  量化了阴离子相比于其共轭酸的稳定性。虽然我们希望了解的是阴离子相比于其与 C 成键时的稳定性，而不是其与 H 成键的稳定性，但  $pK_a$  仍然有其指导作用。

$S_N1$  和  $S_N2$  反应中的卤素离去基团

卤素(X)	C-X键的键能, kJ mol <sup>-1</sup>	HX的pK <sub>a</sub>
氟	118	+3
氯	81	-7
溴	67	-9
碘	54	-10

■ 在 Chapter 10 中对于 C=O 的亲核取代上您接受了相同的观点：氢氧根从来不做离去基团。在 Chapter 17 中的 E1cb 反应出现了这一规则的特例，但特例确实很稀少，您有足够的理由在此阶段忽略它们。

侧边的表格显示了它们共轭酸的 pK<sub>a</sub>，断裂一根 C-I 键很容易，但断裂 C-F 键是最困难的。碘似乎是最好的离去基团。我们从 pK<sub>a</sub> 值的比较中也得到了相同的结论：**H** 是其中最强的酸，因此它很容易电离成 H<sup>+</sup> 和 I<sup>-</sup>。结果很清楚——碘是一个极好的离去基团，而氟是一个很差的离去基团，其他卤素的离去能力位于二者之间。

### 醇上的亲核取代：如何让 OH 基离去

那么对于以 C-O 键连接的离去基团呢？这种离去基团有很多类，其中最重要的是 OH 自身、羧酸酯和磷酸酯。首先我们必须先明确一点：醇不会与亲核试剂反应。换句话说，OH<sup>-</sup> 从来不会作为离去基团。其原因在于，氢氧根阴离子的碱性很强，如果亲核试剂的碱性强到足以取代一个氢氧根下来，那么它首先就必然能够使醇去质子。

氢氧根的  $S_N2$  取代从不发生



如果亲核试剂真的发生反应，它会进攻质子

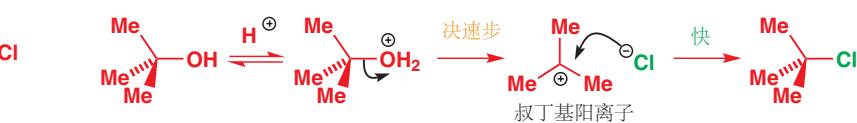


由于醇很容易制得（例如用 Chapter 9 中的方法），我们是很想让其能够参与亲核取代反应的。最简单的方法是使用强酸质子化 OH 基。您需要注意亲核试剂是否与强酸兼容（很多是可以的）。例如，由 t-BuOH 制备 t-BuCl 的办法就是将其与浓 HCl 在一起振荡。这是很明显的  $S_N1$  反应，叔丁基阳离子作为中间体。

叔丁基醇 转化为 叔丁基氯

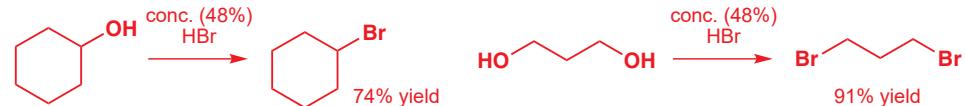


机理

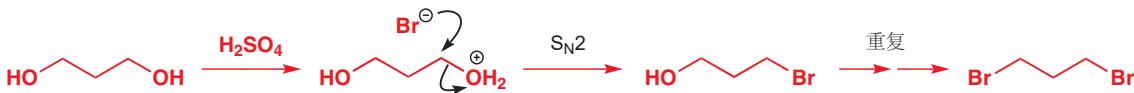


相似的方法可以用于其他情形，仲溴代烷只需要用 HBr 就可以制得，而溴代烷需要 HBr 和 H<sub>2</sub>SO<sub>4</sub> 混合使用。

酸中仲醇的取代

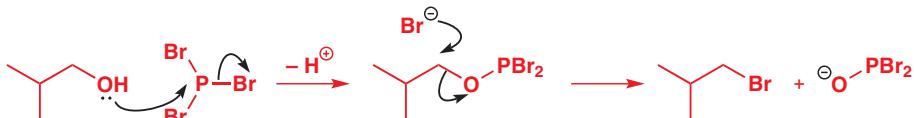
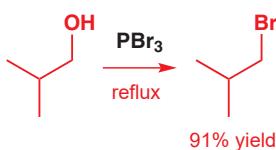


仲醇取代的机理必定是  $S_N2$ ，其中质子化后的羟基被溴取代。



使用一个能够与氧成十分强的键的元素处理 OH，则也可以将其转化为一个好的离去基团，进而使亲核取代能在羟基上发生。最受欢迎的选择是磷和硫。使用 PBr<sub>3</sub> 制备伯溴代物的方法效果很好。

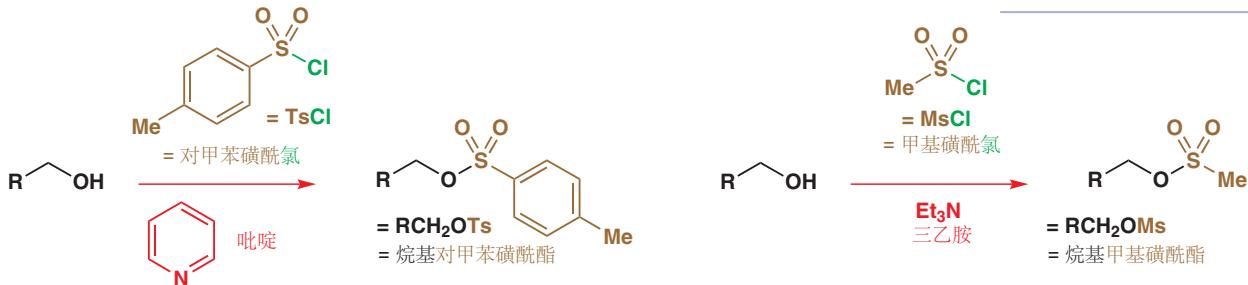
磷试剂首先被 OH 基进攻（一个在磷上发生的  $S_N2$  反应）。然后此时取代反应就可以很好地发生了，因为氧阴离子被磷所稳定。



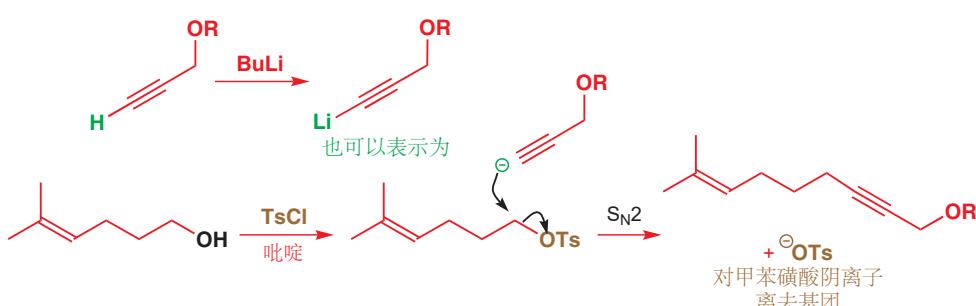
### 由醇制备磺酸酯(对甲苯磺酸酯和甲磺酸酯)

将羟基转化为一个好的离去基团最广泛使用的方法是将其做成磺酸酯。伯醇和仲醇可以在碱性下使用磺酰氯轻易地被转化为磺酸酯。磺酸酯通常是结晶状的。另外，正是由于其使用广泛，两种最常用的磺酸酯有它们自己的俗称——其中对甲苯磺酸酯(*p*-toluenesulfonates)被称作“tosylates”，甲基磺酸酯(methanesulfonates)被称为“mesylates”——这两种酰基(对甲苯磺酰基“tosyl”和甲基磺酰基“mesyl”)也有它们的“有机元素”符号，即 Ts 和 Ms。

对甲苯磺酸酯由醇和对甲苯磺酰氯在吡啶的存在下制得，而甲基磺酰氯也可以以类似的方法与醇制得甲基磺酸酯。这两个反应十分类似，但机理却不同，我们会在 Chapter 17 具体讨论。



磺酸 RSO<sub>3</sub>H 是强酸 ( $pK_a$  大约为 0)，因此任何的磺酸阴离子 RSO<sub>3</sub><sup>-</sup> 都是一个好的离去基团：对甲苯磺酸和甲基磺酸可以被几乎任何亲核试剂所取代。在 Chapter 8 中您知道，通过强碱丁基锂的去质子作用，可以制备炔烃的锂衍生物(炔锂)。在下面的例子中，伯醇的对甲苯磺酸酯可以与炔锂发生 S<sub>N</sub>2 反应。注意对甲苯磺酸阴离子的离去基团是 TsO<sup>-</sup>(而非 Ts<sup>-</sup>)！



在 p. 344 有一个醋酸根阴离子通过 S<sub>N</sub>2 反应取代对甲苯磺酰基(即磺酰基)的过程。醋酸根不是一个好的亲核试剂，通常难以发生 S<sub>N</sub>2 反应，于是这也印证了磺酸酯发生取代反应的能力。

### 通过 Mitsunobu 反应取代醇

与其用两步，先将 OH 基转化为磺酸酯，然后再取代，不如试试另一种可行的方法，我们直接将醇加入反应混合物中，并且仅需一步操作即可得到 S<sub>N</sub>2 产物。这就是 Mitsunobu 反应(光延反应)。在这个反应中，醇做亲电试剂，而亲核试剂通常相对较弱(例如羧酸的共轭碱)，我们需要额外加入两种试剂。



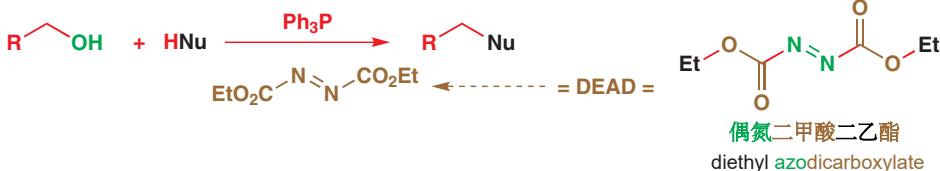
→ 磺酸酯生成的机理会在 Chapter 17 中详细地讨论。



对甲苯磺酸和甲基苯磺酸阴离子：极好的离去基团

光延旺洋(Oyo Mitsunobu, 1934–2003)在东京的青山学院大学工作。西方化学家经常拼错他的名字：请确保您不会！

一个 Mitsunobu 反应



## 偶氮化合物

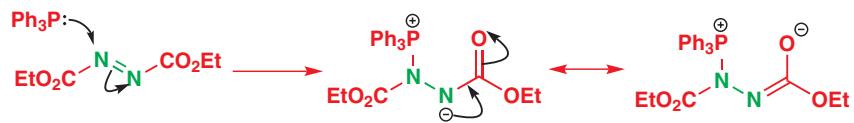
化合物 DEAD 名称中的“偶氮 (azo)”代表一类包含两个氮原子由一根双键连接起来的化合物，例如广为人知的偶氮苯。很多染料的结构中都有偶氮基团——您在 Chapter 1 看到过。另有一类重氮化合物 Diazo compounds (我们会在 Chapter 38 研究)，也含两个氮原子，氮仅有一个与碳相连。



其中一个试剂， $\text{Ph}_3\text{P}$ ，三苯基膦，是您在 Chapter 11 中遇到过的简单磷化物 (膦)。膦做亲核试剂，而不像胺做碱。另一个试剂值得进一步解释。它的全称是偶氮二甲酸二乙酯，简写作 DEAD.

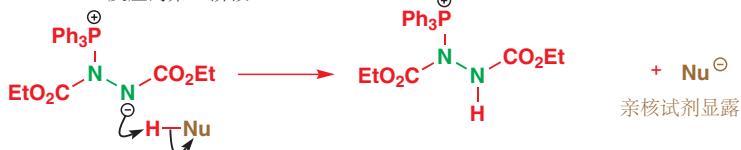
那么 Mitsunobu 反应是如何运作的呢？虽然它的机理很长，但请不要气馁：每一步都有其内在逻辑，我们会引导您一步一步地完成它。第一阶段既不包含醇，也不包含亲核试剂。而是膦加成到脆弱的 N=N π 键上，并且得到由其中一个酯基稳定的阴离子。

Mitsunobu 反应的第一阶段



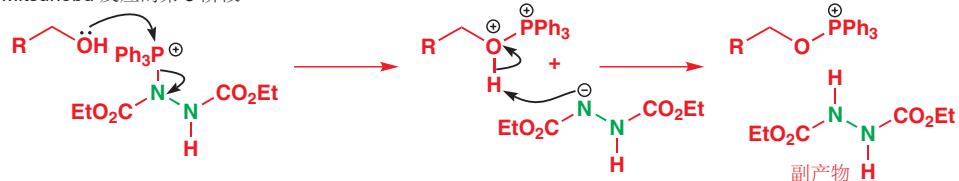
您会注意到，亲核试剂是以其共轭酸 “ $\text{HNu}^-$ ” 的形式添加的——通常可能是羧酸，例如苯甲酸。第一阶段得到的阴离子有足够的碱性，可以将该酸的质子去除，并得到准备参与反应的  $\text{Nu}^-$ 。

Mitsunobu 反应的第 2 阶段



氧与磷的亲和性很强，这一点我们可以在  $\text{PBr}_3$  下醇转化为溴代物的反应 (p. 348)，以及 Wittig 反应 (Chapter 11, pp. 237–8) 中都可见一斑。而回到此处，带正电荷的磷也因此会被醇所进攻，并在磷上发生取代氮阴离子 (第二个氮阴离子) 的  $\text{S}_{\text{N}}2$  反应 (三苯基膦本身是亲核性而不是亲电性的，因此若想利用磷氧的亲和性，我们利用了 DEAD)。这一步生成的氮阴离子还会被酯基的共轭所稳定，但它也能很快地去除另一生成物的质子，并得到亲电试剂  $\text{R}-\text{O}-\text{PPh}_3^+$ ，而其自身变为整个反应的一个副产物，即被还原了的 DEAD.

Mitsunobu 反应的第 3 阶段



最终，亲核试剂阴离子可以通过一个普通的  $\text{S}_{\text{N}}2$  反应进攻醇的磷衍生物中的碳原子，使氧化膦 (三苯氧磷) 作为离去基团。我们得到了最终产物。

Mitsunobu 反应的第 4 阶段



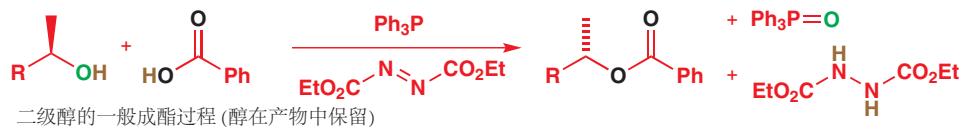
整个过程在一步操作下完成。四个试剂都被加入同一个烧瓶中，产物则是氧化膦、还原后的偶氮酯 (N=N 键被两个 NH 键所替代)，和醇上  $\text{S}_{\text{N}}2$  反应的产物。这个反应的另一种看法是，一分子水会被脱去——一个来自醇的 OH 和一个来自亲核试剂的 H；氢和氧原子最终结束于很稳定的分子——P=O 和 N-H 都是强键，而 N=N 是弱键，它们之间的转换所造成的稳定性提高，弥补了醇中 C=O 强键断裂的牺牲。

如果上述分析是正确的，那么关键的  $\text{S}_{\text{N}}2$  步应该导致构型的翻转 ( $\text{S}_{\text{N}}2$  反应通常所包含的)。这也是 Mitsunobu 反应的一大优点——这一反应也是在构型翻转的要求下，用亲核试剂取代 OH 的一

Interactive mechanism for the Mitsunobu reaction

个可靠方法。这个反应用于成酯是十分引人注目的。相比于一般的成酯过程，它经历了构型翻转。另外，在一般的成酯过程中，都是酸的 C—O 键而不是醇的断裂，而在应用本反应进行的成酯过程中，则恰恰相反；对比下列两个成酯反应，注意有颜色标识的氧和氢原子的去处。

二级醇经历构型翻转成酯：Mitsunobu 反应



二级醇的一般成酯过程（醇在产物中保留）



### 醚做亲电试剂

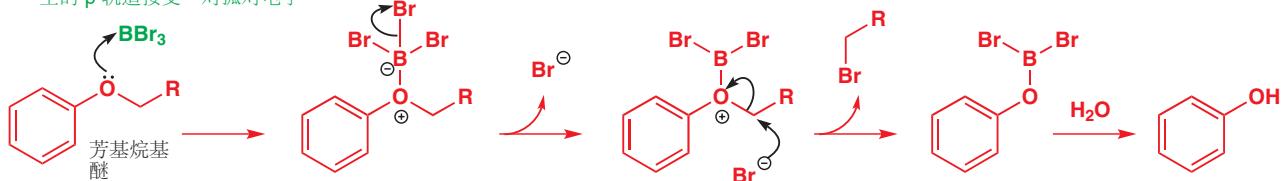
醚是不与亲核试剂反应的稳定分子：正是这个原因，THF 和 Et<sub>2</sub>O 是广泛使用的溶剂。想让它们反应，我们需要让氧带正电荷，使它更乐意接受电子了，而且还要选用好的亲核试剂。一个能够同时满足这两种需求的方法是使用 HBr 和 HI 处理；酸用于质子化氧原子，而碘离子、溴离子都是 S<sub>N</sub>2 反应极好的亲核试剂（见上文）。这一反应更倾向于在更易于发生 S<sub>N</sub>2 反应的碳原子上进行（通常是空阻较小的一个）。芳基烷基醚仅在烷基一侧发生碳氧键的断裂——您总不能让苯环接受进攻。



目前为止，我们只使用了质子酸来帮助氧原子离开。但 Lewis 酸——也有 H<sup>+</sup> 的能接受电子的空轨道的物种——也可以发挥作用，芳基烷基酯与 BBr<sub>3</sub> 的反应是一个好例子。三价硼化合物有一个非常亲电的空 p 轨道，很乐于进攻氧。得到的锌离子可以被 Br<sup>-</sup> 通过 S<sub>N</sub>2 反应进攻。

我们在 Chapter 8, p. 180 介绍了 Lewis 酸。

BBr<sub>3</sub> 充当 Lewis 酸  
—空的 p 轨道接受一对孤对电子



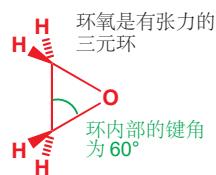
### 环氧做亲电试剂

有一类醚可以在甚至没有质子酸或 Lewis 酸的存在下发生亲核取代反应。他们就是三元环醚，也被称为环氧 (epoxides, 环氧乙烷为 oxiranes)。离去基团着实是难以离去的烷氧基阴离子 RO<sup>-</sup>，因此很明显有一些特殊的特征使这类醚不稳定。这个特征就是环张力，即三元环中的键角不得不不是 60°，而不是理想的四面体角 109°。相减得到，每个原子都有“49°”的张力角度，整个分子共有 150° 的张力角度。因此当环被打开，并使得所有原子恢复理想的四面体角时，分子会稳定许多。这就是亲

您会在 Chapter 19 看到如何从烯烃得到环氧。

核取代的同时所做出的贡献。

► Chapter 16, p. 368 讨论了环张力。

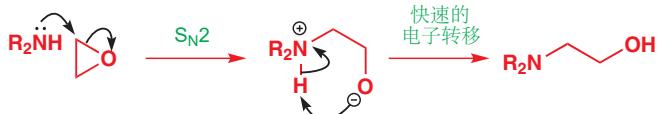


$S_N2$  对环氧的进攻解放了环张力

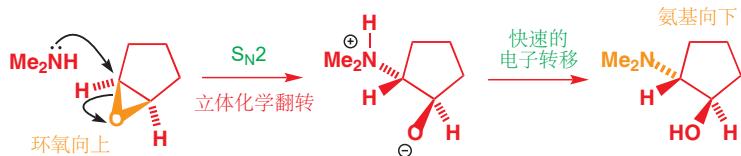


环氧利落地与胺反应得到氨基醇 (amino alcohols). 到目前为止我们还没有讨论过胺做亲核试剂的情况，因为它们与卤代烃的反应经常被反应过度所困扰 (见下一节)，但它们却能与环氧反应得到很好的结果。

■ 亲核试剂进攻环氧的哪一侧是有选择的，控制其选择性的因素会在 Chapter 24 讨论。



当环氧接在 (或“稠和”) 在另一个环上时，您就能很轻易看出  $S_N2$  反应中发生的构型翻转了。下列五元环上的亲核进攻就经历翻转，得到了反式产物。由于起始物中的环氧是向上的，那么亲核试剂一定从下方进攻，因此新的 C–N 键就会是向下的(向上的氧变为向下的氨基，发生了构型翻转)。



## $S_N1$ 反应中的亲核试剂

我们在之前讨论  $S_N1$  反应时已经确定，亲核试剂在速率方面并不重要。反应的决速步是离去基团的离去，离去后无论亲核试剂好与坏都可以得到产物。我们不需要让亲核试剂去质子化以增强反应性 (水和氢氧根的效果是相同的)，因此我们通常采用酸性条件完成  $S_N1$  反应，目的是协助离去基团的离去。

作为对比，以下是制备甲基醚和叔丁基醚的典型条件。甲基醚 (p. 340 曾出现过) 由碘甲烷通过  $S_N2$  反应制备，它需要一个好的亲核试剂，因此需要在 DMF (p. 345 讲过的， $S_N2$  反应的良好溶剂) 中加入氢氧化钠，使醇去质子得到烷氧基阴离子。然而叔丁基醚仅需要叔丁醇和一些酸搅和搅和即可得到；不需要任何碱，反应发生得十分迅速。

制备甲基醚



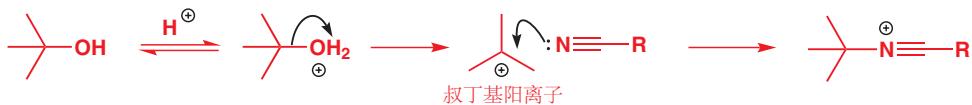
制备叔丁基醚



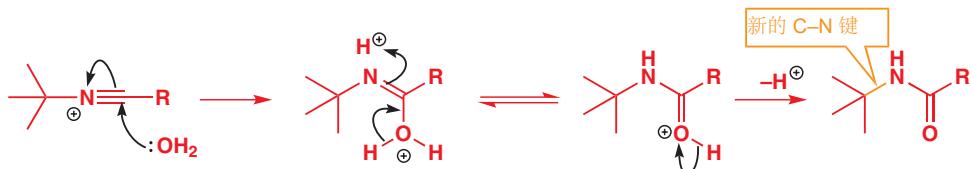
## S<sub>N</sub>1 反应在亲核试剂很差时也能很好地进行：Ritter 反应

亲核试剂对于 S<sub>N</sub>1 反应速率的不重要性引起了一个十分有趣的结果，即在没有更好的亲核试剂存在时，非常差的亲核试剂也能参与反应。例如腈就是非常弱的碱，和非常差的亲核试剂，因为氮原子上的孤对电子在低能的 sp 轨道上。然而，当用腈作溶剂溶解叔丁醇，并加入强酸后，也会发生反应。强酸并不会质子化腈，而会质子化醇，并通过一个非常寻常的 S<sub>N</sub>1 反应的第一步得到叔丁基阳离子。阳离子的反应性足够使其与腈这样弱的亲核试剂相结合。

腈的碱性很弱  
亲核性也很差  
 $\text{R}-\equiv\text{N} \cdot \ddot{\text{:}}$   
sp 轨道含有孤对电子



所得到的腈阳离子会被第一部反应释放的水所捕获，然后质子交换产生二级胺。整个过程被称为 Ritter 反应，它是为数不多的在叔碳中心成 C–N 键的方法。

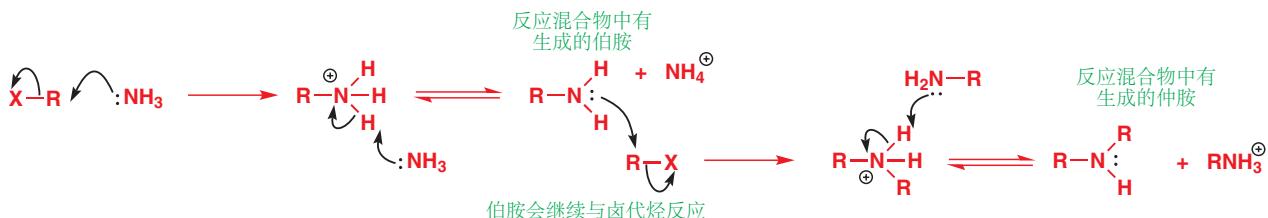


## S<sub>N</sub>2 反应中的亲核试剂

在一个 S<sub>N</sub>2 反应中，好的亲核试剂是最基本的要求。在本章结束之际，我们将对通过 S<sub>N</sub>2 反应与  $\text{sp}^3$  碳成新键的有效选择做一个调查，并且描述决定亲核试剂好坏的因素。

### 氨亲核试剂：一个问题和一个解决方案

胺是很好的亲核试剂，但胺与卤代烃间的反应几乎不会干净利落地得到单一产物。得到的产物是同样具有亲核性的伯胺，它会与起始物的胺竞争与卤代烃的反应。

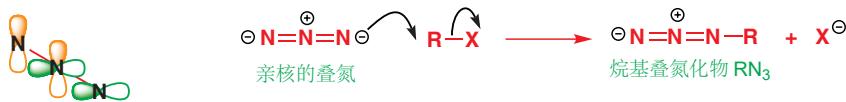


这不只是全部！烷基化 (alkylation) 会继续进行，得到仲胺、叔胺，只会在得到没有亲核性的季铵盐  $\text{R}_4\text{N}^+$  后才会终止。要点在于，当胺被一次次烷基化的同时，新加的烷基也会给予 N 更多的电子密度，使每个产物都比从前的更加活泼。您虽然可以通过加入大大过量的卤代烃 RX 得到纯净的季铵盐，但事实上我们需要的是更多可控的合成伯、仲、叔胺的方法。

一个对于伯胺合成的解决方案是用叠氮根阴离子 (azide ion)  $\text{N}_3^-$  替代胺。这种直线型的三氮物种，其两端都是亲核位点，就像一根细长的电子棒，可以将其自身插入几乎一切亲电位点。我们常用其水溶性钠盐  $\text{NaN}_3$ 。

有时候这种烷基化反应也是可以使用的，但通常只有在烷基化试剂或者胺有非常大的空阻，或者当烷基化试剂含有吸电子基团时（例如环氧开环得到的羟基：环氧是可选的胺烷基化试剂）才可以。尽管如此，您也应当对于陌生的胺烷基化反应保持最坏的看法。

叠氮根阴离子  $\text{N}_3^-$  的结构



■ 叠氮根与二氧化碳是等电子体，具有相同的直线型形状。

叠氮根只会和卤代烃反应一次，因为其产物，烷基叠氮化物不再是亲核试剂。然而，我们很少需要叠氮化物的产物：通常通过催化氢化（Pd 催化剂上有  $\text{H}_2$ ——见 Chapter 23）， $\text{LiAlH}_4$  或三苯基膦将其还原为伯胺。

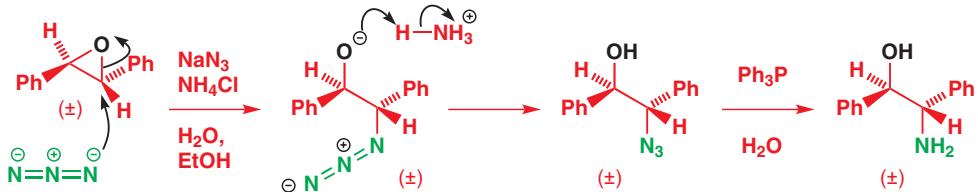
### 关于叠氮化物的警告

叠氮化物可以通过加热——有时甚至只是一次重击——瞬间爆炸为氮气。换句话说，它们是潜在易爆的，尤其是无机（即离子状态的）叠氮化物和小分子量的共价有机叠氮化物。

▶ 叠氮化物被三苯基膦还原的机理可以在 p. 1176 找到。



叠氮根也与环氧发生反应。下图所示的环氧是一种非对映体的外消旋混合物，结构下方的  $(\pm)$  符号会提示您这一点 (Chapter 14)。叠氮根可以进攻三元环的任意一端（两端是相同的），并得到羟基叠氮化物。这个反应在水和有机溶剂的混合溶剂中进行，加入氯化铵作为缓冲物，为中间体提供质子。水中的三苯基膦被用于将叠氮化物还原为伯胺。

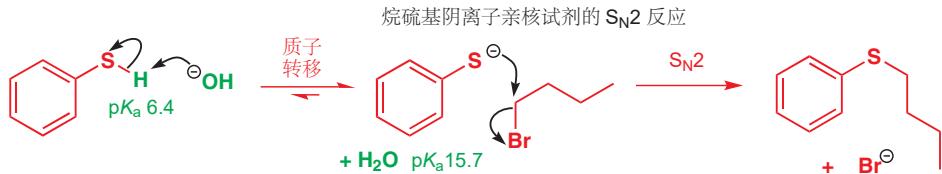


### 硫是 $S_N2$ 反应中比氧强的亲核试剂

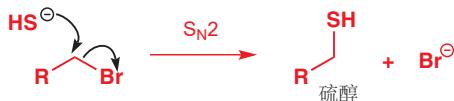
烷硫基阴离子 (Thiolate anions)  $\text{RS}^-$  是对于卤代烃上的  $S_N2$  反应极好的亲核试剂。将硫醇 (thiol)、氢氧化钠和卤代烃混合在一起，可以获得高产率的硫醚 (sulfide)。



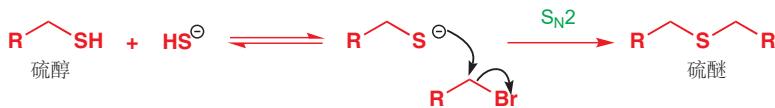
硫醇比水的酸性强 ( $\text{RSH}$  的  $pK_a$  通常是 9–10,  $\text{PhSH}$  的  $pK_a$  是 6.4,  $\text{H}_2\text{O}$  的  $pK_a$  是 15.7)，因此氢氧根与硫醇之间发生快速的电子转移，并得到即将扮演  $S_N2$  反应的亲核试剂的烷硫基阴离子。



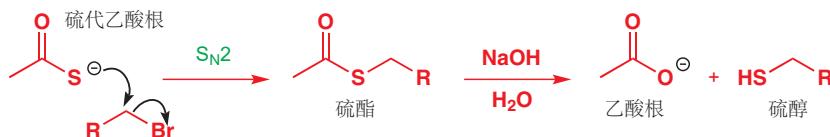
如何制备需要用到的硫醇呢？最明显的制备脂肪硫醇的方法是使用  $\text{NaSH}$  取代卤代烷的  $S_N2$  反应。



这种方法看起来效果很好，但不幸地，其产物很容易失去质子，做亲核试剂进攻另一分子卤代烃，因此这一反应通常得到对称的硫醚——想一想胺取代时发生的事情！



解决方案是使用硫代乙酸 (通常使用其钾盐). 它通过具有亲核性的硫原子干净俐落地进攻得到酯，而酯可以在碱性下水解以释放硫醇。

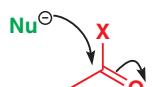


## S<sub>N</sub>2 反应中不同亲核试剂的效果比较

在 Chapter 10 中我们指出，碱性 (basicity) 就是对质子的亲核性 (nucleophilicity). 在那里，我们说过：对羰基亲核加成的亲核性与碱性几乎是完全对应的。我们可以使用  $pK_a$  作为比较羰基上亲核取代反应的亲核试剂的效果的依据。

在本章中，我们曾向您提到：对饱和碳原子的亲核性并不如此直接地与碱性联系。现在我们得郑重其事地考察这一问题，并向您给出有帮助的参考准则。

$\text{HNu}^-$  的  $pK_a$  是研究此类反应速率的一个依据



C=O 上的亲核进攻

但这一类反应要更加复杂



饱和 C 上的亲核取代

- 对于亲电位点 (与碳原子成新键的原子) 为同一原子的几种亲核试剂——例如  $\text{OH}^-$ ,  $\text{PhO}^-$ ,  $\text{AcO}^-$  和  $\text{TsO}^-$  的亲电位点均为氧——那么亲核性就与碱性对应。最弱的酸的负离子是最好的亲核试剂。我刚刚提到的几种亲核试剂的亲核性顺序为： $\text{HO}^- > \text{PhO}^- > \text{AcO}^- > \text{TsO}^-$ . 它们在 EtOH 中对 MeBr 真实的进攻速率相比于水的进攻速率 (= 1) 如下表所示。

在 EtOH 中与 MeBr 反应的相对速率 (水 = 1)

亲核试剂 X <sup>-</sup>	HX 的 $pK_a$	相对速率
$\text{HO}^-$	15.7	$1.2 \times 10^4$
$\text{PhO}^-$	10.0	$2.0 \times 10^3$
$\text{AcO}^-$	4.8	$9 \times 10^2$
$\text{H}_2\text{O}$	-1.7	1.0
$\text{ClO}_4^-$	-10	0

- 如果比较亲电位点不是同一原子的亲核试剂，则还需要考虑另一种重要的因素。在一个很早之前提到的例子中，我们强调过  $\text{RS}^-$  是对饱和碳原子极好的亲核试剂。换种方式说，就是： $\text{RS}^-$  是一个比  $\text{RO}^-$  更好的亲核试剂。这种情况是在  $\text{RO}^-$  比  $\text{RS}^-$  的碱性强 (见下表) 的情况下出现的。

在 EtOH 中与 MeBr 反应的相对速率 (水 = 1)

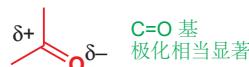
亲核试剂 X <sup>-</sup>	HX 的 $pK_a$	相对速率
$\text{PhS}^-$	6.4	$5.0 \times 10^7$
$\text{PhO}^-$	10.0	$2.0 \times 10^3$

对于饱和碳原子，硫显然是比氧更好的亲核试剂。但这是为什么呢？正如我们在 Chapter 5 讨论过的，双分子反应受两种因素控制：(1) 静电吸引 (相对的电荷、相对的部分电荷之间的吸引) 和 (2) 亲核试剂的 HOMO 与亲电试剂的 LUMO 间的成键相互作用。

质子当然是带正电的，因此静电吸引是碱性(对  $\text{H}^+$  的亲核性)，或者说  $\text{pK}_a$  最重要的影响因素。由于  $\text{C}=\text{O}$   $\pi$  键不均匀的电子分布，碳原子承载了羰基大部分的正电荷，因此亲核试剂与羰基的反应也很大程度地受静电吸引的影响， $\text{HOMO-LUMO}$  相互作用同样在其中发挥很小的作用。

电负性：

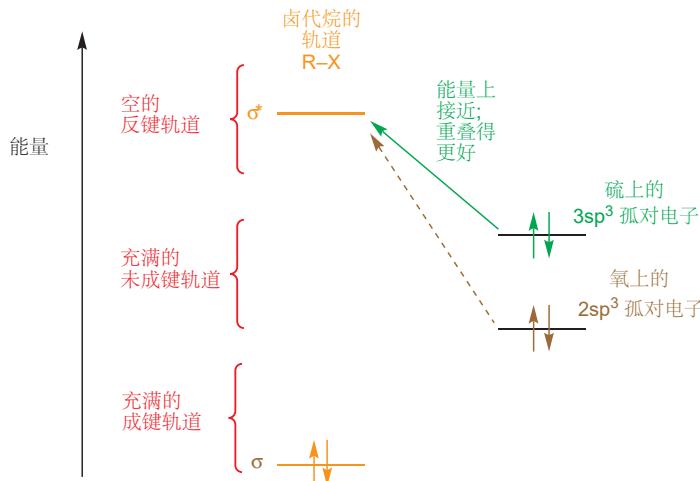
$\text{C}: 2.55 \text{ I}: 2.66 \text{ Br}: 2.96 \text{ O}: 3.44$



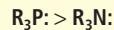
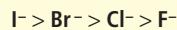
- 静电吸引在  $\text{S}_{\text{N}}2$  反应中通常不重要。

而真正有用的是  $\text{HOMO-LUMO}$  相互作用的强度。在对羰基的亲核进攻中，亲核试剂进入的是低能的  $\pi^*$  轨道；而在对饱和碳原子的亲核进攻中，亲核试剂必须将电子贡献给  $\text{C}-\text{X}$  键的  $\sigma^*$  轨道，例如左侧显示的烷基溴与亲核试剂的非键孤对电子的反应。

$\sigma^*$  反键轨道当然在能量上高于非键孤对电子的轨道，因此亲核试剂的孤对电子能量越高，两个轨道重叠得就越好。硫的  $3\text{sp}^3$  孤对电子与  $\text{C}-\text{X}$  的  $\sigma^*$  轨道重叠得比氧的  $2\text{sp}^3$  孤对电子好，因为硫的轨道能量高，与  $\text{C}-\text{X}$   $\sigma^*$  轨道接近。结论是，周期表下方元素的亲核试剂在  $\text{S}_{\text{N}}2$  反应中比周期表上方元素的亲核试剂更好。



- 一般来说，对饱和碳的亲核能力大致如下顺序：



### 取代反应中的亲核试剂

EtOH 中  $\text{MeBr}$  的相对速率 (水 = 1)

亲核试剂	$\text{F}^-$	$\text{H}_2\text{O}$	$\text{Cl}^-$	$\text{Et}_3\text{N}$	$\text{Br}^-$	$\text{PhO}^-$	$\text{EtO}^-$	$\text{I}^-$	$\text{PhS}^-$
相对速率	0.0	1.0	1100	1400	5000	$2.0 \times 10^3$	$6 \times 10^4$	$1.2 \times 10^5$	$5.0 \times 10^7$

## 软硬亲核试剂

事实上一些亲核试剂，像  $R_3P$  和  $RS^-$ ，与饱和 C 原子的反应十分迅速（它们有高能的孤对电子），但面对  $C=O$  基却很糟糕，这是由于它们要不就是不带电，要不就是电荷被分散在大的轨道中；这与另一类强碱性的亲核试剂，例如  $HO^-$  不同，它们可以十分迅速地进攻  $C=O$  基。我们称易于进攻饱和碳原子的亲核试剂是**软的 (soft)** 亲核试剂；称那些有较强碱性，并能与羰基很好地反应的亲核试剂为**硬的 (hard)** 亲核试剂。这一术语能很好地反映他们的特征，软的亲核试剂的轨道是大而松散的，其携带的电子是被分散开的；而硬的亲核试剂的轨道则是小而尖锐的，其携带的电子十分紧密，有较高的电子密度。

当我们说“硬的”（亲核试剂或亲电试剂）时，我们指的是那些反应时受制于静电吸引的物种；而当我们说“软的”（亲核试剂或亲电试剂）时，我们指的是那些反应时受制于 HOMO–LUMO 相互作用的物种。

(注：英文中通常先说“hard”再说“soft”，而中文则喜欢先说“软”再说“硬”。)

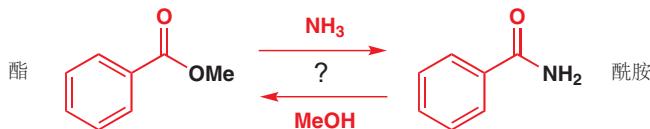
### ● 两类亲核试剂特征的总结

硬亲核试剂 X	软亲核试剂 Y
小	大
带电	中性
有碱性 ( $HX$ 酸性弱)	碱性弱 ( $HY$ 酸性强)
HOMO 低能	HOMO 高能
乐于进攻 $C=O$	乐于进攻饱和碳
例如 $RO^-$ , $NH_2^-$ , $MeLi$	例如 $RS^-$ , $I^-$ , $R_3P$

■ 提醒您：受制于静电吸引的反应仍需要 HOMO 向 LUMO 的电子流动，但受制于 HOMO–LUMO 相互作用的反应不受静电吸引的影响。

## 亲核试剂与离去基团的对比

在 Chapter 10 中我们曾解释过，在对羰基的亲核加成上，一个好的亲核试剂同时也是一个差的离去基团，反之亦然。我们给您的挑战是预测下列反应会向哪一侧进行。

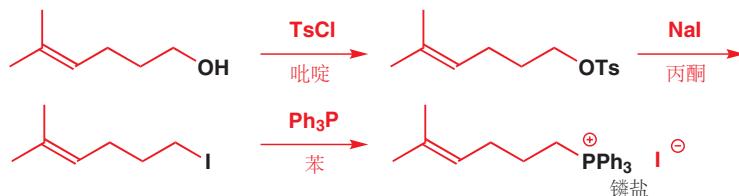


现在您应该很清楚，反应由酯向酰胺进行，而不是反过来，因为  $NH_3$  是比  $MeOH$  更好的亲核试剂， $NH_2^-$  也是比  $MeO^-$  更差的离去基团。

但在  $S_N2$  反应中就不同了：一些最好的亲核试剂同时也是最好的离去基团。最重要的例子是溴离子和碘离子。正如 p. 356 的表格所示，碘离子是对饱和碳原子最好的亲核试剂之一，因为在周期表中，它是卤族底部的元素，它的孤对电子能量很高。氯代烷或者对甲苯磺酰代烷能轻而易举地转化为碘代烷。下面是两个例子。其一是在溶剂丙酮的协助下，使  $NaCl$  沉淀并推动反应向前进行。



第二个例子是在萜烯合成中𬭸盐的制备。一个不饱和伯醇首先被制成对甲苯磺酰酯，然后对甲苯磺酰酯转换为碘代烷，最好碘代烷再转为𬭸盐。



我们在 p. 347 解释了为什么  $\text{I}^-$  是一个好的离去基团：C—I 是特别脆弱的。C 与 I 的原子轨道重叠很差，也意味着  $\sigma^*$  处于较低的位置上，很容易被亲核试剂较大 HOMO 接近。

溶剂二甲苯 (xylene, dimethylbenzene) 也需要一些解释。二甲苯有三种异构体，混合形态的二甲苯可以很方便地从石油中分离，通常作为一个相对的高沸点溶剂 (b.p. 大约 140 °C)，用于高温反应。在本情况中，起始物可以溶于二甲苯，但盐类的产物则很容易在反应过程中沉淀出来。非极性的二甲苯也有利于  $S_N2$  反应 (p. 345)。



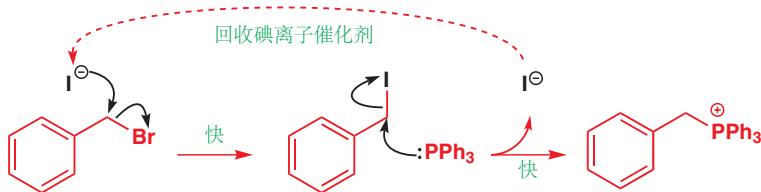
亲核催化剂通过其既是好的亲核试剂，又是好的离去基团的性质加速反应。在 Chapter 10 中，您已见过在酸酐 C=O 基的亲核取代中发挥相似作用的吡啶。

为什么要通过碘代烷，绕一个圈子呢？回答是，碘是一个极好的亲核试剂，也是一个不错的离去基团。卤代烷经常作为促进其他亲核试剂取代的中间体。绕圈子的制法往往比用最终的亲核试剂直接与对甲苯磺酸酯反应产率高。

然而，碘离子是很贵的，但我们可以只使用催化量的碘离子。通过苯溴合成下面的𬭸盐十分缓慢，但添加少量的 LiI 后，速率则大大提升。



碘离子既是比  $\text{Ph}_3\text{P}$  更好的亲核试剂，也是比  $\text{Br}^-$  更好的离去基团。每个碘离子都作为亲核催化剂 (nucleophilic catalyst) 在下列过程中循环。



## 展望：消除反应和重排反应

简单的饱和碳原子上的亲核取代是进行有机化学的基本反应。它们被广泛应用于工业生产和实验室药物合成。它的重要性和意义值得您认真学习。

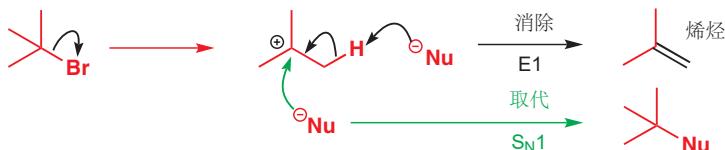
这幅简单的图画还有其另一面。它们是第一批被彻底研究了机理的反应，它们的机理由 Ingold 在 1930s 年提出，从此以后，对它们的研究可能比任何其他反应都要多。我们对有机反应的理解也开始于  $S_N1$  和  $S_N2$  反应，您需要正确地理解它们的基本机理。

本章中您遇到的碳阳离子并不仅仅是  $S_N1$  取代，而且也是其他的一些反应的活性中间体。对于它们的形成的最有力的证据是，除了被亲核试剂加成外，它们还会发生其他的一些反应，例如碳阳离子的碳骨架会发生重排 (rearrange)，我们会在 Chapter 36 中讨论。

一个重排反应



碳阳离子的另一个常见的命运，也是可能替代我们想要进行的  $\text{S}_{\text{N}}1$  或  $\text{S}_{\text{N}}2$  反应的，是消除 (*elimination*)。下面是亲核试剂不添加到分子上，而是扮演碱，消去  $\text{HX}$  并得到烯烃的一个反应。

一个消除反应 ( $\text{E}1$ )

在我们对于立体化学作进一步的探索后，您会在接下来的一章 (17) 遇到消除反应。

## 延伸阅读

每本有机化学教科书都会涉及这一主题，通常作为第一个描述的反应，例如：J. Keeler and P. Wothers, *Why Chemical Reactions Happen*, OUP, Oxford, 2003,

chapter 11 和 F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry A, Structure and Mechanisms*, 5th edn, Springer, 2007, chapter 4.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 16 构象分析

## 联系

### ► 基础

- 如何确定一个分子的结构 ch3 & ch13
- 一些分子以立体异构体形式存在 ch14

### 目标

- 如果我能看到分子，它的三维形状(构象)会是什么样的呢？
- 分子的形状对它的反应有什么影响？
- 单键可以自由旋转，但大多数时间却只停留在两三种确定的排列方式上
- 原子通常并不是平面型的，而是“折叠的”
- “折叠的”六元环中原子确定的排列方式
- 如何准确地绘制六元环
- 如何运用已知的原子在六元环中的排列方式，预测和解释它们的反应

### ► 展望

- 原子的构象和对准如何影响消除反应 ch17
- 用 NMR 光谱法证实本章内容 ch31
- 分子的构象如何支配它们的反应，例如它们会被试剂从哪个方向进攻 ch32 & ch33
- 键的对准如何允许基团在分子中移动(重排反应)，如何允许 C-C 键的断裂(碎片化反应) ch36
- 轨道的对准如何控制反应性(立体电子效应) ch31
- 精确绘制环状过渡态 ch32, ch34, & ch35

## 键的旋转使原子链采取不同构象

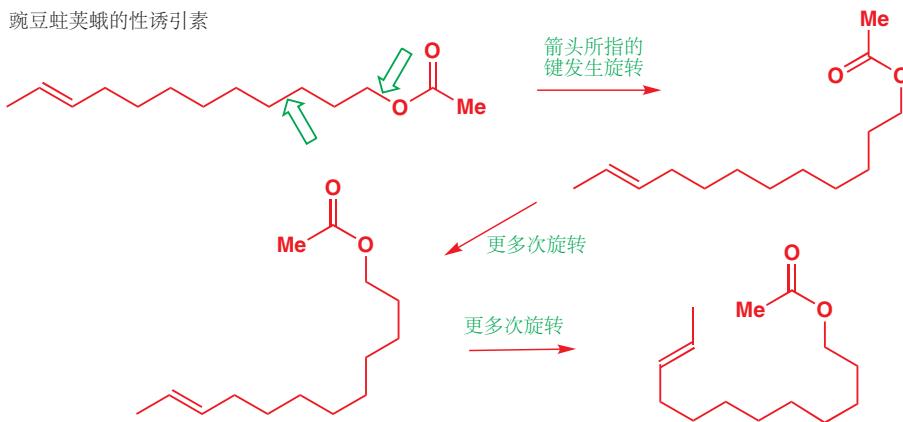
本书中有好几章都在讨论如何找出分子的结构。X-ray 晶体学图像可以揭示晶体中原子的确切位置；IR 光谱可以告诉我们有关于分子中化学键的信息；NMR 光谱则为我们提供了分子中原子，以及它们结合方式的信息。到目前为止，我们兴趣的重点一直聚焦于哪个原子与哪个原子相连，以及基团局部的情况。例如，一个甲基基团包含三个氢原子和一个碳原子相连，该碳原子周围的四个原子占据一个四面体的四个顶角；一个酮包含一个碳原子与其他两个碳原子成单键，再与一个氧原子成双键，这几个原子都在同一平面内。

但是，如果研究较大范围的形状，就不能很明确地界定了。因为单键的旋转是允许的，所以当分子局部的形状不变(饱和碳原子始终是四面体型)时，整个分子的形状却会千变万化。下一页展示了同一分子可能形成的多种姿势——这是豌豆蛀莢蛾用于吸引配偶的性诱引素。虽然这几个结构看上去如此的不同，但仔细观察会发现仅仅是一个或多个单键发生了旋转造成的。整个分子的形状是不

同的，但局部仍然是相同的：四面体型  $sp^3$  碳原子；平面三角型  $sp^2$  碳原子。注意另一点我们之后还会继续提及的：由于双键的是不能旋转的，因此双键两侧基团的排练方式始终是相同的。

■ 在 Chapters 4 和 12 中我们也谈到了这一点。

豌豆蛀茎蛾的性诱引素



Interactive conformations of pea moth pheromone

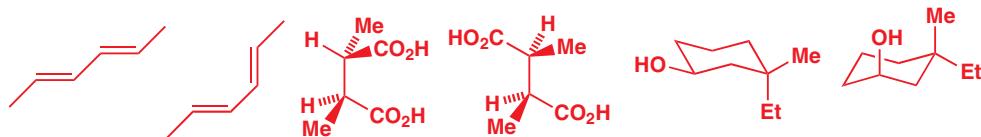
在室温下的溶液中，分子内的一切单键都始终在旋转——两个分子在同一时间处于完全相同的形状的机会是很小的。

虽然两个分子不会在同一时间处于完全相同的形状，但它们仍然是同一化合物——它们有相同的原子，这些原子也都以相同方式链接。我们称同一化合物处于的不同形状为它们不同的构象 (conformations)。

## 构象与构型

使分子从一个构象转换为另一个构象，我们可以旋转任意多的单键；但唯一不能做的是破坏化学键。这也是为什么我们不能旋转双键——因为这样做的同时需要破坏和重新形成  $\pi$  键。下面每对结构都可以通过旋转单键加以转换：它们是同一分子的不同构象。

三种化合物，每种都以两个不同的构象呈现

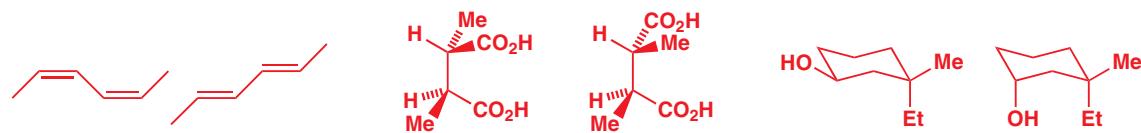


而在下面的这几对分子都是完全不同的：每一对之间的转换都需要破坏化学键。这说明它们有不同的构型 (configurations)——构型之间的转换必须经历化学键的破坏。我们在 Chapter 14 中已经讨论过了：具有不同构型 (但有相同构造) 的化合物是一对立体异构体。

### ■ 搭建模型

如果您觉得这很难理解，请搭建每一对结构的模型；您会轻易地发现如何旋转单键以达到它们之间的转换。对于本章，我们的建议是：当您对由于二维书的限制我们仅能展示的二维图感到难以理解时，请建立三维模型。

三对立体异构体：每对中的两个结构都有不同的构型



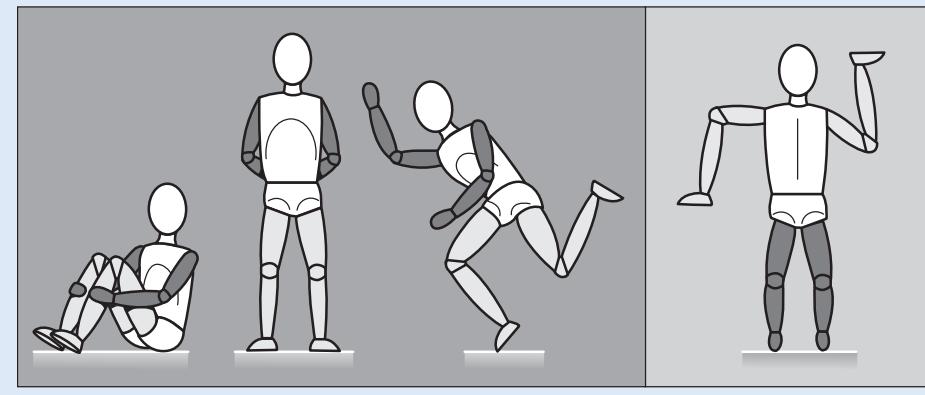
#### ● 旋转还是断键？

- 仅通过单键的旋转就能完成转换的结构是同一分子的不同构象。
- 必须经历断键才能完成转换的结构有不同构型，它们是一对立体异构体。

## 构象和构型

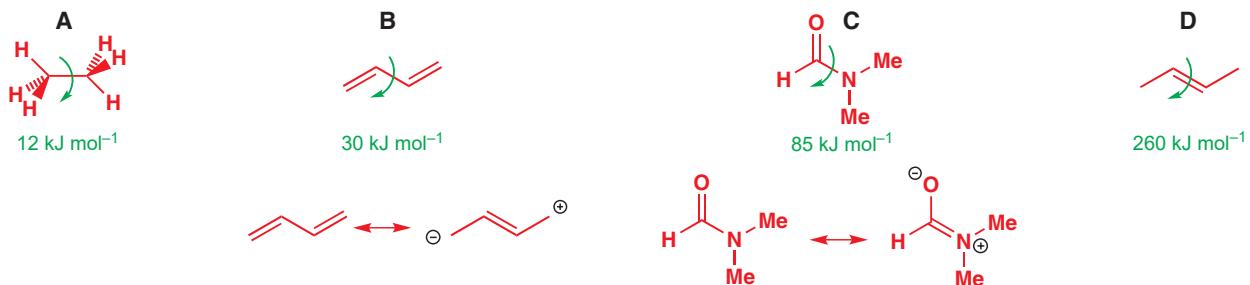
同一个人的不同构象——其中一些会比另一些更稳定 ...

与之不同的构型



## 旋转能垒

在 Chapter 7 中我们曾看到：室温下酰胺的 C–N 键旋转相对缓慢—DMF 的 NMR 谱清楚地显示了两个分开的甲基信号 (p. 156). 在 Chapter 12 中我们谈到：一个化学过程的速率与其能垒密切相关（这一结论不但适用于反应，也适用于键的旋转）：速率越慢，能垒越高。例如乙烷 (A) 中单键在室温下的旋转速率很快，它的能垒约为  $12 \text{ kJ mol}^{-1}$ .



丁二烯 (B) 中单键旋转的能垒略大，这源于双键的共轭作用，但在这个分子中此作用较微弱。对比 2-丁烯 (D) 中名副其实的双键，则能垒很大，不能自发旋转。但 DMF (C) 中绕 C–N 键旋转的能垒约为  $80 \text{ kJ mol}^{-1}$ ，在  $20^\circ$  下的旋转速率约为  $0.1 \text{ s}^{-1}$ ，比丁二烯要更困难，这是由于酰胺中的共轭作用产生的影响较大，使得 C–N 键具有显著的双键特征。

## 速率和能垒

让我们回忆一下 Chapter 12 中关于速率和能垒之间关系的几个简单结论。例如：

- 25 °C 下  $73 \text{ kJ mol}^{-1}$  的能垒允许其每秒旋转一次 (即速率为  $1 \text{ s}^{-1}$ )。
- 25 °C 下能垒每增加  $6 \text{ kJ mol}^{-1}$ , 速率相应减小到  $1/10$ 。

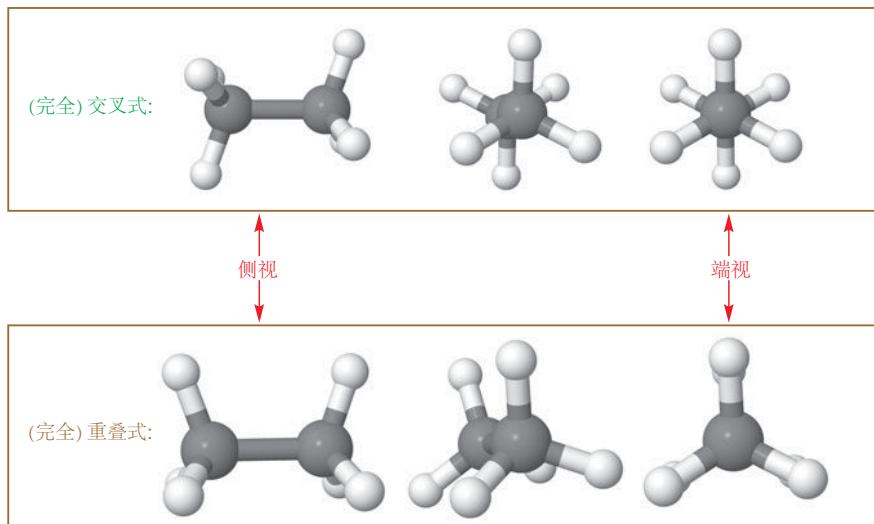
为了在 NMR 光谱中看到两种不同的构象，它们的旋转速率不能超过 (非常粗略地)  $1000 \text{ s}^{-1}$ ——25 °C 下跨越  $55 \text{ kJ mol}^{-1}$  能垒旋转的速率。这就是为什么 NMR 可以分别检测到 DMF 中的两个甲基信号，但却只能在丁二烯中检验到一组信号。

为了使旋转速率慢到将二者区分成两个不同的化合物，能垒必须超过  $100 \text{ kJ mol}^{-1}$ . C=C 双键旋转的速率是  $260 \text{ kJ mol}^{-1}$ ——这也是为什么我们将 E 和 Z 异构体分开。

## 乙烷的构象

为什么单键的旋转存在能垒呢？为了回答这个问题，我们会从最简单的 C–C 键开始研究——也就是乙烷中的。乙烷有两种极限构象，分别为完全交叉式 (staggered) 和完全重叠式 (eclipsed) 构象，下图以三种不同的视角分别展示了这两种构象。

乙烷的两种极限构象，完全交叉式和完全重叠式，  
每种以三种视角展现

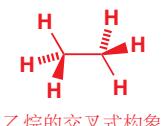


请观察端试图，您会明白这两种构象名字的由来。重叠式构象中，离镜头近的三个 C–H 键完全挡住了离得远的三个，就像一次日食 (solar eclipse) 中，地球上不能看到被挡月球挡住的太阳。在交叉式构象中，离得远的 C–H 键处于离得近的 C–H 键组成的缝隙中——这些键是交叉排列的。

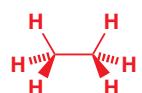
化学键有两种不同的方式用于快速表示这些构象，每种都有各自的优点。右侧展示的是第一种方法，即表示分子的侧视图，其中在纸面上和下的键分别用实楔形键和虚楔形键 (Chapter 14 中介绍过) 形象地画出来。特别需要注意哪些键在平面中，哪些在其上方和下方。

第二种方法表示的是分子的端视图，沿着 C–C 键从一端看。这种观察方法被称为纽曼投影式 (Newman projection)，绘制纽曼投影式有下列习惯：

- 靠近观察者的碳原子以三根键的交汇点表示。
- 远离观察者的碳原子 (我们不能在端视图中看到的哪一个) 被表示为一个大圆。这种表示方法并不严谨，但它是一种习惯。

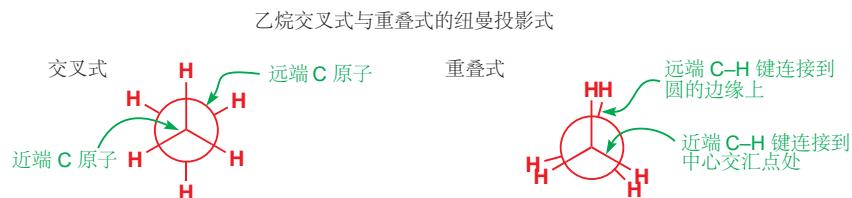


乙烷的交叉式构象



乙烷的重叠式构象

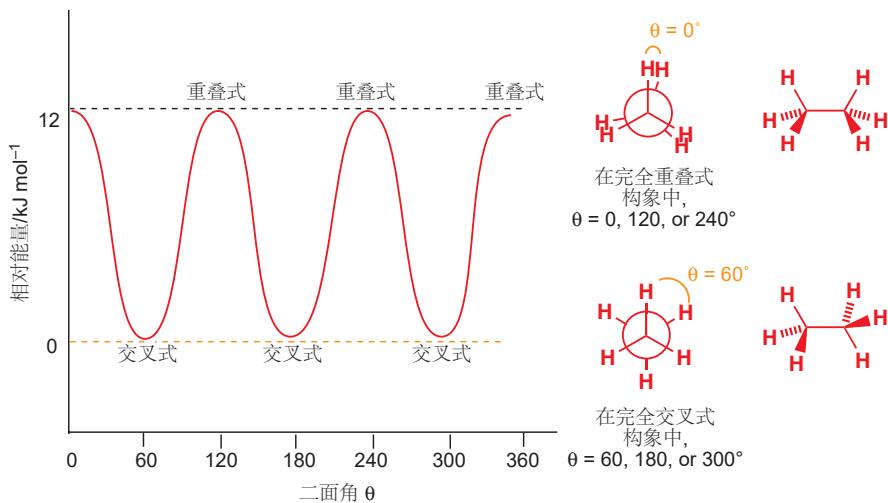
- 远端碳原子成的键连接在圆的边缘上，并不相交到中心。
- 为了清晰起见，重叠式中重叠的几对键均需要略微偏离——就好像旋转了一小点。



■ 画出二面角有时候很难——有一种方法是想想两个C-H键分别被画在一本书的两个对着的页上。而二面角即为垂直于书脊测量的两页之间的夹角。见 Chapter 31.

乙烷的交叉式和重叠式构象在能量上并不完全相等：交叉式构象的能量比重叠式构象的能量低  $12 \text{ kJ mol}^{-1}$ ，这一值即为旋转能垒。当然，在这两种极限式之间还有很多其他可能的构象，我们可以用一个图表表示 C-C 键旋转时系统能量的变化。我们将近端与远端 C-H 键的夹角称为二面角 (dihedral angle),  $\theta$  (或称为扭转角 torsion angle)。在交叉式构象中,  $\theta = 60^\circ$ ；而在重叠式构象中,  $\theta = 0^\circ$ 。

能级图显示：交叉式构象是最低能的状态，重叠式构象是最高等能的状态。这意味着重叠式构象并不是一个稳定的构象，任何轻微的旋转都会使之转变为一个更低能的构象。事实上，分子大多数时候都会处于完全交叉式构象，或者近似完全交叉的构象，而重叠式仅仅作为前往下一个交叉构象过程中的短暂经历。



但是为什么重叠式构象比交叉式构象能量高呢？共有两点原因。第一点原因是两对成键电子之间的排斥，这种排斥在重叠式构象中达到了最大值。第二点原因是一个碳原子上的 C-H  $\sigma$  成键轨道和另一个碳原子上的 C-H  $\sigma^*$  反键轨道可能存在一种使体系稳定的相互作用，当两个轨道平行时这种作用达到最大值：即发生在交叉式中。一切键的旋转引起的构象稳定性都同样受这两种效应影响——成键轨道间的排斥作用 (空间效应的一种，见 p. 129) 和对反键轨道贡献引起的稳定作用。



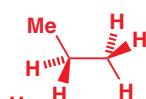
## 丙烷的构象

丙烷是第二简单的烃类。在考虑丙烷可能的构象前，我们首先要了解这个分子中最基本的几何要求。C—C—C 键的夹角并不是我们预想的  $109.5^\circ$  (即四面体角, 见 Chapters 2 和 4), 而是  $112.4^\circ$ 。随之, 中心碳原子的 H—C—H 键角同时会比理想的  $109.5^\circ$  要小, 仅为  $106.1^\circ$ 。这一特征不能用空间位阻 (中心碳原子上的两个甲基相互抵触) 简单地解释, 而应当解释为两根 C—C 键间的排斥比两根 C—H 间键的排斥大。

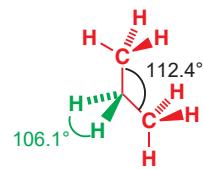
和乙烷的情况一样, 丙烷也存在两个极限构象——其中一个是 C—H 和 C—C 键完全交叉, 另一种是完全重叠。



丙烷的交叉式构象



丙烷的重叠式构象



两个 C—C 间的排斥比两个 C—H 键间的排斥大

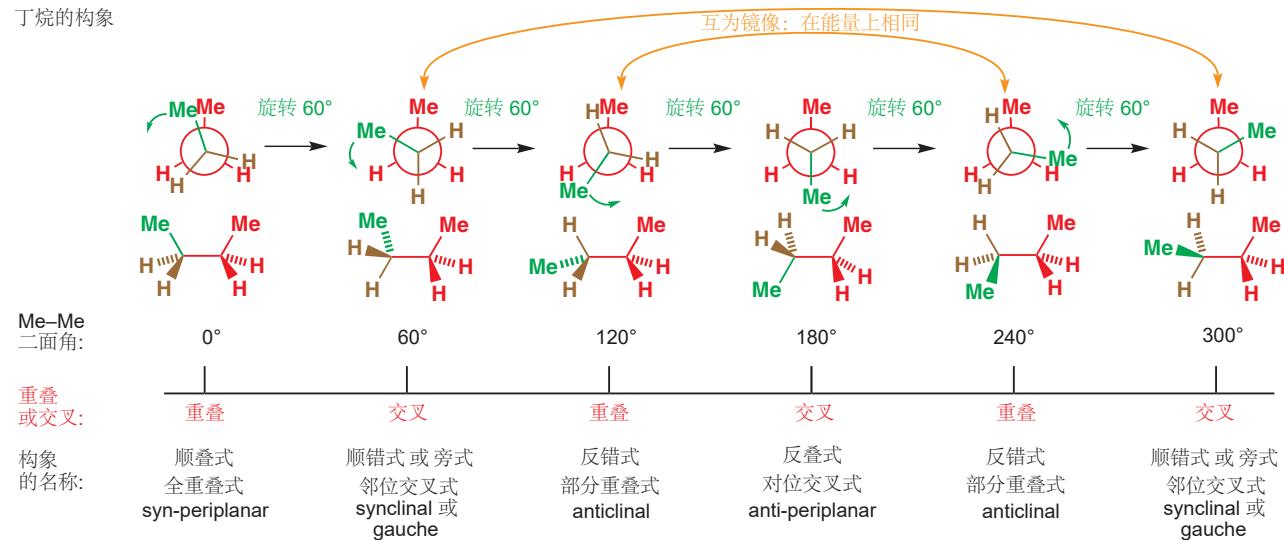
■ 注意: 在画重叠式构象的纽曼投影式时, 虽然我们要将前后两根键稍稍偏移, 但事实上, 一个是在另一个的正后方。

丙烷的旋转能垒比乙烷稍高:  $14 \text{ kJ mol}^{-1}$  (乙烷为  $12 \text{ kJ mol}^{-1}$ )。这再次反映了重叠式构象中共面键的电子排斥 (而非空阻效应)。丙烷中键旋转的能级图, 除去能垒变为  $14 \text{ kJ mol}^{-1}$ , 其余与乙烷完全一致。

## 丁烷的构象

由丁烷开始, 事情变得稍稍复杂。我们现在将丙烷中的两个氢都换成了较大的甲基, 它们足够产生相互的排斥, 近而空阻效应成为了控制能垒的一个显著因素。然而, 最能使问题复杂化的地方其实在于, 并不是所有的重叠式都相同, 也并不是所有的交叉式都相同。当中心以  $60^\circ$  的间隔旋转时, 丁烷会产生如下六种构象。其中绿色的 Me 基和棕色的氢原子在旋转, 而另一个碳原子上保持静止。

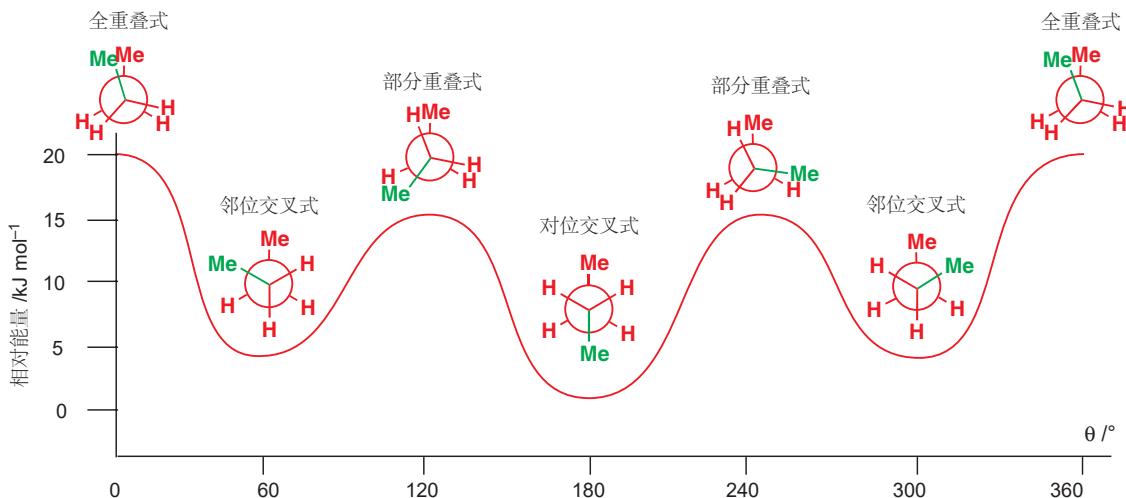
### 丁烷的构象



仔细观察这几种不同的构象。其中二面角为  $60^\circ$  和  $300^\circ$  的两个, 和  $120^\circ$  和  $240^\circ$  的两个都是彼此的镜像。这意味着如果画出能级图, 将会有四个峰: 两个重叠式构象形成高峰, 两个交叉式构象形成低谷。上图最底下一行是这些构象的名字, 在顺叠式构象 (注: 分析反应原理时有时被称作“两个基团处于顺式共平面”, 反叠式同理“反式共平面”, 英文为同一词) 中, 两个 C—Me 键位于同一平面中; 在顺错式和反错式构象中, 它们朝向同一方向 (syn) 或朝向不同方向 (anti)。

注: “构象的名称”的第二行是常会被用到代替它们的中文名称, 但由于太过冗长, 本译本后文不采用, 但您需要知道如何对应。

在画能级图前，让我们先停下来想象一下，它会是怎么样的。两个重叠式构象都处在高峰上，其中顺叠式构象 ( $\theta = 0^\circ$ ) 会比两个反错式构象 ( $\theta = 120^\circ$  和  $240^\circ$ ) 更高：顺叠式构象中，两个甲基彼此重叠；而在反错式构象中，每个甲基与一个氢重叠。两个交叉式构象都处在低谷上，其中反叠式中两个甲基距离最远，因此比顺错式低能。



### Interactive conformations of butane

■ 这种旋转着实很迅速：  
20 kJ mol<sup>-1</sup> 的能垒对应室温下  $2 \times 10^9$  s<sup>-1</sup> 的速度。不同异象体间的转化速度已经快到 NMR 无法区别了  
(见 p. 363): 丁烷的 NMR 光谱仅能看到由全部构象的平均值构成的一组信号。

■ 在 Chapter 17 的消除反应中，您会看到详细的构象分析对于无环化合物有多么重要；因为消除反应的产物仅能通过考虑反应物和过渡态的构象解释。但接下来，我们首先要使用以上思路来解决另一个分支——环状结构的构象。

与乙烷一致：在继续旋转到一个更稳定的构象前，两种重叠式构象都是不稳定的；而处在势阱中的两个交叉式构象都是稳定的。两个甲基在其中处于对面位置的反叠式是最稳定的。由此我们可以想象，丁烷分子始终迅速地在顺错式、反叠式两种构象间转换，而停留在两种能量很高的重叠式的时间很短，它们仅作为转换到另一稳定状态途中的过渡状态。

如果我们尽可能减缓烷构象转换的速度（例如降低到十分低的温度），我们就可以分离出三种稳定的构象——一种反叠式和两种顺错式。与乙烷不同的是，丁烷的稳定构象（处在势能极小值处的）有三种，它们在某种程度上可以被称为异构体，即构象异构体（conformational isomers，简称异象体 conformers）。

#### ● 构象和异象体

丁烷有无数种构象（我们仅选择了六种最主要的），但仅有三个异象体（势能的三个低谷）——两种顺错式，和一种反叠式。

我们在 Chapter 2 中曾向您介绍，将碳链画作锯齿状是贴近现实的，而到目前为止，您对这一结论已经有了更全面的理解。如果您将全部的 C—C 键排列成反叠式，即锯齿状形状，那么这将是任何线性烷烃最稳定的构象。

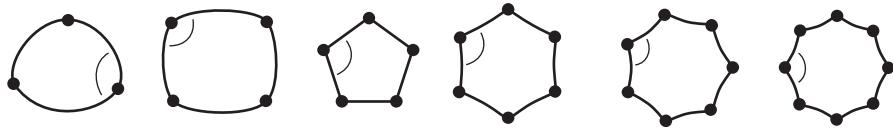
## 环张力

到目前为止，我们对环状化合物都还没有一个完全准确的印象。我们一直将它们视作平面型的，但事实上这并不贴切。在本节中，您会学习如何更准确地绘制环，并理解其所采用的不同构象的性质。

如果我们假设饱和碳环中的碳原子都是 sp<sup>3</sup> 杂化的，那么每个键角都最好是 109.5°。然而在一个平面环中，碳原子并没有决定自己键角的自由：因为多边形的内角已经由顶点原子数决定好了。如

过内角偏离理想的  $109.5^\circ$ , 分子中就会存在某种张力 (strain). 下图中的原子被强制排列成平面型的, 它们形象地展示了这一特点。分子的掌力越大, 键便会越弯曲——在无张力的分子中, 键是直的。

■ 我们之前已经多次使用环张力解释环状分子的反应性了 (p. 352).



所有内角均为  $109.5^\circ$

注意在超小的环中键向外形成张力, 而在超大的环中键向内形成张力。右表给出了规则的平面多边形的内角值; 并给出了这些大小的环为了形成理想的四面体角  $109.5^\circ$ , 每个碳原子所均分到的张力角度。

这一数据最好用图来表示, 下一页展示了一直到 17 元碳环中每个碳原子所均分到的环张力角度。键的张力到底向内还是向外并不重要, 重要的是其大小。

从这些数据 (在 p. 368 中呈现的), 整理得:

- 它们都是假设的平面环的计算数据。如您所见, 真实的碳环与之大不一样。
- 计算的环张力在三元环时最大, 并在四元环处迅速下降, 在五元环时达到最小。
- 计算的环张力在超过 5 元环的最小值后又重新增加 (虽然比之前缓慢)。

环中的 原子个数 ring	规则 平面环 的内角	$109.5^\circ$ - 内角 <sup>a</sup>
3	$60^\circ$	$49.5^\circ$
4	$90^\circ$	$19.5^\circ$
5	$108^\circ$	$1.5^\circ$
6	$120^\circ$	$-10.5^\circ$
7	$128.5^\circ$	$-19^\circ$
8	$135^\circ$	$-25.5^\circ$

<sup>a</sup> 每个碳原子均分的张力量。

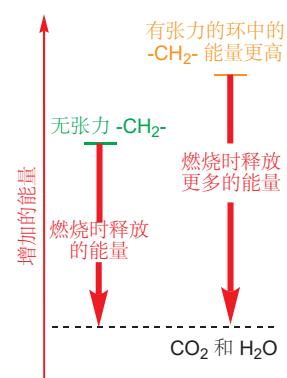
相比于假想的平面环, 我们更需要一个对真实化合物中环张力的量度。燃烧热就是一种很好的量度。下表中展示了直链烷烃的燃烧热; 最引人注目的是, 每增加一个原子, 随之增加的燃烧热几乎是一个常数, 在  $-660 \text{ kJ mol}^{-1}$  附近。

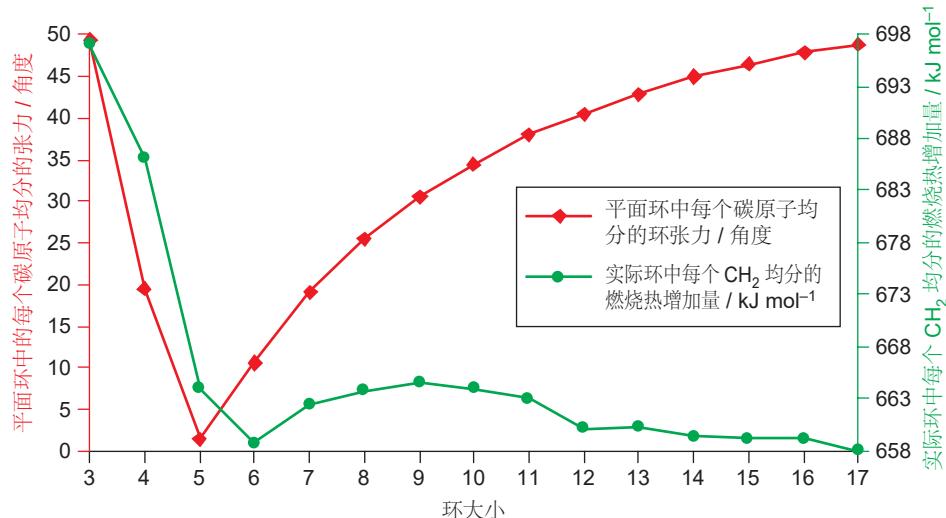
■ 在 Chapter 7 中我们为了探究苯的芳香性所造成的稳定性, 也用了燃烧热作为量度。

### 一些直链烷烃的燃烧热

直链烷烃	$\text{CH}_3(\text{CH}_2)_n\text{CH}_3, n =$	$-\Delta H_{\text{燃}}$ , $\text{kJ mol}^{-1}$	差值, $\text{kJ mol}^{-1}$
乙烷	0	1560	
丙烷	1	2220	660
丁烷	2	2877	657
戊烷	3	3536	659
己烷	4	4194	658
庚烷	5	4853	659
辛烷	6	5511	658
壬烷	7	6171	660
癸烷	8	6829	658
十一烷	9	7487	658
十二烷	10	8148	661

如果我们假设直链烷烃没有张力 (这是合理的), 那么每增加一个亚甲基,  $-\text{CH}_2-$ , 对烷烃燃烧热的贡献就为  $658.7 \text{ kJ mol}^{-1}$  (平均值)。环烷烃  $(\text{CH}_2)_n$  不过是由数个亚甲基组合而成的: 因此如果某个环烷烃没有张力, 它的燃烧热应当是  $n \times 658.7 \text{ kJ mol}^{-1}$ ; 而如果有张力, 则会导致环不稳定 (也就是增加它的能量), 燃烧时也会释放更多的能量。现在让我们将它们放入一个图中, 对于每一种大小的环: (a) 每个  $\text{CH}_2$  基团均分的张力角度和 (b) 每个  $\text{CH}_2$  基团均分的燃烧热增加量。





从上图中观察到的几个要点：

- 环丙烷远远比其他环的环张力都大 ( $n = 3$ ).
- 环张力迅速下降，并在环己烷处达到了最大值（而不是计算中预测的环戊烷）.
- 随后环张力开始增加，比计算的结果要缓慢；在  $n = 9$  时达到最大值并再次开始下降。
- 环张力不再随着环的扩大而增大，在  $n = 14$  之后大致保持恒定。
- 环己烷 ( $n = 6$ ) 和较大的环烷烃 ( $n \geq 14$ ) 中每个  $-\text{CH}_2-$  的燃烧量都处在与直链烷烃等同的  $658 \text{ kJ mol}^{-1}$  左右，也就是说它们是基本无环张力的。

化学家根据环的大小，将其分为小环、普通环、中环和大环。

小环,  $n = 3, 4$

普通环,  $n = 5, 6, 7$

中环,  $n = 8$  到大约 14

大环,  $n >$  大约 14

这是由于这几组环之间的性质和合成方法都是各不相同的。上图中的张力变化的规律也与这种分类方式相吻合。

您可能会问自己一些问题：

为什么六元环和较大的环几乎无环张力？

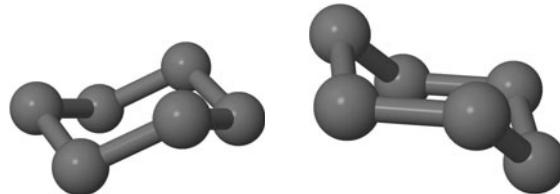
为什么纵使平面五元环的键角如此贴近  $109.5^\circ$ ，它却仍然有一些环张力？

也许您已经猜到这两个问题的答案了，也就是，我们初期对于“碳环在一个平面上”的假设是错误的。很容易看出，较大的环也可以像无环化合物那样扭出多种多样的构象；但对于六元环，就不太容易猜出来了。

## 六元环

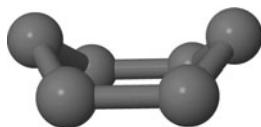
如果您将六个四面体型的碳原子放在一起，您大概会发现得到了如下形状的产物。

■ 掌握这些形状最最最简单的办法是建立模型。我们强烈地建议您这样做！



所有的碳原子并不在同一个平面上，所有的键角都是  $109.5^\circ$ ，因而也没有环张力。如果您将一个六元环的模型压在桌上，强迫它保持一个平面，那么在您松手的时候，它就会自动弹成如图的形状。如果您从模型的侧面看（上图中第二张），您会发现有四个碳原子在同一平面内，第五个在平面上方，第六个在平面下方（不过六个原子是完全等价的，认识到这一点很重要——请旋转自己的模型）。它有一个十分创造性的名字——**椅式构象 (chair conformation)**——正是来源于此。

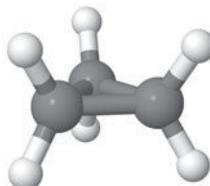
环己烷还有如下的另一种构象。



这种构象被称为**船式构象 (boat conformation)**。在这种构象中，仍然有四个碳原子在同一平面内，但剩下的两个碳原子则都在平面的上方。现在，所有的碳原子就不完全等价了——四个在平面内的碳与两个在平面上方的碳是不同的。然而，虽然同样没有环张力 (所有的键角均为  $109.5^\circ$ )，但这并不是环己烷的一个稳定的构象。为了知道这一问题的原因，我们首先要回到之前的另一个问题：为什么在平面型构象中没有环张力的环戊烷，在真实情况下仍然受环张力？

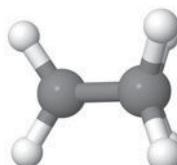
### 小环 (三、四、五元环)

在任何位置点三个点都必有一平面同时穿过，因此环丙烷中的三个碳原子必然是平面型的。三根 C–C 等长，这也意味着三个碳原子在正三角形的三个顶点处。从每个亚甲基均分到的巨大的燃烧热看 (p. 368)，我们知道这个分子中存在相当大的环张力。主要是由于键角偏离理想的四面体角  $109.5^\circ$  太大，但只是主要原因——而不是全部。如果我们沿着其中一根 C–C 键观察，我们会看到更深层次的原因——所有的 C–H 键都是彼此重叠的 (后文简称重叠式相互作用)。

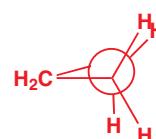


环丙烷的侧视图

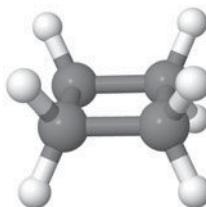
沿着 C–C 观察



沿着一根 C–C 键可以观察到所有的 C–H 键都是彼此重叠的

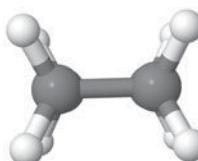


乙烷的重叠式构象能量最高，任何旋转都会使其进入一个更稳定的构象；但环丙烷的 C–C 键则根本没有机会旋转，因此 C–H 键是被强制彼此重叠的。事实上，在任何平面型的构象中，C–H 键都会与相邻的一个重叠。环丁烷会扭曲，不形成平面型；即使这样做会由于减小键角而增大环张力，但为了减弱重叠式的相互作用，它仍然这样做了 (全面考虑)。环丁烷采用折叠式构象 (puckered conformation, 也称“翼式”构象 “wing-shaped” conformation)。

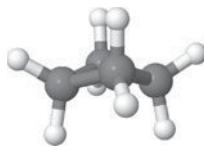


平面型环丁烷 (并非真实构象)

沿着 C–C 观察

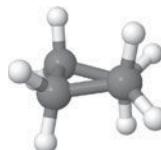


环丁烷的侧视图展示了彼此重叠的 C–H 键



环丁烷的折叠式构象

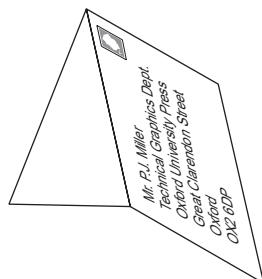
沿着 C–C 观察



C–H 键不再完全重叠



环戊烷的  
信封式构象

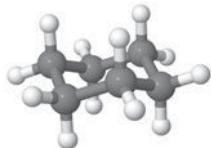


这也解释了为什么环戊烷并不完全没有环张力，因为即使平面型的构象内保证 C–C–C 键角接近  $109.5^\circ$ ，但仍然存在邻位 C–H 键重叠的相互作用问题。燃烧热的数据给了我们综合全部因素的总指标，但键角的计算只是其中一个方面。就像环丁烷中一样，环会扭曲以减少重叠式的相互作用，同时免不了增加张力角度。无论如何，系统中总是会有一些张力；最低能的构象是两种效果相反的因素的平衡结果。环戊烷采用了一种类似于“打开的信封”的形状（称为信封型构象 envelope conformation），其中四个 C 原子在一个平面上，另一个在平面上方或下方。这些原子迅速地轮流处在平面上，或不在平面上。环戊烷的构象性质远没有环己烷定义明确，我们接下来要回到环己烷了。

## 细看环己烷

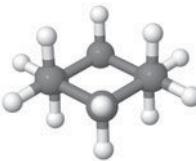
■ 我们将会在 Chapter 32 继续讨论环戊烷的构象和反应性。

在 p. 368 的燃烧热数据显示，环己烷几乎无环张力。这说明无论是张力角度，还是重叠式的相互作用都不存在。环己烷的椅式构象所包含的氢原子如下模型所示。

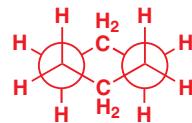


环己烷椅式构象的侧视图

沿着 C–C 看

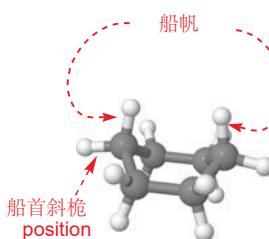


沿着相对的两根 C–C 键  
看环己烷的椅式构象



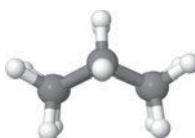
绘制成组曼投影式

沿着两根 C–C 键的试图显示了，环己烷的椅式构象中没有任何重叠式的 C–H 键——事实上，所有的键都是交叉式的，进而给出了可能的最低能量。这就是为什么环己烷是无环张力的。而在船式构象中，四对 C–H 键都是重叠式的，而且在“船帆”位置的两个 C–H 键还有相互作用。

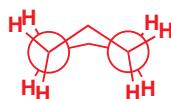


环己烷船式构象的侧视图

沿着 C–C 看

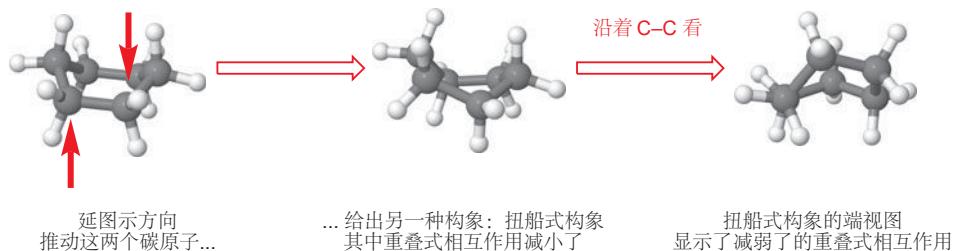


沿着相对的两根 C–C 键  
看环己烷的船式构象



绘制成组曼投影式

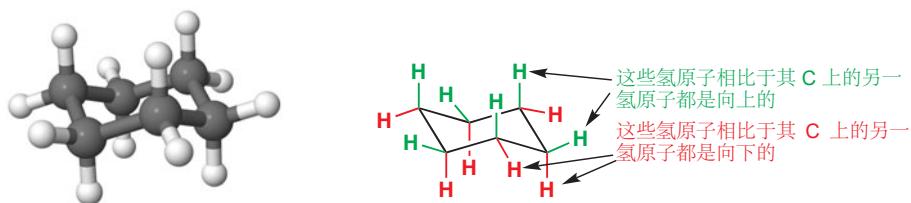
这解释了为什么船式构象没有椅式构象重要。虽然两种构型都不存在张力角度，但船式构象的重叠式相互作用导致了大约  $25 \text{ kJ mol}^{-1}$  的能量上升。事实上，我们会在将来看到，环己烷的椅式构象是能量最低的构象，而船式构象是能量最高的构象。之前说过，环丁烷和环戊烷可以通过扭曲减小重叠式的相互作用，这一点同样适用于船式环己烷。如果一条“侧边”的两个 C–C 键可以都朝反方向扭曲，那么重叠式相互作用会稍稍减小。



船式构象的扭曲得到了环己烷的另一种构象，它被称为**扭船式构象 (twist-boat conformation)**，虽然舍弃了在张力角度上的优势，但最终结果却比船式稳定（能量低  $4 \text{ kJ mol}^{-1}$ ），而且它是一个局部能量最小值（我们接下来会了解）。环己烷有两个稳定的异象体，椅式和扭船式，其中椅式大约比扭船式低能  $21 \text{ kJ mol}^{-1}$ 。

## 直立式和平伏式

重新回到 p. 368 的椅式构象。全部的六个碳原子都是等同的，但却有两种类型的氢原子——一种是竖直地向下或向上插上去的，被称为**直立 (axial) 氢原子**；另一种从侧面伸出来的，被称为**平伏 (equatorial) 氢原子**。如果您环视整个环，就会发现每个  $\text{CH}_2$  基都有一个直立的氢原子和一个平伏的氢原子。然而，所有的直立键（简称直键）和平伏键（简称平键）都在不断交替。



在继续学习之前，您首先要知道如何准确地画环己烷。为了不使 Cs 和 Hs 杂乱，化学家会将其画成如下三种结构中的一种。



到目前为止，我们一直在使用六边形 A 的表示方法来表示环己烷。我们会看到，虽然这是这三种画法中能传递的信息最少的，尽管如此它仍然是有用的。信息量更大的结构 B 和 C（实际上同一分子的不同视角）需要一些练习才能画的准确，但您必须掌握如何画出令人信服的环己烷，因此花费这些时间去学习是值得的。

## 环己烷绘制准则

### 碳骨架

试图一笔画出环己烷的椅式构象时，可能会得到一些糟糕透顶的图。绘制环己烷的椅式构象最简单的方法是由其中一端出发。

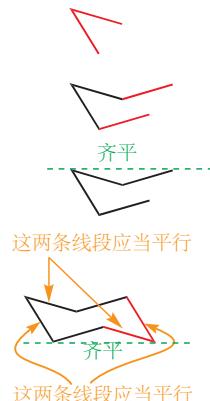
然后画两条等长的平行线段。

在这一阶段，新线段的顶部应与第一次画的一端的顶部齐平。

最后，添加最后两条线，补全另一端。如图所示，此端的两条线段应与另一端的两条线段分别平行，底端也要与第二步线段的底端齐平。

■ 一个局部能量最小值 (local energy minimum) 是一个势阱的底端，但并不一定是最深的势阱，最深的势阱的底端称为全局能量最小值 (global energy minimum)。对于处在局部能量最小值的构象，任何小的能量变化都会增加能量，而大的能量变化才有可能减小能量。例如邻位交叉式是丁烷的一个局部能量最小值，而对位交叉式是丁烷的全局能量最小值。

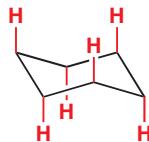
■ 可以与地球的赤道 (equator) 和地轴 (axis)：平伏键 (equatorial bonds) 是环绕在分子的赤道的一周。注意拼写（不是 equitorial!）。



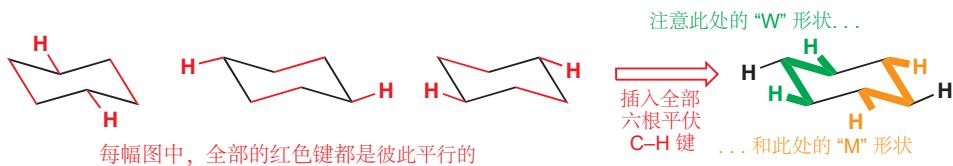
### 添加氢原子

这是最棘手的部分。请记住您需要将每个氢原子都表示作四面体型（注意，在画椅式构象时，我们通常不使用楔形键表示键的前后顺序，那样的话会使事情变得混乱。）

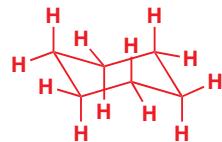
直立键相对好画一些。先围绕整个环，上下交替画出，使其竖直整齐地排列。



画平伏键时需要多一点点注意。需要注意的是每个平伏键都需要与两根 C–C 键平行。



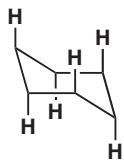
下图是包含全部氢原子的成品图。大多数时候您并不想画出全部 Hs，但为了不时之需，您需要知道它们的位置在哪里。



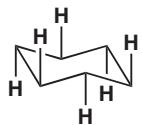
### 常见错误

如果您按照上述规则绘制，您很快就会得到很好的构象图。然而，有一些常见的错误是您需要注意的！

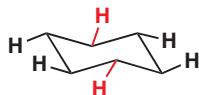
如何错误地画环己烷...



当椅子中间两根键被画成水平的后，两个顶端和两个底端都不再齐平。这意味着直立氢不能再被画成竖直的。



直立氢的上下与碳的走势有关，本图中全部画反了。这一结构是不存在的，因为任何一个碳都不是四面体构型。



红色的氢伸出的角度错误了——请找找平行的先线，以及“W”和“M”形状。

## 环己烷的环翻转

鉴于椅式构象是环己烷的理想构象，那么您希望它的  $^{13}\text{C}$  NMR 光谱是什么样的呢？全部的六个碳原子都是相同的，因此应当只有一个信号（确实是，在 25.2 ppm）。但对于  $^1\text{H}$  NMR 光谱呢？两种不同的质子（直立键和平伏键的）应该会在不同频率处共振，因此会出现两个信号（一个碳上的两个氢分别在两组中）。但事实上，氢谱仅有一组共振信号，在 1.40 ppm。在单取代的环己烷中会出现两个可检测到的异构体，一个是取代基处于直立键的，一个是取代基处于平伏键的。但在室温下仍然同样仅有一组信号。



单取代环己烷的环翻转  
注意氢原子在直立到平伏的转换过程中变化

在低温下的 NMR 光谱中这一现象会有所影响。这时两种异构体是可区分的，这给了我们对于刚刚的事实解释的线索：两种异构体是会相互转化的异构体，在室温下转化迅速，在低温下放缓。回想一下，NMR 不能区分丁烷的三种异象体（两种邻位交叉式和一种对位交叉式），因为它们的转化速率太快了，只能观测到平均值。环己烷与之相同——也是通过键的旋转（即不需要断键！），即可发生环翻转。在环翻转发生时，所有原先直立的键现在都平伏了，反之亦然。

整个环翻转的过程可以拆分成如下几种构象。绿色箭头表示为了到达下一个构象，某些碳原子需要移动的方向。

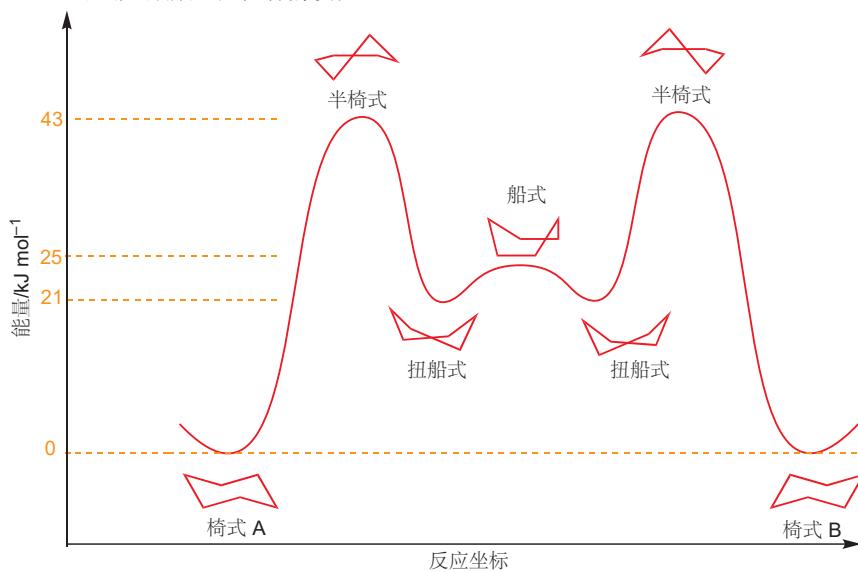
■ 建立环己烷的模型，并自行体验环翻转。



环翻转过程中能量变化大致如下示意图所示，半椅式构象是能量最高点，是由椅式向扭船式转换的过渡状态。船式构象也是能量最高点，是两种扭船式之间转换的过渡状态。

Interactive conformations of cyclohexane

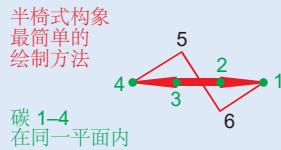
环己烷环翻转过程中的构象变化



■ 正好领您回顾 Chapter 12。这张能量示意图展示了两种椅式构象，经历一个扭船式过渡状态（局部能量最小值）实现转化的过程。在两个能量最小值之间，是能量最大值，也就是过程的过渡态。环翻转反应的过程由较随意的“反应坐标”展示。

### 画出其他的环己烷构象

在环己烷的半椅式构象 (half-chair conformation) 中，四个相邻的碳原子在同一平面上，而第五个在平面上方，第六个在平面下方。您会在将来再次遇到它——例如对于环己烯，这种构象是其能量最小值。



绘制扭船式异象体也有许多种方法，下面是最简单的一种：



从图中可以清楚地看到，环己烷环翻转的势垒为  $43 \text{ kJ mol}^{-1}$ ，因此在  $25^\circ\text{C}$  下速率为  $2 \times 10^5 \text{ s}^{-1}$ 。环翻转同样可以交换直立键和平伏键上的质子，因此它们在  $25^\circ\text{C}$  下也会以  $2 \times 10^5 \text{ s}^{-1}$  的速率交换——超过了 NMR 可区分的速率，这就是为什么它们以平均信号的形式出现的原因。

### 转换速率和光谱法

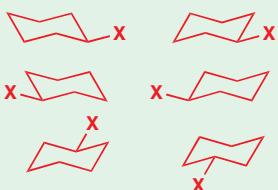
NMR 光谱仪就像照相机一样，它的快门速度是  $1/1000 \text{ s}$ 。任何比这个间隔快的变化在照片中都难以区分；事情发生的越慢，在照片上就越清晰。事实上，NMR 光谱仪的“快门速度”有一个精确的数值（不是真正的快门速度——是比喻的说法），由下列等式给出：

$$k = \pi \Delta v / \sqrt{2} = 2.22 \times \Delta v$$

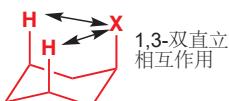
其中  $k$  是能使两种信号独立的转换速率的最大值， $\Delta v$  是 NMR 光谱上可以分开显示的两个信号的间隔，以赫兹为单位。例如在一个  $400 \text{ MHz}$  的光谱仪上，可以分开显示两个间隔为  $0.25 \text{ ppm}$  也就是  $100 \text{ Hz}$  的信号，那么任何慢于  $222 \text{ s}^{-1}$  的转换过程会分成两个信号，任何快于  $222 \text{ s}^{-1}$  的转换过程会显示一个平均信号。

上述等式适用于任何光谱方法，只需要我们具体考虑两个信号或峰的间隔即可。例如，两个  $100 \text{ cm}^{-1}$  的 IR 吸收可以显示  $0.01 \text{ cm} (1 \times 10^{-4} \text{ m})$  的波长或  $3 \times 10^{12} \text{ s}^{-1}$  的频率。因此 IR 可以侦查的转换速率要可以比 NMR 的快很多——它的“快门速度”在十万分之一秒数量级。

■ 单取代环己烷只有一种平伏键异象体，和一种直立键异象体。说服自己，下列图片均是同一种构象，仅观察角度不同：



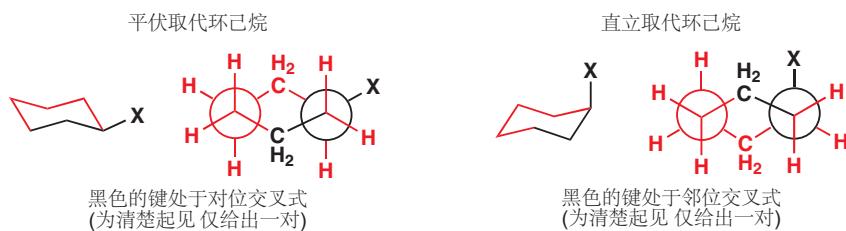
我们在 Chapter 12 中讨论过能量差与平衡常数的关系。



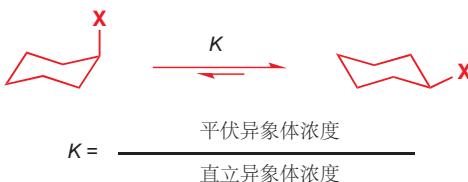
例如，对于甲基环己烷 ( $X=\text{CH}_3$ )，甲基处于直立键的构象比处于平伏键的构象高能  $7.3 \text{ kJ mol}^{-1}$ 。这种能量差导致在  $25^\circ\text{C}$  下前者和后者的比例为 20:1。

关于直立构象比平伏构象能量高，有两种原因。其一是，直立构象中，直立的 X 基团与环上处于同侧的另两个直立的氢存在排斥，使得体系不稳定，这种相互作用被称为 1,3-双直立相互作用（或 1,3-二直键相互作用）。X 基团越大，这种相互作用就越严重，直立键构象占比也就越小。第二个原因是在平伏键构象中，

C–X 键与两个 C–C 键处于对位交叉式；而在直立键构象中，C–X 键与两个 C–C 键处于邻位交叉式。



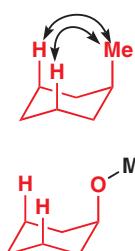
下表展示了多种单取代环己烷在 25°C 下平伏异象体比直立异象体的优势。

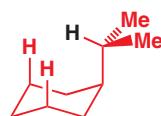


X	平衡常数 K	直立取代与平伏取代的能量差, kJ mol <sup>-1</sup>	平伏取代的百分数
H	1	0	50
OMe	2.7	2.5	73
Me	19	7.3	95
Et	20	7.5	95
i-Pr	42	9.3	98
t-Bu	>3000	>20	>99.9
Ph	110	11.7	99

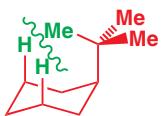
注意以下几点 (在 Chapter 12 中提到过的思路)。

- 表格中三列是相同信息的不同表达侧面。然而，只看百分数这一列，并不能马上准确地看出平伏构象有多少优势——甲基、乙基、异丙基、叔丁基和苯基环己烷的平伏构象都占 95% 或更多。平衡常数的观察相对更清晰。
- 平伏异象体的数量确实按序列 Me < Et < i-Pr < t-Bu 增加，但并不完全在意料之中。乙基的体积比甲基大很多，但在平衡常数上却上升不明显。从 Et 到 i-Pr 取代的平衡常数仅上升了两倍；但对于叔丁基取代，平伏异象体的浓度却是直立异象体的大约 3000 倍。
- 在甲氧基的位置也出现了反常——甲氧基取代的直立异象体比甲基取代的直立异象体多。这违反了甲氧基比甲基体积大的事实。
- 平衡常数并不取决于取代基的具体体积，而是取决于它与另两个直立氢相互作用的大小。在甲基环己烷的直立异象体中，甲基与另两个氢间有直接的相互作用。
- 而在甲氧基环己烷的直立异象体中，氧原子将甲基拽离了环，因此减弱了相互作用。





- Me, Et, *i*-Pr, 和 *t*-Bu 都需要将一些原子推向另两个直立的氢。在 Me, Et, 和 *i*-Pr 中, 这个原子是 H.

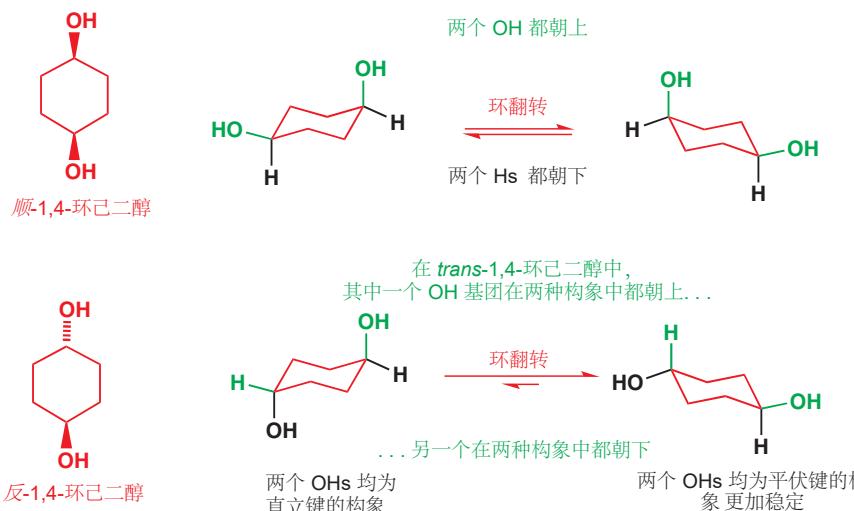


- 而只有在 *t*-Bu 取代的直立异象体中, 一个甲基被推向了环中央, 因此 *t*-Bu 比其他基团更倾向于处在平伏键上。事实上, 直立的 *t*-Bu 基团与直立氢原子间的相互作用十分严重, 以至于这种基团总是处在平伏键位置上。在后面的学习中, 这一点十分有用。

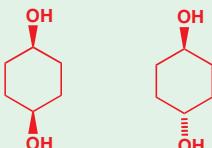
### 环上有一个以上取代基时

■ 环翻转时所有的平伏键和直立键互换, 但不会改变它们相对于环的朝向。如果一个平伏取代基翻转前朝上(与附着在同一个 C 上的氢相比); 那么翻转后, 它仍然朝上, 只是由平伏键变成了直立键。平伏键和直立键是构象的规定, 而朝向则取决于化合物的构型。

当环上有两个或更多取代基时, 就会出现立体异构体。例如, 1,4-环己二醇 有两种异构体——一种(顺式异构体) 中两个取代基都朝上或朝下(处于环的上方或下方); 另一种(反式异构体) 中一个羟基朝上, 一个羟基朝下。对于任何同一取代基取代的顺式 1,4-二取代 环己烷, 环翻转过程的两侧是完全相同的构象; 而对于反式构型, 则会有一个全直立构象, 和一个全平伏构象。



■ 顺式和反式的化合物互为非对映异构体。因此, 它们有不同的化学和物理性质, 并不能仅通过键的旋转而转化。

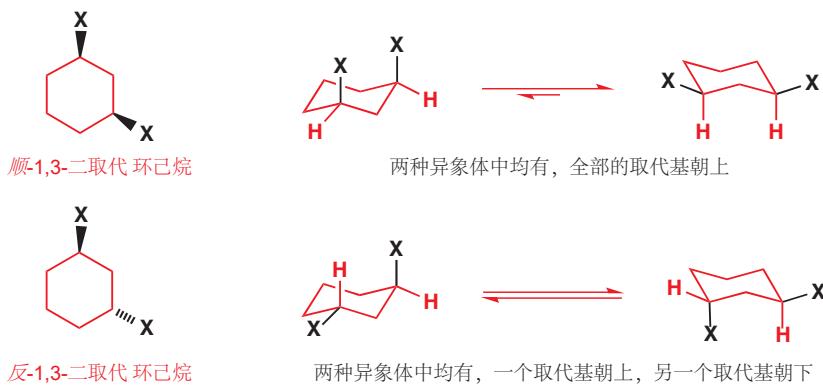


m.p. 113–114 °C m.p. 143–144 °C

这与 反-1,4-环己二醇(的双直立或双平伏的两种异象体)形成了对比它们可以在室温下迅速地转化, 并不需要破坏任何键。

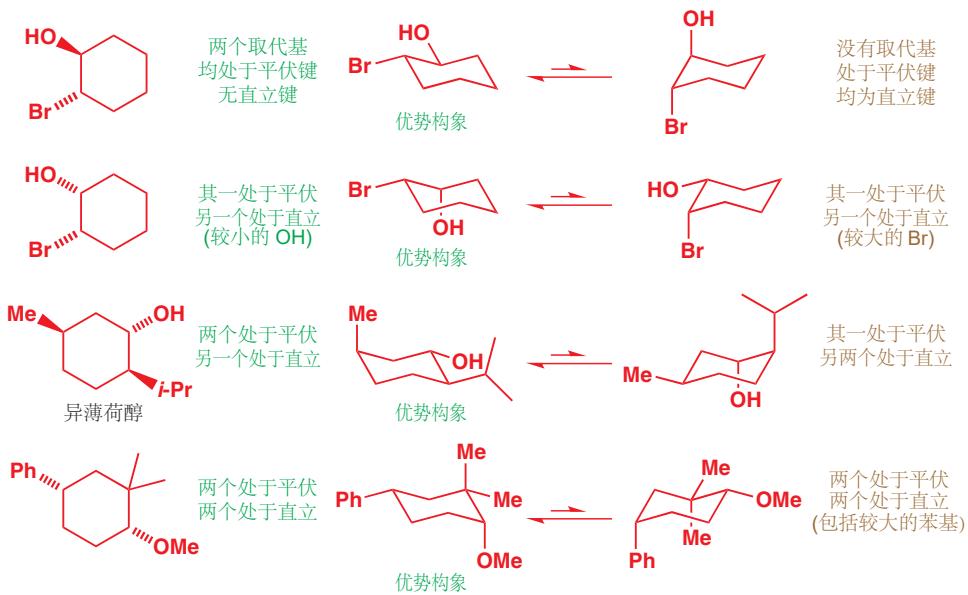
椅式结构图包含了比简单的六边形结构图更多的信息。前者同时表达了构型和构象——它既能表达我们讨论的是哪种立体异构体(顺式的还是反式的), 还能表达这种立体异构体所采用的构象(例如在反式异构体中, 是双直立还是双平伏)。相比之下, 简单的六边形结构图不能表达任何关于构象的信息——只能说明我们讨论的是哪种异构体。在讨论化合物的构型, 而不需要具体说明构象时, 这种图示更加实用; 而当您需要通过原料所采用的构象, 预测反应产物的构型时, 则通常由椅式结构图出发, 在结束时重新整理成六边形结构图。

在 顺-1,4-二取代 环己烷的椅式异象体中, 有一个取代基平伏, 一个取代基直立。这一点并不适用于其他位置的二取代环己烷, 例如 顺-1,3-二取代 环己烷的两个取代基或全直立, 或全平伏。记住, “顺式”和“反式”的前缀仅表示取代基处在环己烷的同侧或异侧; 而取代基是一直立一平伏, 还是全直立/平伏, 是取决于取代方式的。每当您遇到一个分子的时候, 先绘制构象图或者做一个模型, 来找出处于直立的、和处于平伏的键。



决定平伏键取代基是朝上还是朝下总是不容易的。判断的关键在于将其与相同 C 原子上的氢原子相比较——直立键的氢原子的朝向是非常好判断的。如果它的直立键同伴朝上，那么这个平伏键取代基就必定朝下；反之亦然。

那么，当环上的两个取代基不相同的时候呢？例如在 顺-1,3-二取代环己烷中，优势构象无疑是两个取代基均为平伏键的构象。但在两个取代基必定一直立一平伏的时候（例如反式构型中），优势构象取决于这两个取代基本身。一般来说，平伏键取代基多的构象更有利；而两个有同样多数平伏取代基的构象中，大取代基处于平伏键的构象更有利，这种情况下小取代基可以屈居直立键。下面展示了很多个可能的例子。



这只是一个参考，而在很多情况下，优势构象都不是那么容易确定的。相比于将自己困扰在这些不确定的问题中，我们不如了解一些能够确定优势构象的、特殊取代的环己烷。

### 锁定基——叔丁基

我们知道，一个环中的叔丁基总是倾向于处在平伏键位置上。这使得判断下一页的两个化合物所采用的构象十分容易。

## 顺-4-叔丁基环己醇



在顺式非对映体中，羟基会被强制处于直立键

两个化合物中，叔丁基都处于平伏键

## 反-4-叔丁基环己醇

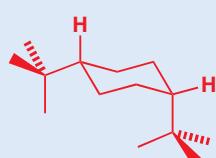
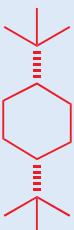


在反式非对映体中，羟基会被强制处于平伏键

## 顺-1,4-二叔丁基环己烷

一个直立的叔丁基真的很不舒服。在 顺-1,4-二叔丁基环己烷 的椅式构象中，一个叔丁基会被强制处于直立键。为了避免这种情况，这一化合物更倾向于折叠成一个扭船式构象，这样两个大基团就均可处在平伏键位置（平伏键是椅式构象中的称呼，此处应称之为“假平伏键 (pseudoequatorial)”。

## 顺-1,4-二叔丁基环己烷



扭船式构象（其中两个叔丁基都处在假平伏键位置）比椅式构象能量低。

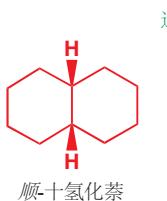
## 十氢化萘



十氢化萘

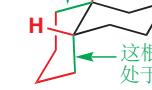
环己烷的构象还可以通过与另一个环稠合得以锁定，两个环己烷在一根普通的 C–C 键处稠合得到的化合物称为十氢化萘。基于桥头的两个氢原子的顺式或反式构型，十氢化萘有两种非对映异构体。在顺-十氢化萘中，两个环连接的键必有一根直立键和一根平伏键；而在反-十氢化萘中，这两根键则同时处于平伏键。

Interactive conformations of decalins

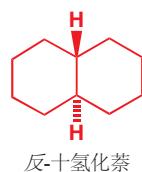


顺-十氢化萘

这根键在黑色环上  
处于平伏键

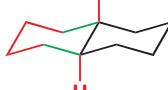


这根键在黑色环上  
处于直立键



反-十氢化萘

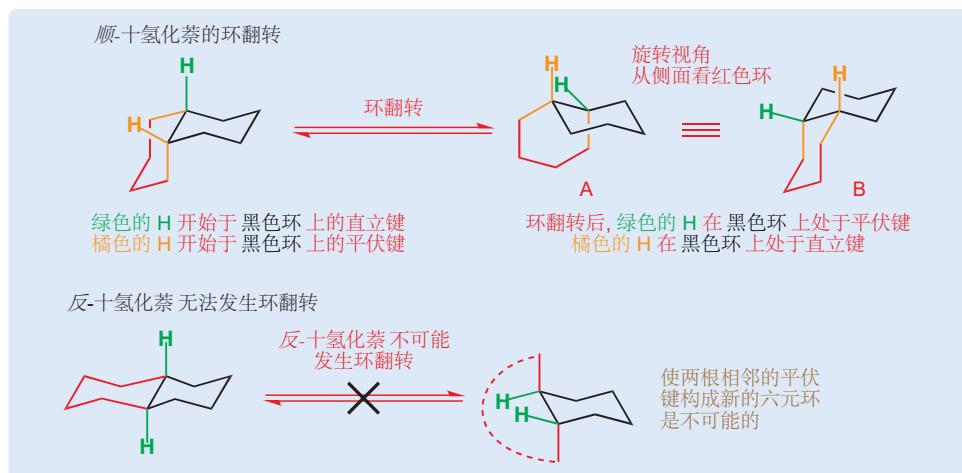
两根绿色的键  
在黑色环上  
都处于平伏键



当环己烷发生环翻转时，原来处于平伏键的取代基转变为了直立键，反之亦然。这对于顺-十氢化萘是可以的，因为它的两个桥头（junction）是一组可交换的直立—平伏式；但这对于反-十氢化萘就行不通了。如果让反-十氢化萘发生环翻转，那么两个桥头会变成直立—直立式，六元环相邻的两个直立键是无法连接在一起的。另一方面，顺-十氢化萘的环翻转十分容易。

## 顺-十氢化萘的旋转：并不困难的原因

如果您发现自己很难想象顺-十氢化萘的环翻转过程，您并不孤单！最好的办法是在思考过程中始终忽略红色的环，仅关注黑色环上发生的事情，即桥头上的氢原子、橘色的键。翻转黑色的环，橘色键和氢原子都会从直立键翻转到平伏键，或从平伏键翻转到直立键。画出结构，但不要补全红色的环，因为在这个时候补全它，常常会得到一个平面六边形（如图 A）。相反，绕纵轴将黑色的、已经画好的环旋转 60°，这时再补全红色的环就会顺利地得到椅式（如图 B）。想要画出椅式而不是正六边形，您需要先让橘色的两根键朝内摆放，即 B 中而不是 A 中的摆法。

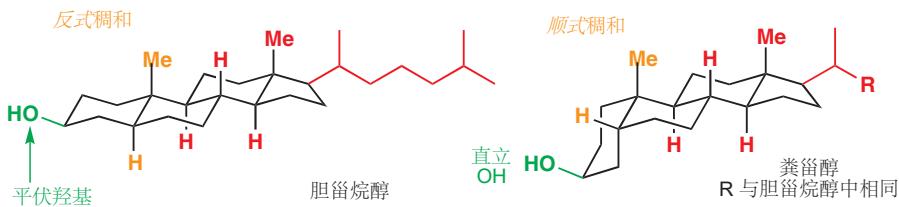


Interactive ring inversion of cis-decalin

## 甾族

甾族/类固醇 (Steroids) 是存在于动植物体中的一类重要化合物，对于从调节生长 (促蛋白合成甾族)，性冲动 (所有的性激素都是甾族)，到植物、青蛙、海参的自我防卫机制都有重要的作用。甾族的性质由其结构决定：甾族化合物的骨架包含四个稠和的环——三个环己烷环和一个环戊烷环——如右图所示连接。

正如十氢化萘的体系一样，每对桥头都可以是顺式，或是反式；但事实证明，除了环 A 和环 B 连接的地方有时会是顺式，其他地方全部都是反式的。下面分别是胆甾烷醇 cholestanol (均为反式) 和粪甾醇 coprostanol (A 和 B 顺式稠和)。



因为甾族 (包括 A-B 顺式稠和的) 本质上是取代的反-十氢化萘，因此它们不能翻转。因此，胆甾烷醇中的羟基在环 A 上永远处于平伏键，而粪甾醇中的羟基在环 A 上处于直立键。甾族化合物的骨架相当稳定——有  $1.5 \times 10^9$  年历史的底泥样本中的甾族化合物，稠和处仍然保持相同的立体化学。

## 直立键和平伏键取代基反应性的不同

我们将在本书的其余部分使用环结构，您需要学习它们的构象如何广泛地影响它们的化学性质。很多包含六元环的反应的结果，往往取决于官能团在直立键或是平伏键。我们将用两个例子结束这一章的讨论，例子中的官能团会被叔丁基，或者通过稠环体系 (如反-十氢化萘) 锁定在直立键或平伏键位置。

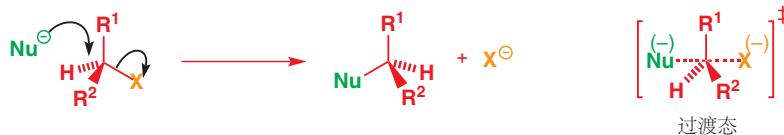
在上一章中我们谈了两个亲核取代反应的机理： $S_N1$  和  $S_N2$ 。其中  $S_N2$  反应涉及中心碳的构型翻转。回想一下，亲核试剂进攻  $C-X$  的  $\sigma^*$  轨道，意味着它必须从离去基团的反方向接近，导致了构型翻转。



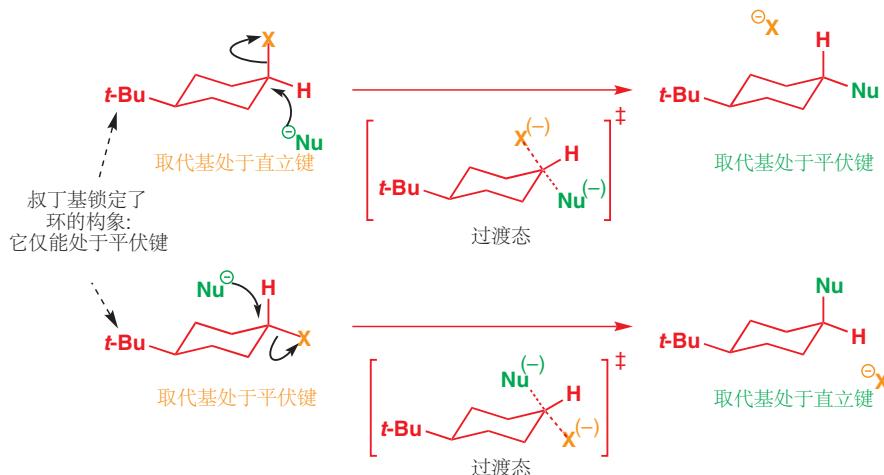
巴顿爵士 (Sir Derek Barton, 1918–98) 正是出于对自己发现的甾族化合物的反应性进行解释的渴望，于 1940s 和 1950s 描述了本章所讲的构想分析原则。他于 1969 年因此工作获得诺贝尔化学奖。

■ 叔丁基不能处于直立键 (p. 375)，反-十氢化萘不能发生环翻转 (p. 378)，这是它们锁定构象的方法。

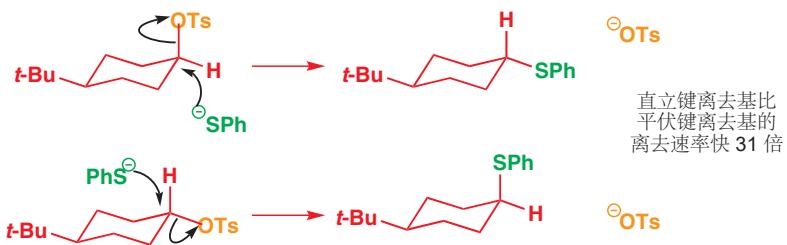
饱和碳上的亲核取代 中的构型翻转



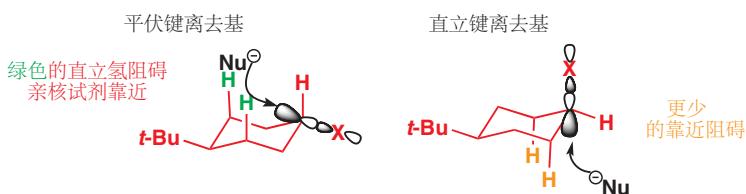
对于环己烷衍生物的  $S_N2$  反应，如果分子的构象被锁定基所固定，那么  $S_N2$  反应的构型翻转机理就意味着：如果离去基团原来处于直立键，那么亲核试剂进攻后就会停在平伏键，反之亦然。



环己烷上的取代反应并不常见。环己烷上的亲电碳是一个仲碳——在上一章中我们看到仲中心并不能通过  $S_N1$  或  $S_N2$  机理很好地反应 (p. 347). 为了促进  $S_N2$  机理的发生，我们需要一个好的亲核试剂和一个好的离去基团。下面是一个可行的例子—— $\text{PhS}^-$  进攻，离去对甲苯磺酸负离子。

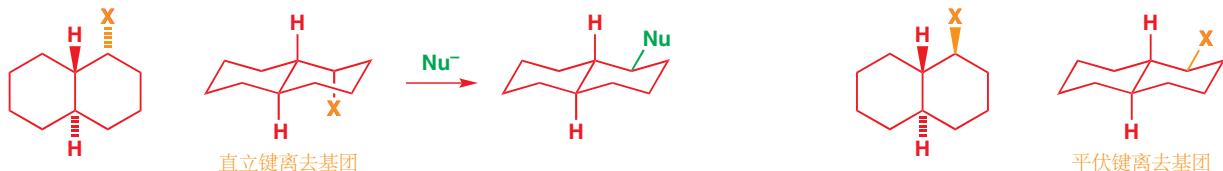


直立键取代基比平伏键取代基反应进行得快。造成这一速率差异的贡献因素有一些，其中最重要的是亲核试剂靠近的方向。亲核试剂必须进攻离去基团的  $\sigma^*$ ，因此必须恰好从  $\text{C}-\text{X}$  键的背后进攻。对于平伏键取代的化合物，进攻路线被 (下图中绿色的) 直立氢原子所阻碍——它需径直穿过这些氢原子占据的空间区域；而对于直立键取代的化合物，进攻方向是与 (橘色的) 直立氢原子平行的——直立氢原子与离去基团对位交叉式，因此亲核试剂靠近的过程阻碍少了很多。



我们必须假设即使在简单的未取代环己烷中也是如此，例如环己基溴的取代反应，大多数发生在其镜像，即直立异象体上。这一现象减慢了反应速率，因为它们必须先从更为普遍的平伏异象体翻转到直立才可以发生反应。

如果离去基团无法翻转到直立键，可能这个反应干脆不能发生。这正是常在反-十氯化萘中发生事情，下面有两种反-十氯化萘的取代物（互为非对映异构体）：其一的离去基团处于平伏键，另一个则处于直立键（X 可以是 Br, OTs, 等）。



对于后者的进攻是直接的，亲核试剂直接沿着 C-X 键的轴靠近，并发生伴随着翻转的普通 S<sub>N</sub>2 反应即可——得到的产物是平伏化合物。而另一边，对于前者的取代，则要求亲核试剂从分子的中间靠近，这是无法做到的，相反，这个分子会发生一个完全不同的反应——一个您会在 Chapter 36 中遇到的重排反应。

## 小结

您可能会不解：为什么我们在六元环上花了这么多时间，而几乎完全忽略了其他尺寸的环。除去六元环是有机化学中分布最广的环尺寸的理由外，六元环的反应也是最好解释和理解的。我们之前略述的六元环的构象规则（环张力的缓解，交叉式优于重叠式，平伏键优于直立键，进攻方向等）在稍加修改后也同样适用于其他环尺寸。这些环表现的不如六元环好，因为它们缺少六元环幸运地享有的，无环张力的构象。我们现在会暂时离开立体化学；在 Chapters 31 和 32，关时于环状化合物立体化学的两章，我们会重新讨论一些更难的内容。

## 延伸阅读

关于构象，请主要参考：E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*. Wiley, New York, 1994.

更加详细的分析烷烃构象偏好的原因：V. Popovitsic and L. Goodman, *J. Phys. Chem. A*, 2002, 106, 1642–1646.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 17 消除反应

## 联系

### 基础

- 立体化学 ch14
- 饱和碳原子上亲核取代反应的机理 ch15
- 构象 ch16

### 目标

- 消除反应
- 什么因素使消除反应有利于取代反应
- 三个重要的消除反应机理
- 构象在消除反应中的重要性
- 如何用消除反应制备烯烃(和炔烃)

### 展望

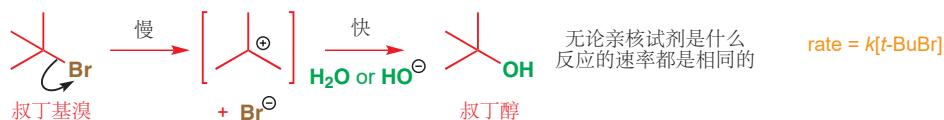
- 对烯烃的亲电加成(本章反应的逆反应) ch19
- 如何控制双键几何结构 ch27

## 取代与消除

想想火车站闸机的例子(见 p. 332).

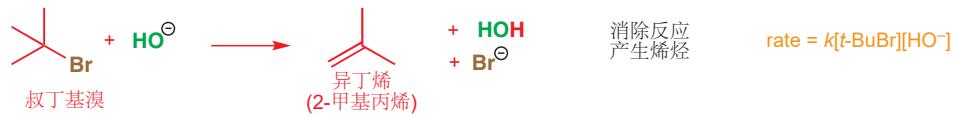
您应当还记得在 Chapter 15 中我们提到, 叔丁基卤的取代反应一贯遵循  $S_N1$  机理, 这类反应的决速步是单分子的——决速步仅涉及卤代烃这一个反应。这意味着, 无论使用什么亲核试剂, 发生取代反应的速率都是相同的。例如, 若使用氢氧根离子代替水, 或者增加氢氧根的浓度, 都不能加速  $S_N1$  反应的发生。我们说, 这只是浪费时间。(见 p. 332).

### $t\text{-BuBr}$ 的亲核取代反应



当您使用氢氧化钠的浓溶液, 试图完成取代反应时。不仅会浪费您的时间, 事实上, 还会浪费您的卤代烃。

### $t\text{-BuBr}$ 与 $\text{NaOH}$ 的浓溶液发生的反应



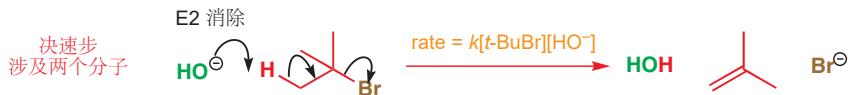
反应已不再是取代反应，而是生成了一个烯烃。大体上，可以说是从卤代烃上脱去了 HBr，这种反应称作消除反应 (elimination, 也称消去反应)。

本章中我们会讨论消除反应的机理——就像取代反应一样，消除反应也不只有一种机理。我们会对比消除与取代反应——这两种反应在几乎完全相同的反应物体系下进行，您会学习如何预测更倾向于发生哪一种。大多数机理的讨论与 Chapter 15 关系密切，我们建议您在处理本章之前先确保自己理解了那一章的所有重点。本章还会讲述消除反应的应用，除去在 Chapter 11 中略略谈到的 Wittig 反应，本章将是您遇到的第一种构筑简单烯烃的反应。

## 当亲核试剂进攻氢而不是碳时，发生消除反应

叔丁基溴发生消除反应，是由于亲核试剂的碱性。请回顾 Chapter 10 中的内容，碱性和亲核性间有一些联系：强碱通常是好的亲核试剂。氢氧根，作为好的亲核试剂，并不对取代反应的速率产生影响，因为它并未出现在决速步的速率等式中。而作为好的碱，它却对消除反应的速率产生了贡献，因为它参与了消除反应的决速步，也出现在了速率表达式中。这就是机理。

■ 在对 C=O 的亲核进攻上，碱性和亲核性之间的相关性得以体现。在 Chapter 15 中您见过的对于饱和碳原子亲核取代好的亲核试剂 (例如 I<sup>-</sup>, Br<sup>-</sup>, PhS<sup>-</sup>) 都不是强碱。



氢氧根在消除反应中充当碱的角色，因为它进攻的是氢原子，而不是取代反应中进攻的碳原子。氢原子并不是酸性的，但由于溴是一个好的离去基团，在溴离子离去的同时，氢原子便可以以质子形式离开。当氢氧根进攻时，溴携带着负电荷，被迫离开。这两个分子——叔丁基溴和氢氧根——都涉及在反应的决速步中。这意味着这两者的浓度都会出现在速率等式中 A，因此这是个二级反应，这种消去机理被称作 E2，代表双分子消除 (Elimination, Bimolecular)。

■ 注意：没有上标或者下标，只有非常朴素的 E2。

$$\text{rate} = k_2 [t\text{-BuBr}][\text{HO}^-]$$

现在让我们看另一种类型的消除。我们可以通过思考另一种 S<sub>N</sub>1 取代反应来认识它，即与本章开头的反应相反的：醇转变为卤代烃的反应。

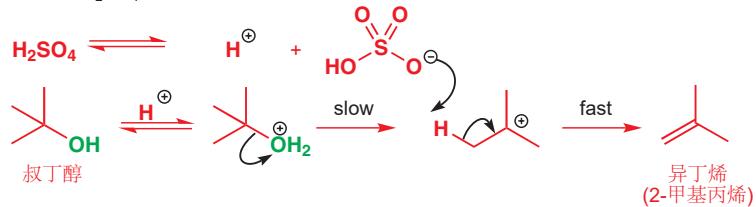
HBr 对 t-BuOH 的亲核取代



决速步中不涉及亲核试剂溴离子，因此我们知道这一反应的速率也不受 Br<sup>-</sup> 浓度的影响。第一步生成阳离子的反应，也确实与根本没有溴时发生的一样快。但在这种情形下，消除反应的发生是不同的。为了找到答案，我们需要用一种酸，要求其共轭碱的亲核性很弱，无法进攻碳阳离子中的正电碳的。例如，叔丁醇在硫酸中不会发生取代反应，仅能发生消除反应。

 Interactive E1 elimination mechanism

### E1 消除: $\text{H}_2\text{SO}_4$ 中的 $t\text{-BuOH}$



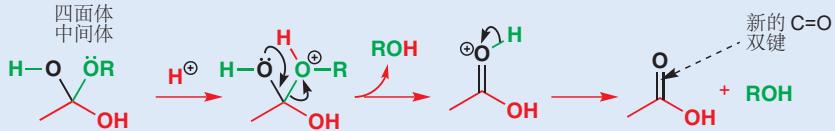
碳阳离子生成的决速步中并不涉及  $\text{HSO}_4^-$  离子。而且它也是一个很差的亲核试剂，并不能进攻碳阳离子中的 C 原子；它的碱性也十分弱；但在机理中您看到，由于它实在不能做亲核试剂，因此它勉强充当了碱（拔去质子）。速率方程中也不涉及  $\text{HSO}_4^-$  的浓度，决速步与  $\text{S}_{\text{N}}1$  反应类似——质子化的  $t\text{-BuOH}$  单分子脱水。这种消除机理因此称为 E1 (*Elimination, unimolecular*)。

我们不久会回到这两种消除机理，还有第三种；但在此阶段值得注意的是，选择发生 E1 和 E2 机理与从前选择发生  $\text{S}_{\text{N}}1$  和  $\text{S}_{\text{N}}2$  需要考虑的理由是不同的：您刚刚见到，分别发生 E1 和 E2 的两个底物都仅发生  $\text{S}_{\text{N}}1$ 。这两个反应的区别在于碱的强度，因此我们需要首先回答一个问题：什么时候亲核试剂会充当碱？

### 羰基化学中的消除反应

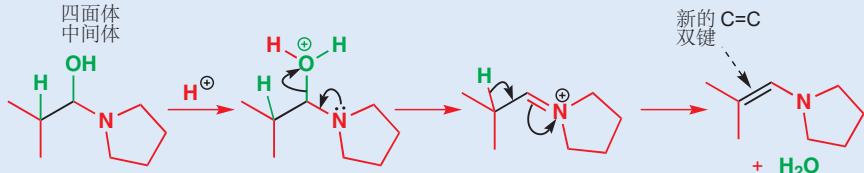
本章中我们会详细讨论烯烃的生成，但此前我们已经在 Chapters 10 和 11 中使用过“消去”一词来描述四面体中间体上的离去基团的离开。例如，在酸催化的酯水解的最后一步就涉及  $\text{ROH}$  的 E1 消除，所生成的双键是  $\text{C}=\text{O}$  而不是  $\text{C}=\text{C}$ 。

#### E1 消除：酯水解中消去 $\text{ROH}$



在 Chapter 11 中您也见过 E1 消除得到烯烃的过程。得到的烯烃是烯胺。

#### E1 消除：得到烯胺的同时消去 $\text{H}_2\text{O}$



## 亲核试剂对取代、消除竞争的影响

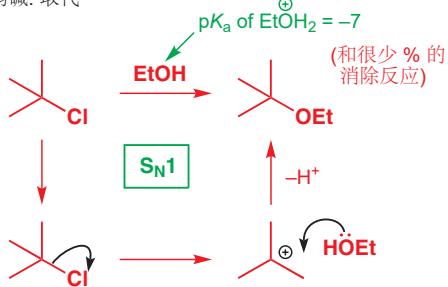
### 碱性

带有离去基团的分子会在两个不同类的亲电位点被进攻：连接离去基团的碳原子，或与该碳相邻的碳上的氢原子。进攻碳原子导致取代反应，进攻氢原子导致消除反应。一般来说，“亲核试剂”的碱性越强，越容易进攻质子，即消除反应相比于取代反应占据主要。

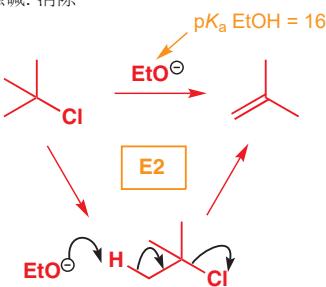
下面是应用这一思路的一个例子：弱碱 ( $\text{EtOH}$ ) 导致取代反应，而强碱 (乙氧基阴离子) 导致消除反应。



弱碱: 取代



强碱: 消除



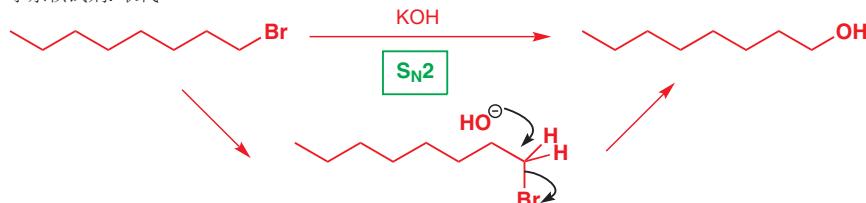
### 消除、取代和软硬度

我们还可以通过亲电试剂的软硬 (p. 357), 来解释发生消除还是取代的选择性, 即进攻 H 还是 C 的选择性。在一个  $S_{\text{N}}2$  取代反应中, 中心碳是软的亲核试剂——它基本上不带电, 并且其与离去基团, 例如与卤素的 C-X  $\sigma^*$  是相对低能的 LUMO; 因此当亲核试剂的 HOMOs 与其 LUMO 最容易相互作用——即亲核试剂较软时, 就会倾向于取代。相比之下, C-H  $\sigma^*$  的能量更高, 因为两个原子的电负性都很小, 再加上氢体积小, 使得 C-H 碱是一个硬亲电位点; 因此硬的亲核试剂更倾向于消除。

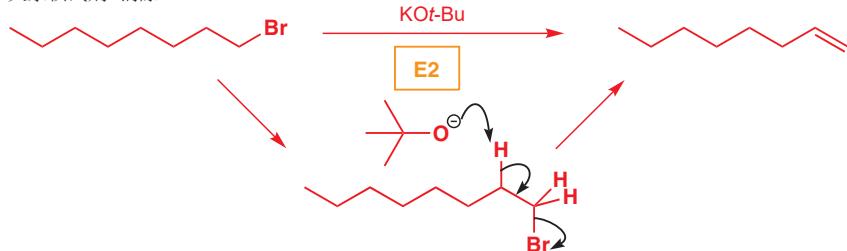
### 大小

对于一个亲核试剂, 攻击碳原子就意味着挤掉它原有的取代基——甚至对于伯卤代烃, 仍然有一个烷基予以阻碍。这是在有阻碍的卤代烃上发生  $S_{\text{N}}2$  反应十分缓慢的原因之一——亲核试剂很难到达反应中心。但在消除反应中得到更加暴露的氢原子就很容易了, 这意味着, 如果我们使用个头很大的碱性亲核试剂, 消除反应就会更倾向于发生, 即使在伯卤代烃中也是一样。叔丁醇钾是一个常用的, 避免取代反应, 而促进消除反应的碱; 大的烷基取代基使带负电的氧难以进攻碳, 导致取代反应, 但对于进攻氢原子并无大碍。

小亲核试剂: 取代



大亲核试剂: 消除



### 温度

在决定发生消除反应还是取代反应时, 温度起很重要的作用。两个分子通过消除反应产生了三个分子 (数一数); 而在取代反应中, 则是两个分子产生了两个新分子。因此两个反应过程的熵变不同: 消除反应的  $\Delta S$  高于取代反应。在 Chapter 12 中, 我们讨论了如下方程:

■ 这个解释被简化了, 因为重要的是反应速率而不是产物的稳定性。更详细的解释超出了本书的讨论范围, 但总体观点仍然成立。

$$\Delta G = \Delta H - T\Delta S$$

这个方程显示，在高温下， $\Delta S$  越正，反应越利于正向进行 ( $\Delta G$  会越负)。因此高温有利于发生消除反应，而事实也确实如此：您将见到的大多数消除反应，都在室温甚至更高的温度下发生。

► 相关的例子见 Chapter 12, p. 247

### ● 消除还是取代

- 强碱性的亲核试剂倾向于消除。
- 大体积的亲核试剂（碱）倾向于消除。
- 高温倾向于消除。

## E1 和 E2 机理

现在您已经见识了一些消除反应的例子了，是时候回到我们对于消除反应的两种机理的讨论了。总结我们之前所说的：

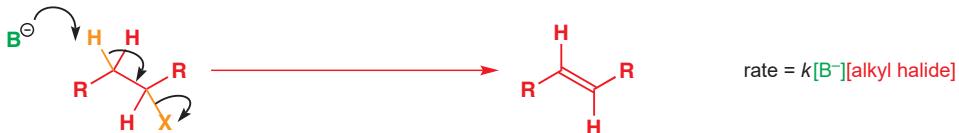
- E1 描述的是决速步是不包含碱参与的单分子反应 (1) 的消除反应 (E)。离去基团在这一步离去，而质子的去除则在与之分开的第二步中。

### E1 消除的一般机理



■ 在 E2 消除中，离去基团的离去与质子的去除是协同的 (concerted)。

### E2 消除的一般机理



有很多因素会影响消除反应按 E1 还是 E2 机理进行。其中一个是从速率方程中一看就明白的：只有 E2 机理受碱的浓度的影响，因此高浓度的碱有利于 E2。而 E1 反应的速率不受碱的影响——因此 E1 无论面对强碱还是弱碱都不会求全责备，而 E2 在强碱中要比弱碱中进行得快：任何浓度的强碱都相较 E1 更有利于 E2。如果您看到一个消除反应依赖强碱，那么它无疑是一个 E2 反应。下面是本章介绍的第一个例子。

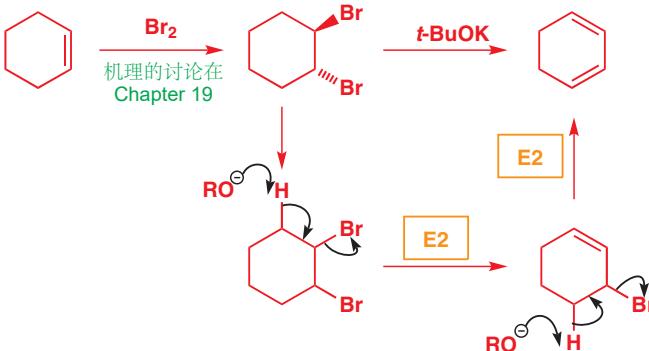
### 叔丁基溴与高浓度氢氧根的反应



阻碍较小的烷基卤代物不是与氢氧根发生消除反应的好选择，因为氢氧根的体积相当小，在此情境下很乐意进行  $S_N2$  取代反应（甚至是叔烷基卤代物，在碱的浓度低时，取代反应也会超过消除反应）。

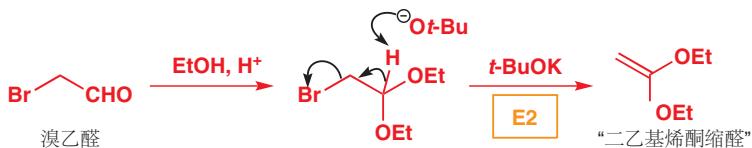
我们之前提到过，大块头的叔丁氧基阴离子——是理想的 E2 反应试剂，因为它既庞大又是强碱 ( $pK_a$  of  $t\text{-BuOH} = 18$ ). 在下面的过程中，连续两次的 E2 消除使二溴代物 (dibromide) 转化为了双烯/二烯 (diene)。由于二溴代物可以通过烯烃制得（下下章中），下面的过程也是一个通过两步将烯烃转化为双烯的实用反应。

通过两步 E2 反应的双烯合成



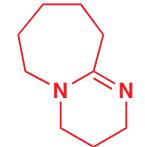
Interactive mechanism for double E2 to form diene

下一个反应的产物被称为“烯酮缩醛 (ketene acetal)”。与其他缩酮不同的是，它不能直接由烯酮 (ketene,  $\text{CH}_2=\text{C=O}$ , 十分不稳定) 制备，因此这种缩醛的制备通常按下列方法，即使用  $t\text{-BuOK}$  从溴乙醛上消除 HBr.



下一章简要地介绍了烯酮。

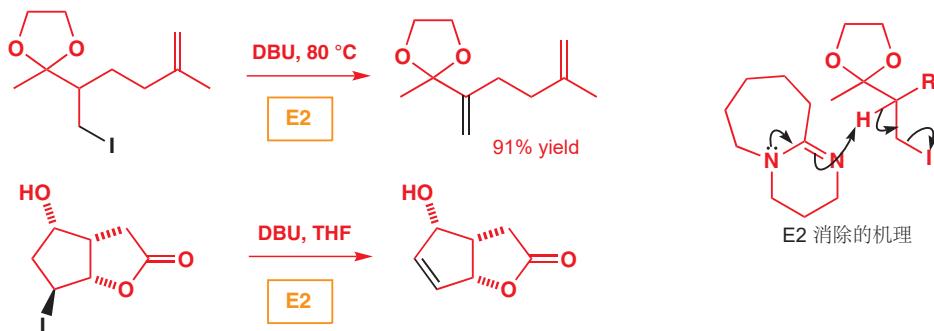
卤代烷转化为烯烃所常用的碱是您在 Chapter 8 见过的: DBU. 这种碱是一种脒 (amidine)——其中一个氮上的孤对电子在其与另一个氮之间离域，质子化后的镁阳离子/脒𬭩离子 (amidinium ion) 的稳定性使脒的碱性增强，镁阳离子的  $pK_a$  大约为 12.5. 而且，它庞大的稠环结构使其不易进入那些狭小的角落——因此相比于抵达碳原子发生取代反应，它们先抵达质子。



DBU  
1,8-二氮杂双环-[5.4.0]-7-十一碳烯

在 p. 175 了解 DBU.

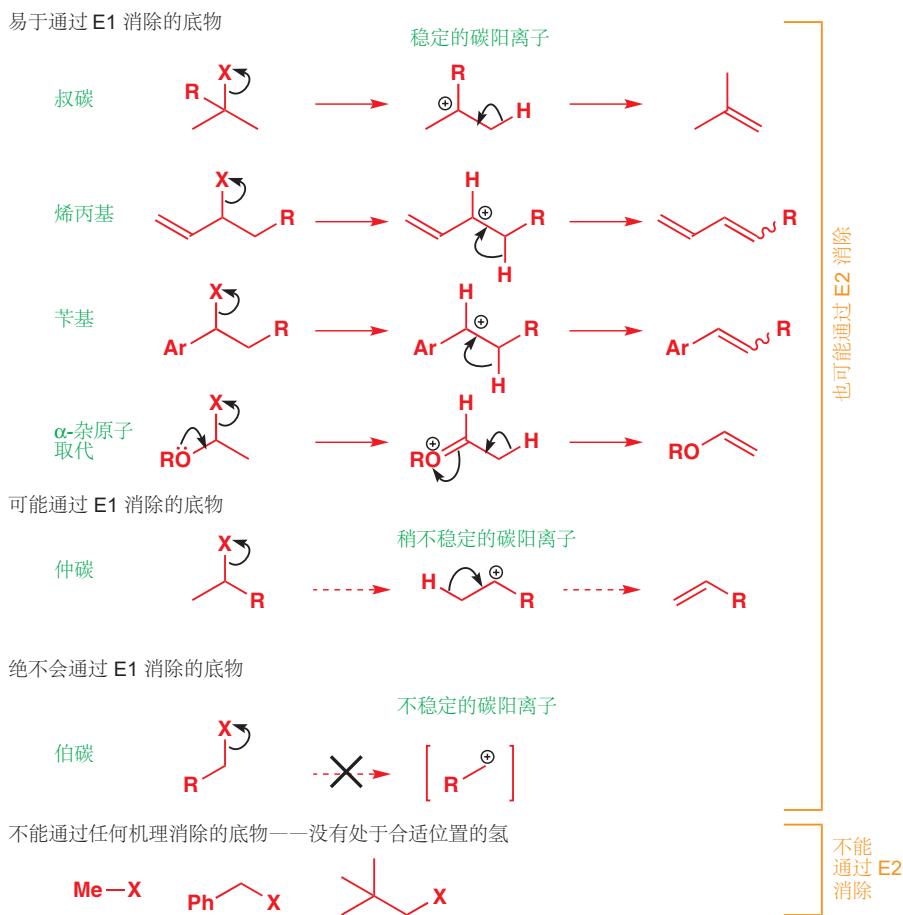
DBU 通常会从卤代物中消去  $\text{HX}$  从而生成烯烃。在下面的两个例子的生成物，都是某两个天然产物合成的中间体。



■ 注意，高温驱动消除反应。

## 允许 E1 的底物结构

本章提到的第一个消除反应 (*t*-BuBr 加氢氧根) 说明了一件非常重要的事情：叔烷基卤代烃的起始物仅会通过 S<sub>N</sub>1 取代，但却能既通过 E2 (与强碱) 又能通过 E1 (与弱碱) 消除。不利于 S<sub>N</sub>2 的立体化学因素，即反应中心的空阻并不影响消除反应。尽管如此，E1 仍只能在底物可以电离生成稳定的碳阳离子的情况下才能发生——例如叔烷基、烯丙基或者苄基卤。仲卤代烃可能通过 E1 消除，而伯卤代烃无论如何只能通过 E2 消除，因为发生 E1 所要求的伯碳阳离子太不稳定了。下图总结了可以采用 E1 消除的底物——但要记住，下列底物中的任何一种，在合适的情况下 (例如强碱的存在下) 都仍然可能采取 E2。最后一行列举了三种卤代烃，由于它们的离去基团所在碳原子的邻位根本没有氢原子，进而不能发生任意一种机理下的消除反应。



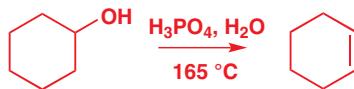
### 质子可以从阳离子上直接“脱落”吗？

在 E1 机理中，当离去基团离去后，几乎任何东西都可以充当碱移去碳阳离子中间体的质子。例如溶剂分子 (水或醇)，作为一种弱碱既是足够的。您会在反应机理中经常看到质子直接“脱落”，这种表示方法就是假定有来自某个地方的弱碱捕获了它。在上个例子和本页的图表中我们都使用了这种省略方法。

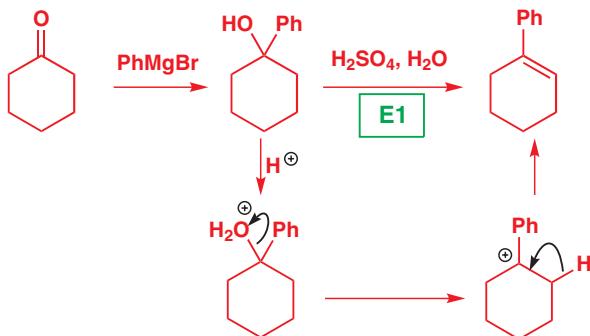


在极其稀少的情况下，例如在 Chapter 15 (p. 335) 中我们描述的强酸性溶剂中，碳阳离子被例如 BF<sub>4</sub><sup>-</sup> 或 SbF<sub>6</sub><sup>-</sup> 的反荷离子稳定，这样的反荷离子没有亲核性，并且也没有碱性，因此它们不会接受质子。这一事实告诉我们，尽管通常不用考虑 E1 机理中质子的去处，但弱碱的存在也是必要的。

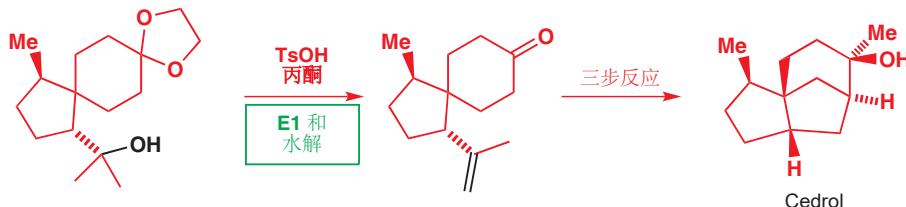
极性溶剂也有利于 E1 反应，因为它们能够稳定中间体碳阳离子。水溶液或者醇溶液中进行的醇的 E1 消除尤其常见，而且十分实用。这个反应需要用酸性催化剂以促进水（质子化后的羟基）的离去，例如在稀的  $H_2SO_4$ ,  $H_3PO_4$  和  $HCl$  中，都没有好的亲核试剂会导致取代反应的发生。在磷酸的存在下，二级的环己醇可以得到环己烯。



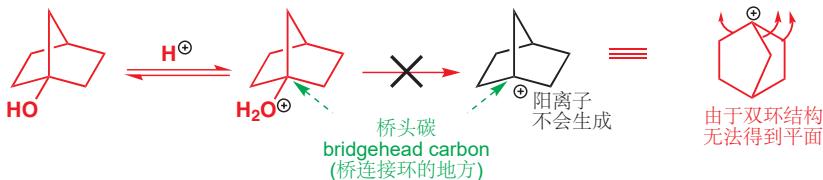
但最好的 E1 消除是叔醇发生的。这种醇可以使用 Chapter 9 中的方法制备：有机金属化合物亲核进攻羰基化合物得到。亲核加成，随后 E1 消除，是制备例如这种取代的环己烯极好的方法。注意羟基离去所需的质子在消除后得以回收——整个反应仅需催化量的酸。



雪松醇 (cedrol) 在香水工业中十分重要——它有雪松的香味。雪松醇的合成就包含下列步骤——酸催化下 (对甲苯磺酸，见 p. 227) E1 消除与缩酮的水解一同发生。



在上一章的末尾，您见到了一些双环 (bicyclic, 或二环) 结构。它们在发生消除反应时，有时会引起问题。例如下面的化合物就既不能通过 E1，也不能通过 E2 机理发生消除。



我们马上将会看到 E2 反应在这种结构中遇到的问题，但 E1 的问题很清楚，就是在生成平面型碳阳离子时遇到了问题。双环的结构会阻止桥头碳转变为平面型，因此即使是这个阳离子将会是稳定的叔碳，它也是非常高能，而且无法得到的。您可以说，非平面的结构迫使碳原子有一个空的  $sp^3$  轨道，而不是一个空的  $p$  轨道，而我们在 Chapter 4 曾说过，空置最高能的轨道往往是最好的。

► 在 p. 335 (Chapter 15) 中，您看到过一个与之类似的例子，即非平面的碳阳离子使  $S_N1$  反应无法进行。

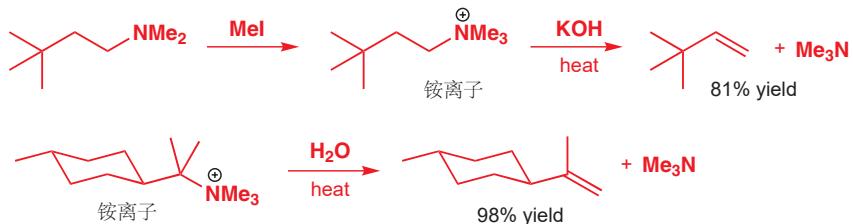
**Bredt 规则**

平面桥头碳阳离子的不现实，也意味着桥头碳上双键的生成几乎不可能。这一规则被称为 Bredt 规则 (Bredt's rule)。就像其他所有的规则一样，知道其名称远没有知道其背后的原因重要，而 Bredt 规则仅仅是对平面桥头碳引起的张力的总结。

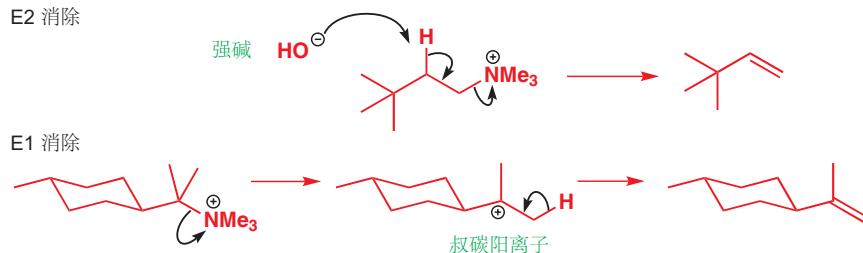
**离去基团的角色**

我还没有对消除反应离去基团的选择做出探讨：目前为止您看到的 E2 反应都来自卤代烃，E1 反应都来自质子化的醇。这两种选择都是经过了思考的：这两类消除反应中的绝大多数都采用这两种起始原料中的一个。因为 E1 和 E2 的决速步速率方程都包含离去基团，一般来说，好的离去基团导致快的消除反应。您可能会看到例如季铵盐的消除中，胺作为离去基团的情况。

铵离子的消除



E1 和 E2 都是可能的，从您目前读到的内容分析，下列两种情况分别为其中一种机理：第一个例子中，无法生成稳定的碳阳离子 (因此 E1 是不可能的)，而所添加的强碱也促使 E2；在第二个例子中，可以生成稳定的叔碳阳离子 (因此 E1 或 E2 都可能发生)，而由于没有强碱的参与，因此为 E1.



在之前的例子中，羟基有过在酸性下作为好的离去基团的情况，这种情况仅会发生在允许 E1 消除的底物中。而羟基永远不会在 E2 消除，即碱性下作为离去基团。强碱反而会移去 OH 基的质子。

- OH<sup>-</sup> 绝不会作为 E2 反应的离去基团。

对于伯醇和仲醇，羟基可以先与 对甲苯磺酰氯 (TsCl) 或甲磺酰氯 (MeSO<sub>2</sub>Cl/MsCl) 发生磺酰化 (sulfonylation) 转化为一个好的离去基团后，再进行消除。



您在 Chapter 15 (p. 344) 学习了这些磺酸酯——甲基磺酸酯和对甲苯磺酸酯。

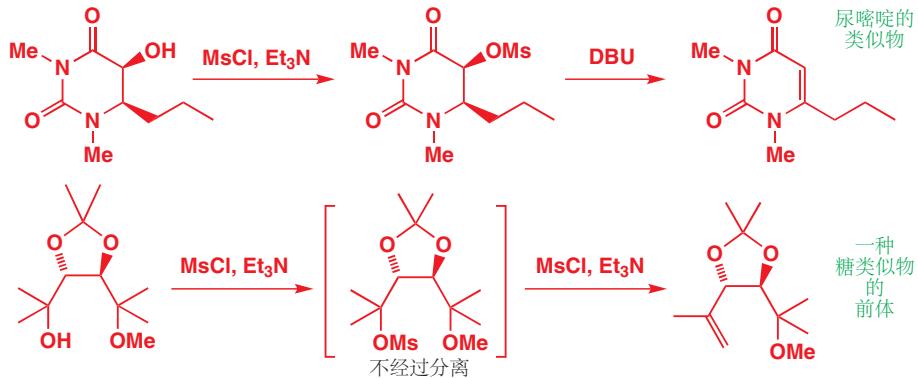
对甲苯磺酸酯可以由醇 (吡啶中与  $\text{TsCl}$  反应) 制备。我们在 Chapter 15 中介绍了磺酸酯，因为它们在非碱性的亲核取代反应中，是一类相当好的亲电试剂。在  $t\text{-BuOK}$ ,  $\text{NaOEt}$ , 或 DBU 的参与下，它们会非常效率地发生消除反应。下面是两个例子。

对甲苯磺酸酯的 E2 消除



甲磺酸酯 (Chapter 15) 可以使用 DBU 发生消除，而使用醇制备烯烃的一种好方法，是直接在体系中混入  $\text{MsCl}$  和同一种碱 ( $\text{Et}_3\text{N}$ )，这样甲磺酰化和消除反应都可以进行。下面是制备生物学上重要分子的两个例子。在第一个例子中，甲磺酸酯被分离出来，然后再通过 DBU 下的消除得到尿嘧啶 (RNA 中核苷酸碱基的一种) 的合成类似物 (synthetic analogue). 在第二个例子中，则使用  $\text{Et}_3\text{N}$  同时进行甲磺酸酯的生成和消除，得到一种糖类似物的前体。

在 Chapter 42 中有更多关于 RNA 中的碱基、糖类的内容。



第二个例子中我们要消除的是叔醇——那么为什么不能用酸催化的 E1 反应呢？问题在于该分子含有一个对酸敏感的缩醛官能团，而这个问题被甲磺酸酯的使用所解决了。酸催化的反应也可能从右侧的叔碳中心消去甲醇。

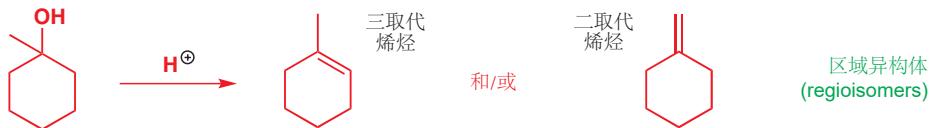
## E1 反应可以是立体选择性的

有些化合物的消除反应结果仅有一种可能，但还有一些，则有烯烃位置不同，或双键的立体化学不同的两种 (或以上) 选择。接下来我们将要对控制 E1 反应产物烯烃的立体化学 (几何构型——顺式或反式)，和区域化学 (regiochemistry, 双键的位置) 的因素展开讨论。

只有一种可能的烯烃(产物)



有两种可能的区域异构 (regioisomeric) 烯烃



有两种可能的立体异构 (stereoisomeric) 烯烃

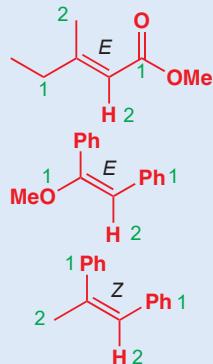


区域异构体  
(regioisomers)

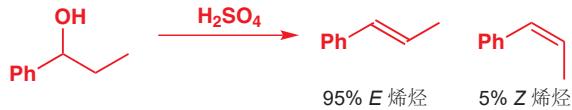
立体异构体  
(stereoisomers)

### E 和 Z 烯烃

Chapters 3 和 7 中, 我们向您介绍了烯烃在几何上的顺反 (*cis*, *trans*) 异构体, 但当您阅读到现在, Chapter 14, 我们需要使定义变得更加明确。虽然顺和反在很多时候十分管用, 但它们是十分不严谨的定义 (就像 *syn* 和 *anti* 一样). 对几何结构更正式的表示, 是立体化学描述符号 *E* 和 *Z*. 对于双取代的烯烃, *E* 对应反式, 而 *Z* 对应顺式。对于三或四取代的烯烃, 则需首先按 Chapter 15 中判断 *R* 和 *S* 使所用的次序规则给双键每一边的两个基团排序。如果两个高次序的基团相对是顺式的, 那么烯烃的构型为 *Z*; 如果它们是反式的, 则为 *E*. 当然, 分子并不懂得这些规则, 有时 (第二个例子中) *E* 型烯烃可能比 *Z* 型更不稳定。

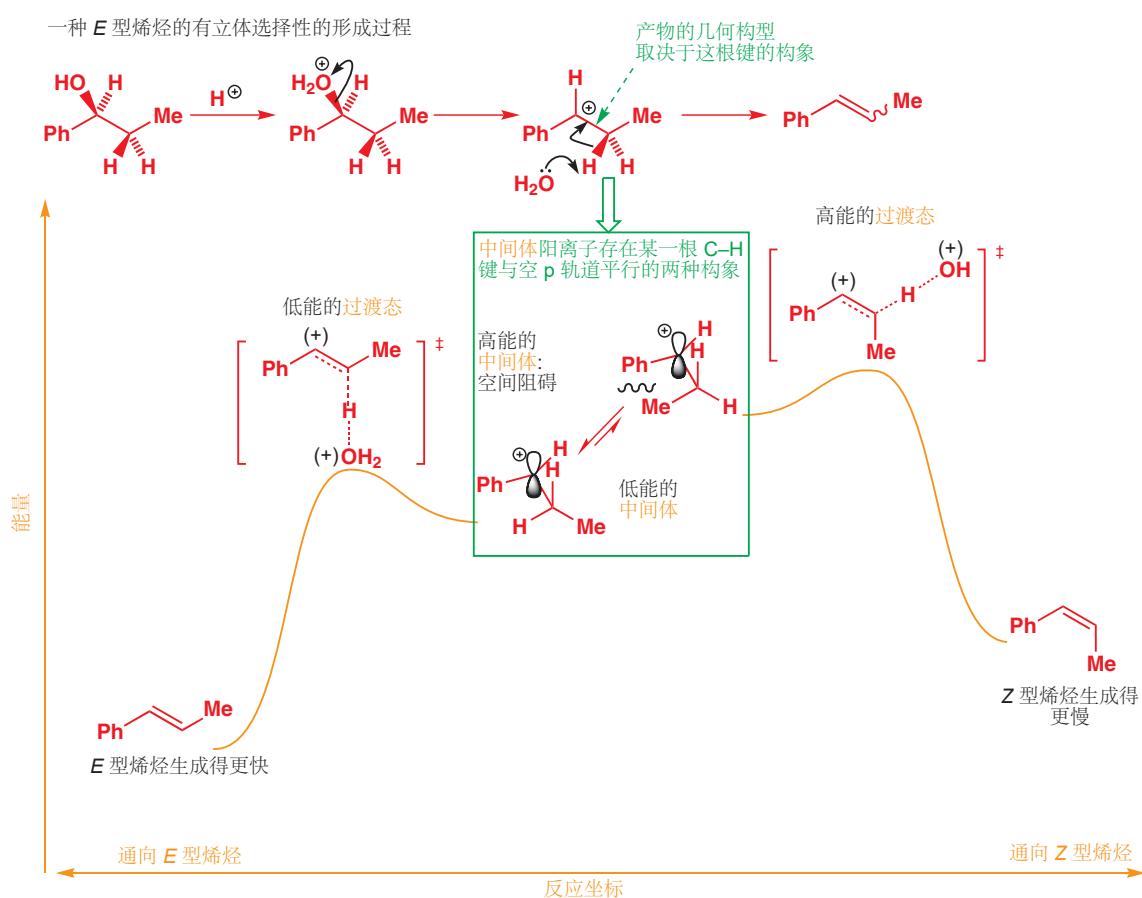


*E* 烯烃 (和通向 *E* 烯烃的过渡态) 通常比 *Z* 烯烃 (和通向它们的过渡态) 能量低, 这是由于立体原因: 取代基可以彼此离得更远。因此, 可以选择生成这两种产物的反应, 通常倾向于生成 *E* 型。例如 E1 消除生成的烯烃就正是如此: 小空阻的 *E* 型烯烃是有利的。下面是一个例子。



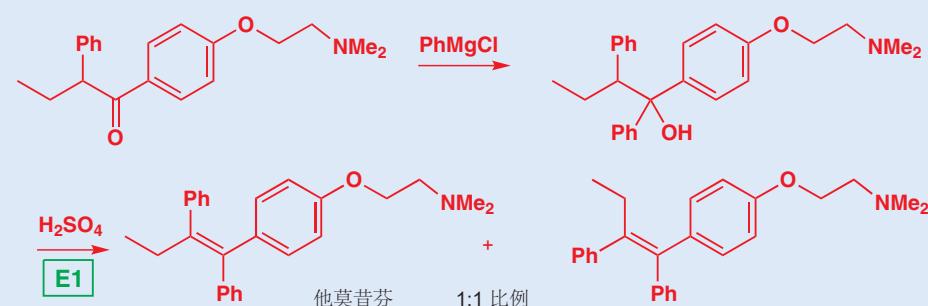
产物的几何构型在碳阳离子中间体离去质子的一步被决定。新的  $\pi$  键只能在碳阳离子的空 p 轨道与将要断的 C–H 键平行时, 才可能形成。在下面的例子中, 碳阳离子中间体有两种可以消除的 (有与空轨道平行的碳氢键的) 可能构象, 由于空阻原因, 其中一个比另一个稳定。这两种构象生成烯烃时的过渡态的稳定性关系也与上述一致——通往 *E* 型烯烃的过渡态能量较低, 因此这一反应生成的 *E* 型烯烃要比 *Z* 型多。这一反应是立体选择性的 (stereoselective), 因为反应主要选择生成两种可能的立体异构产物中的一种。

► 在 Chapter 39 中, 我们会讨论为什么碳阳离子这种高能的中间产物, 分解时的过渡态与其本身在结构上非常相似。



### 他莫昔芬

他莫昔芬 (Tamoxifen) 是一种对抗最常见的癌症之一，乳腺癌的重要药物。它通过阻断女性荷尔蒙激素的活动而发挥作用。该分子中的四取代双键可以通过 E1 消除引入：这一过程会得到双键的位置没有区别的两种立体异构体，它们以大约相同的数目生成。他莫昔芬是 *Z* 异构体。

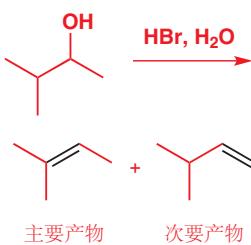


► 我们会在 Chapter 27 中介绍如何控制双键生成的几何构型的方法。

### E1 反应可以是区域选择性的

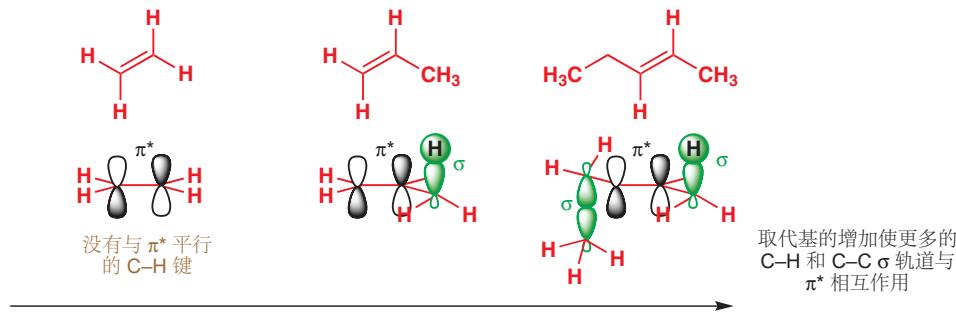
我们可以以相同的思路思考 E1 消除会得到的多个位置异构烯烃。下面是一个例子；其主要产物是有较多取代基的烯烃，因为它在两种可能的产物中较稳定。

- 越多取代基的烯烃越稳定。

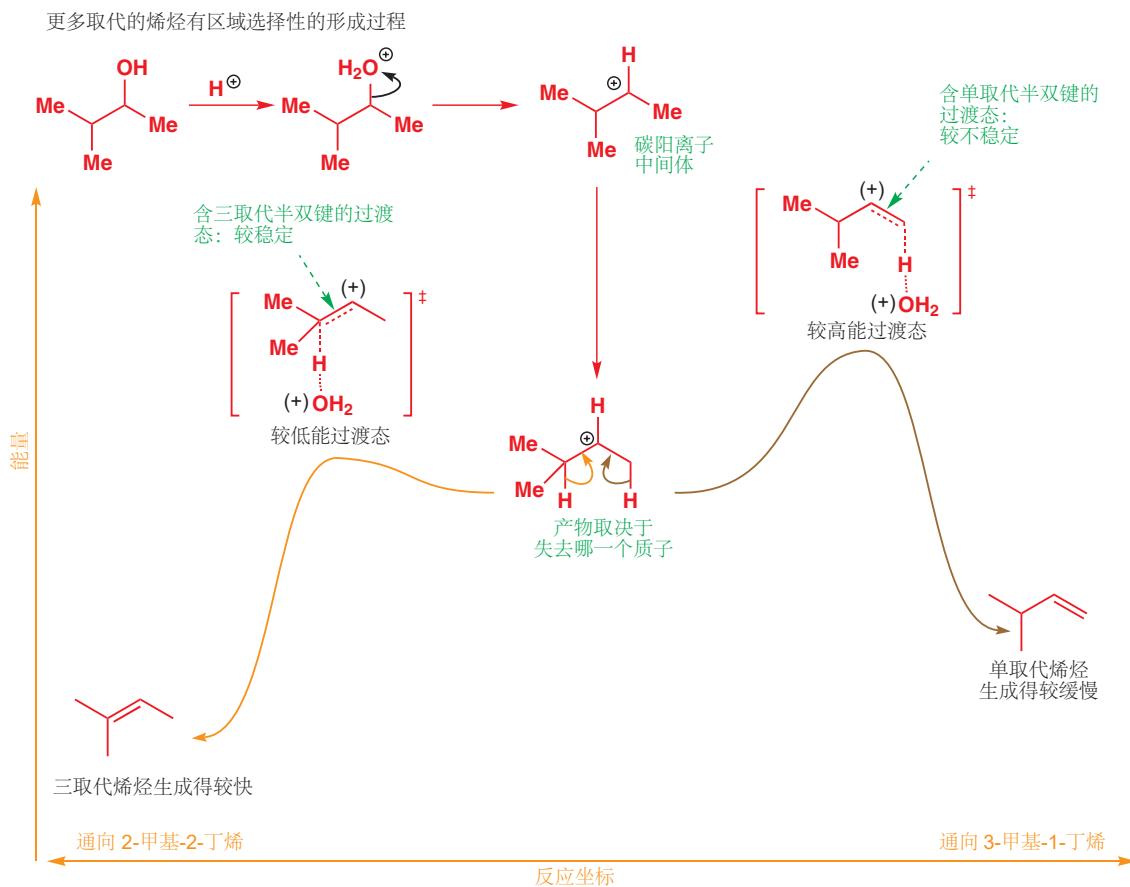


这是一个相当普遍的原则。但为什么它是正确的？其原因与多取代的碳阳离子稳定密切相连。在 Chapter 15 中我们说过，当碳阳离子的空 p 轨道可以与与之平行的充满的 C–H 和 C–C 键相互作用时，碳阳离子会更加稳定。双键的  $\pi$  体系与之类似——当空的  $\pi^*$  反键轨道可以与与之平行的充满的 C–H 和 C–C 键轨道相互作用时，烯烃会更加稳定。因此有越多的相邻碳可以提供 C–C 或 C–H 键（与之相互作用），烯烃就会越稳定。

■ 对于 E1 反应的立体和区域选择性——哪一种烯烃生成得更快的解释都是基于动力学 (kinetic) 论证的。但事实上也有一些 E1 消除是可逆的：烯烃会被酸重新质子化，并生成回碳阳离子（您将在下章看到的内容）。这种重质子化 (reprotonation) 过程允许在热力学 (thermodynamic) 控制下，更有倾向地/更多地生成更稳定的产物。在任何一个案中，可能都不清楚到底是哪一方在运作。然而，对于接下来的 E2 反应，仅有动力学控制——E2 反应永远不会是可逆的。



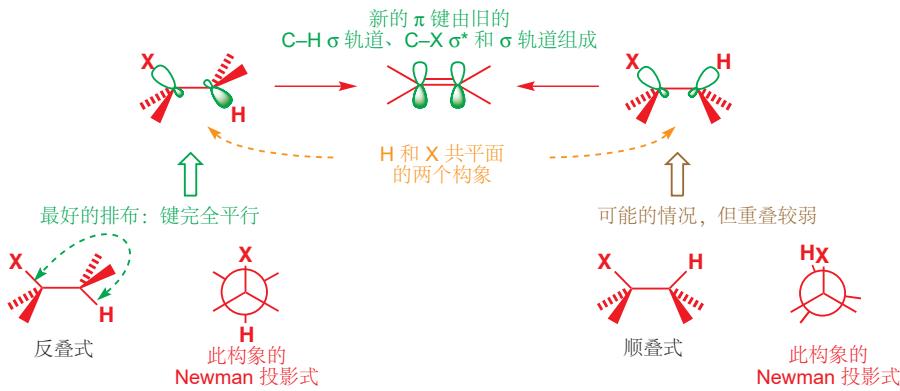
我们知道了，更多取代的烯烃更稳定，但这不见得能解释为什么它生成得更快。相反，我们应该看向导致这两种烯烃生成的过渡态。它们都是由同一个碳阳离子形成的，而生成哪种过渡态取决于失去哪一个质子。失去右侧的质子（棕色箭头）会导致单取代双键部分地形成；而失去左侧的质子（橘色箭头）则会导致三取代半双键(partial double bond)的形成。含三取代半双键的过过渡态比含部分单取代半双键的过渡态稳定，这解释了为什么多取代的烯烃生成得更快。



## E2 消除有非平面的过渡态

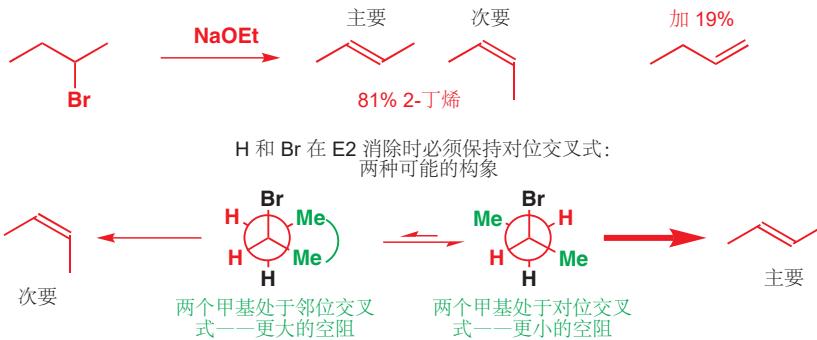
虽然 E1 反应表现出了一些立体和区域选择性，但 E2 反应选择性的程度要比它高很多，这是由于 E2 消除对过渡态的要求更加严苛所导致的。在 E2 消除中，新的  $\pi$  键在 C–H  $\sigma$  键和 C–X  $\sigma^*$  反键轨道重叠时形成。最好的重叠，要求这两个轨道处于同一个平面上，现在则有两种构象符合这一要求。其中一种是 H 和 X 处于反叠式（反式共平面）的构象，另一种则是它们处于顺叠式（顺式共平面）的构象。其中反叠式比顺叠式稳定，因为两个基团处于交叉而不是重叠；但最重要的是，只有反叠式构象中的两根键（和它们所在的轨道）是彼此平行的。

如果您需要回顾 C–C 单键各种构型的形状和名称，请回到 p. 365.



Newman 投影式是分子的某一种构象，由一根键的侧端观察得到的投影图。如果您需要回顾如何绘制和领悟它们，请回到 p. 364.

因此 E2 消除倾向于发生在反叠式构象中，等会儿也会有很多例子证明情况属实。现在我们要讨论的是一个会生成两种立体异构体的 E2 消除反应。2-溴丁烷有两种 H 和 Br 处于反叠式的构象，其中一个又因比另一个空阻小，而作为通向主要产物 (E 型烯烃) 的构象。



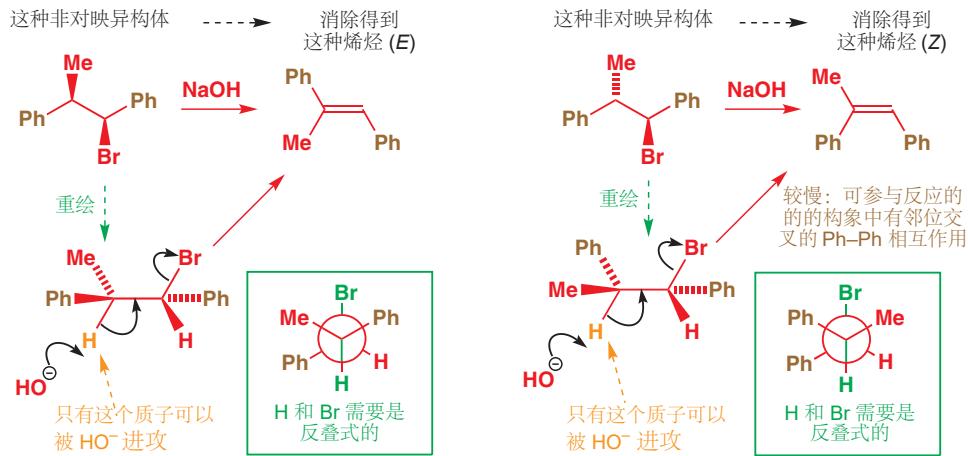
哪一个质子与离去基团处于反叠式，哪一个质子就会参与消除。但这存在一个选择，而且这种选择直接决定产物的立体化学。因此这一反应是立体选择性的。

Interactive mechanism for stereoselective E2

## E2 消除可以是立体专一性的

在下一个例子中，仅有一种质子可以参与消除反应。反叠式过渡态的要求是没有可选择的余地的，不论产物会是 E 还是 Z，E2 反应都必须遵守这个原则。其结果的立体化学取决于起始原料使用的是哪种非对映异构体。我们首先需要将非对映异构体结构重绘（旋转），使质子和溴处在所需的反

叠式构象上。这时，左侧的非对映异构体中，两个苯基一个在纸平面上方，一个在纸平面下方。当氢氧根进攻 C–H 键并消去 Br<sup>-</sup>时，这种排列被保留了下来，并且得到两个苯基处于反式(烯烃构型为 E)的产物。这一点在 Newman 投影式中更为直观。



而右侧的非对映异构体则会以相同的原因，最终生成 Z 型烯烃：在可参与反应的构象中，两个苯基现在在 H–C–C–Br 平面的同一侧，因此产物烯烃为 顺式 构型。上述两种非对映异构体各自得到了不同几何结构的烯烃，而它们的反应速率也不同。第一个反应的速率大约是第二个反应的速率的十倍。这是因为虽然反叠式始终是唯一可反应的构象，但它不见得是最稳定的。第二个反应中，可参与反应的构象的 Newman 投影式很清楚地显示了，两个苯基需要以反叠式排列：这两个大基团的空间相互作用很大，这意味着消除反应所能采取的构象在任何时间占比都很少，故减缓了反应速率。

产物立体化学取决于起始物立体化学的反应被称为有立体专一性 (stereospecific) 的。

立体专一性反应并不是指立体选择性强的反应！这两个术语有机理层面上不同的涵义，而不是相同含义的不同程度。

### ● 立体选择性和立体专一性

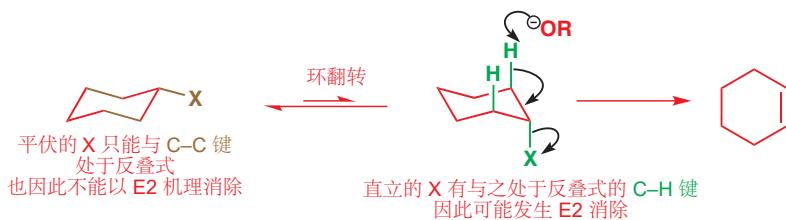
- **立体选择性反应**可以由于在反应进程上的选择，有倾向地得到某一产物。要么选择活化能较低的路径(动力学控制)，要么选择会得到较稳定产物的路径(热力学控制)。
- **立体专一性反应**直接地由反应机理和起始物的立体化学，单一地得到某一异构体。没有选择的余地。起始物的每一种异构体定向地得到生成物的每一种非对映异构体。

### 环己烷的 E2 消除

刚才这些反应的立体专一性，都是 E2 反应经历反叠式过渡态的证据。我知道反应由哪种非对映异构体起始，也知道了我们会得到哪一种烯烃，因此在反应过程上已经没有疑问了。

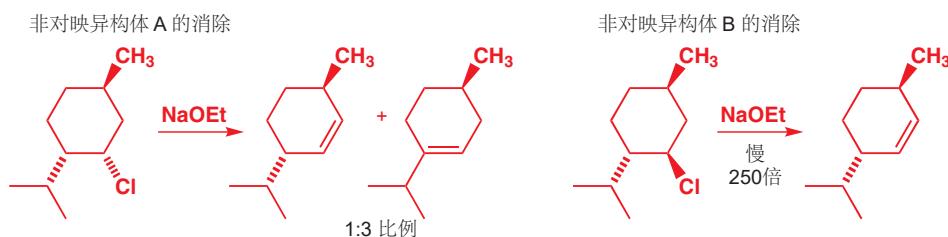
取代环己烷的反应会给我们更多证据。在 Chapter 16 中您看到，环己烷的两个取代基如果想要彼此平行，那么它们必须都处于直立键。一个平伏的 C–X 键只可能与 C–C 键处于反叠式，并因此不能参与消除反应。用碱处理一卤代环己烷时，这不构成一个问题，因为虽然直立键构象较不稳定，但仍会以显著的数目存在(见 p. 375 表格)，而消除反应可以在这种构象上发生。

► 在下一章中 (p. 415)，您会看到，轨道重叠的一对直立键也会鲜明地产生大的 <sup>1</sup>H NMR 耦合常数。



● 对于环己烷上的 E2 消除, C-H 和 C-X 都必须处于直立键。

在乙醇钠做碱的相同条件下, 下面的两种非对映异构体环己基氯却已完全不同的方式反应。它们都消去了  $\text{HCl}$ , 但非对映异构体 A 迅速地反应, 并给出两种产物的混合物; 而非对映异构体 B (只有氯原子所连的碳的构型有所区别) 却非常缓慢地得到单一产物烯烃。我们可以放心地将 E1 机理排除, 因为这两种起始物所得的碳阳离子是相同的, 这意味着产物和产物的比例都应该是相同的 (速率不见得相同)。



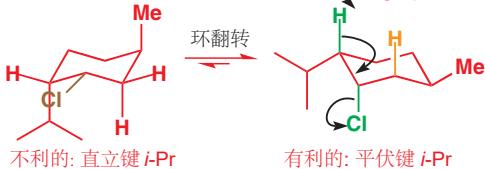
解释这类反应的关键在于画出分子的构象。两种都采用椅式构象, 并且通常最大的取代基处于平伏键 (或更多数目的取代基处于平伏键) 是最稳定的。在这两个例子中, 异丙基都是最有影响力的基团——它是带有支链的, 因此如果占据直立键, 则会产生十分严重的 1,3-二直立相互作用。在这两种非对映异构体中, 平伏的  $i\text{-Pr}$  都意味着平伏的 Me: 唯一的区别在于氯原子的朝向。对于非对映异构体 A, 氯原子被迫在主要构象中处于直立键: 构象被异丙基锁定, 无法被改变。直立键对 Cl 原子本身, 与平伏键相比较不稳定, 但这对于 E2 消除十分理想。另外, 有两个氢原子与其处于反叠式, 在碱的作用下可以被夺去。夺去这两种质子所形成的两种烯烃, 由于多取代烯烃稳定的缘故以 3:1 的比例形成。

对于非对映异构体 B, 氯原子在最低能构象中处于平伏键。同样由于锁定而无法被改变。但平伏的离去基团无法通过 E2 消除: 在这个构象中, 没有与之处于反叠式的质子。这说明了这两种非对映异构体速率上的差异。A 在几乎任何时间里, 都有准备参与 E2 的直立氯; 而 B 只能在极小比例的, 不但不是最低能, 而且全部三个取代基都处于直立键的构象里, 才能使离去基团处于直立。全直立 (all-axial) 的异象体在能量上高不可攀, 但只有这一种才能使  $\text{Cl}^-$  被消去。可反应的分子浓度越低, 速率就越低。另外, 只有一个质子与之处于反叠式, 因此消除反应得到单一烯烃。

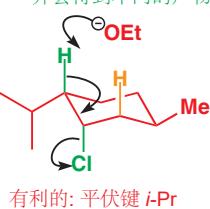
■ 这是检验您是否能以椅式构象画出环己烷的好时机。如果您忘记了, 我们在 pp. 371–2 的准则会指导您。

非对映异构体 A 的构象

没有 C-H 键与 C-Cl  
键处于反叠式:  
没有消除发生

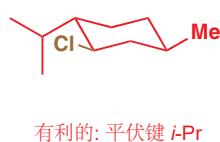


两个反叠式 C-H 键:  
都可以消除  
并会得到不同的产物



非对映异构体 B 的构象

没有 C-H 键与 C-Cl  
键处于反叠式: 没有  
消除发生



只有一个反叠式  
C-H 键:  
形成单一烯烃

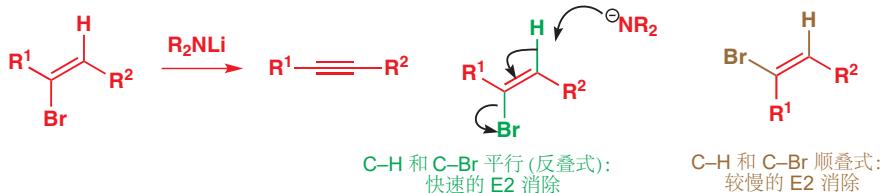
Interactive mechanism for  
diastereoisomer A

Interactive mechanism for  
diastereoisomer B

### 乙烯基卤的 E2 消除：如何制备炔烃

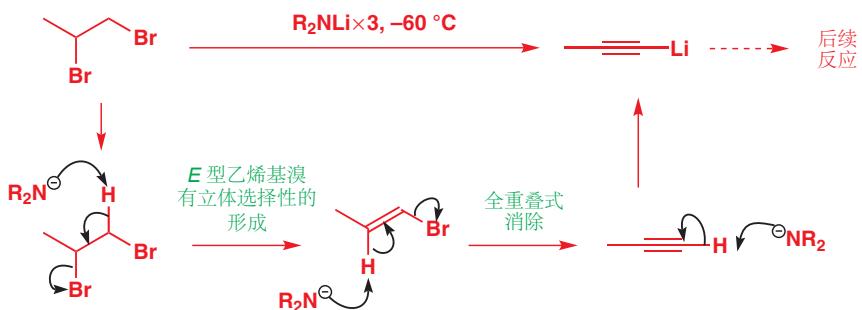
乙烯基溴也有 C–Br 和 C–H 反叠式排列的情况，即在 Br 和 H 彼此反式时。由乙烯基溴的 Z 型异构体发生 E2 消除得到炔烃的反应，要比由 E 型异构体快很多，因为 E 型异构体中的 C–H 和 C–Br 键处于顺叠式。

■ 此处使用的碱是 LDA (二异丙基氨基锂, lithium diisopropylamide), 它由 *i*-Pr<sub>2</sub>NH 在 BuLi 去质子制得 (见 p. 174). LDA 是一种强碱, *i*-Pr<sub>2</sub>NH 的  $pK_a$  大约 35; 且由于空阻较大, 不易做亲核试剂——理想的 E2 消除试剂。



乙烯基溴本身可以通过 1,2-二溴丙烷的消除反应制备。下面是 1,2-二溴丙烷在三当量的 R<sub>2</sub>NLi 处理下所发生的变化: 首先, 消除得到乙烯基卤, 然后乙烯基卤消除得到炔烃。终点炔烃充足的酸性足够使其被 R<sub>2</sub>NLi 质子化, 这是第三当量的角色。总地来说, 这个反应有一个饱和起始物, 得到了一个炔锂 lithiated alkyne (并为后续反应做准备). 这可能是您遇到的第一个从不含三键的起始物合成炔烃的反应。

由 1,2-二溴丙烷 制备炔烃



### E2 消除的区域选择性

下面是两个看起来很相似的消除反应。离去基团和反应条件都不相同，而整体上看都是消除 HX，并生成两种烯烃中的一个的过程。



第一个是酸催化下叔醇上水的消除，得到三取代烯烃。第二个反应则是相应的叔碳上 HCl 的消除，使用了空阻非常大的烷氧基碱 (比 *t*-BuOK 的空阻更大，因为三个乙基内部需要保持距离)，反应专一地得到较不稳定的二取代烯烃。

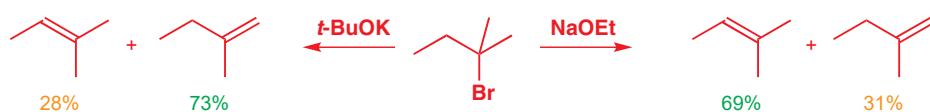


这两个反应区域选择性的区别，其原因在于机理上的区别。我们已经讨论过了，酸催化下叔醇上水的消除通常是 E1，而您也知道了为什么在 E1 反应中，形成多取代烯烃的过程速率快 (p. 394). 而您也应该不会感到奇怪，第二种在大空阻强碱下的消除是一个 E2 反应。但为什么 E2 会给出少取代的产物呢？毫无疑问，如果消除反应在环上发生，则环需要处于 C–H 键与离去基团反叠式的构

象中: Cl<sup>-</sup> 处于直立键时, 环上有两个等价的氢可用于消除, 对任意一个氢的消除都会得到三取代的烯烃。但此外要考虑到, 无论 Cl<sup>-</sup> 在环上处于平伏键还是直立键, 甲基上的三个等价氢都可用于 E2 消除, 并得到单取代烯烃——大位阻碱夺去并且只夺去这三个氢中的一个。下面的图表总结了这两种可能性。



由于甲基氢所处的伯碳空阻较小, 碱进攻甲基氢, 并不会靠近环上的直立氢。通常, 大位阻碱进行的 E2 消除得到较少取代的双键, 因为最快的 E2 反应需要在最少取代的一侧去质子。并且, 在少取代碳上的氢原子酸性也更强。考虑它们的共轭碱: 叔丁基阴离子的碱性比甲基阴离子更强 (三个给电子的烷基使叔丁基阴离子不稳定), 因此对应的烷烃, 叔丁烷就比甲烷酸性更弱。下面几个 E2 反应也有显而易见的空间因素, 当将乙醇钠换成叔丁醇钾后, 主要产物也从多取代烯烃转变为少取代烯烃。



### ● 消除反应的区域选择性

- E1 反应给出多取代烯烃。
- E2 反应可能给出多取代烯烃, 但在更大位阻的碱下对少取代烯烃有更强的区域选择性。

### Hofmann 和扎伊采夫

传统上, 这两个相反的倾向性——生成少取代烯烃还是多取代烯烃——分别被称作扎伊采夫规则 (Saytsev's rule) 和 Hofmann 规则 (Hofmann's rule)。您会看到这些名称的出现 (Saytsev 是俄文的音译, 因此还会出现不同的拼写; 请误拼错 Hofmann, 这个 Hofmann 有一个 f 和两个 n), 但记住它们的名字 (或者它们的拼写) 意义并不大——更重要的是理解烯烃生成的倾向性的原因。

## 阴离子稳定基的存在准许另一机理—E1cB

在本章结束之际, 我们要来考虑一个乍一看似乎与我们之前所说相矛盾的反应。它是强碱 (KOH) 催化下的消除反应, 因此看起来像是 E2, 但离去基团是氢氧根, 我们断然地 (也是诚实地) 告诉您, 氢氧根无法成为 E2 消除的离去基团。



关键在于羰基的变化。在 Chapter 8 中我们提到, 羰基可以稳定负电荷, p. 176 也有事实证明了羰基邻位质子的酸性。上述消除反应中, 羰基邻位的质子也有相当强的酸性 ( $pK_a$  大约 20), 因此首先会被夺去。这意味着质子的去除与羟基的离去不在同一时间——所生成的阴离子由于能在羰基上

■ 去质子后的阴离子被称为烯醇 (enolate) 阴离子, 我们会在 Chapter 20 和后面的章中介绍。

离域，因此足以稳定存在。



虽然阴离子被羰基所稳定，它仍然愿意失去离去基团，并得到一个烯烃。这是下一步的反应。

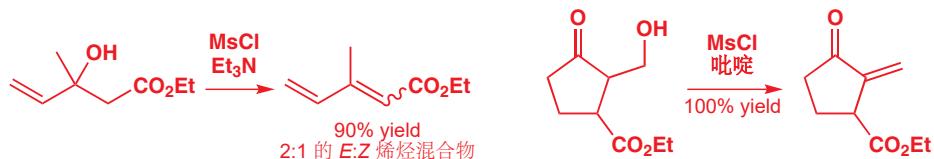


此消去过程是整个消除过程的决速步，它是单分子的，因此这类消除反应也是 E1 反应的一种。但离去基团并不是起始物分子失去的，而是其共轭碱失去的，因此我们称这一类由去质子化开始的消除反应为 E1cB (cB 指共轭碱 conjugate base)。下面是完整的机理，是其他羧基化合物普遍适用的机理。

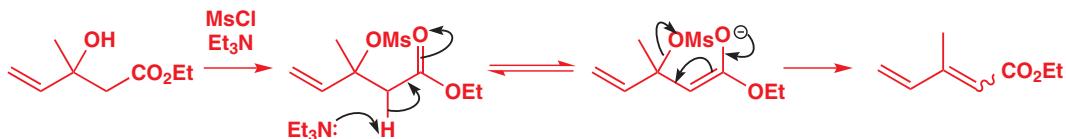


■ “E1cB”没有上下标，其 c 为小写，B 为大写。

一定要记得， $\text{HO}^-$  绝不会成为 E2 反应的离去基团，但它可以是 E1cB 反应的离去基团。失去氢氧根的阴离子本身已经是一个烷氧基阴离子（醇阴离子）——并不会因为  $\text{HO}^-$  的离去，伴随氧阴离子的生成而不易进行。并且  $\text{HO}^-$  的离去还会在产物中形成共轭。上述图表也暗示了，其他的离去基团也是可行的。下面是两个甲磺酸离去基团的例子。

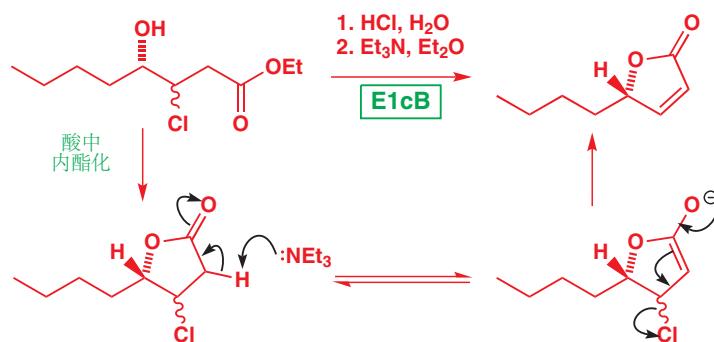


前一个看起来像 E1 (稳定的碳阳离子)，而后一个看起来像 E2——但事实上这两者都是 E1cB 反应。判断一个消除反应是否为 E1cB 机理最可靠的办法，是观察产物烯烃是否与一个羰基共轭，如果是这样，那么机理有可能就是 E1cB。

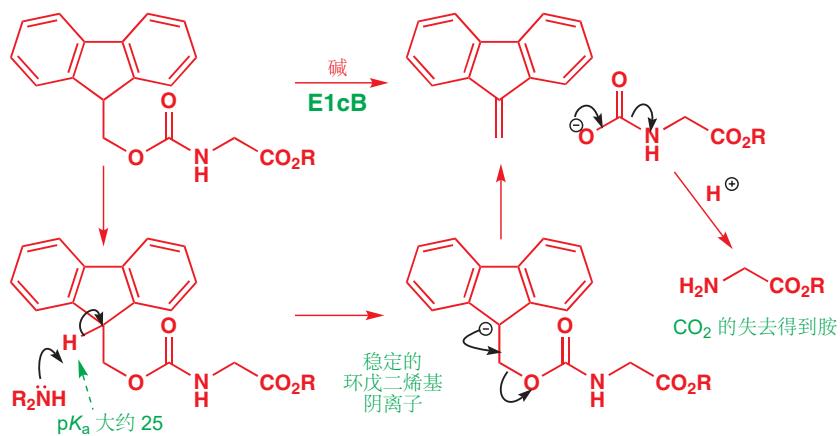


$\beta$ -卤代羰基化合物 可以是相当不稳定的：一个好的离去基团，与一个酸性的质子的结合，将使 E1cB 机理极其容易进行。非对映异构体混合物的起始物，会首先在酸性下内酯化 (Chapter 10)，然后再在三乙胺的作用下发生 E1cB 消除，得到一种被称作丁烯酸内酯 (butenolide) 的产物。

丁烯酸内酯在天然产物的结构中很常见。



您会注意到，我们将上面几个机理中去质子的步骤，都画成了一个平衡。它们都更偏向平衡左侧，因为无论三乙胺 ( $\text{Et}_3\text{NH}^+$  的  $\text{pK}_a$  大约 10) 还是氢氧根 ( $\text{H}_2\text{O}$  的  $\text{pK}_a$  为 15.7) 的碱性都不足以完全夺去羧基邻位的质子 ( $\text{pK}_a > 20$ )。然而，由于离去基团离去的步骤是基本不可逆的，于是少量去质子后的羧基化合物就足以使反应一直进行下去了。底物能够进行 E1cB 最重要的一点，是在要夺去的质子的邻位，有某种形式的阴离子稳定基 (anion-stabilizing group)——不需要特别好地稳定阴离子，只要它能使质子酸性增强，那么 E1cB 机理就有可能发生。下面是一个两个苯环稳定阴离子，氨基甲酸阴离子 ( $\text{R}_2\text{N}-\text{CO}_2^-$ ) 作为离去基团的例子。

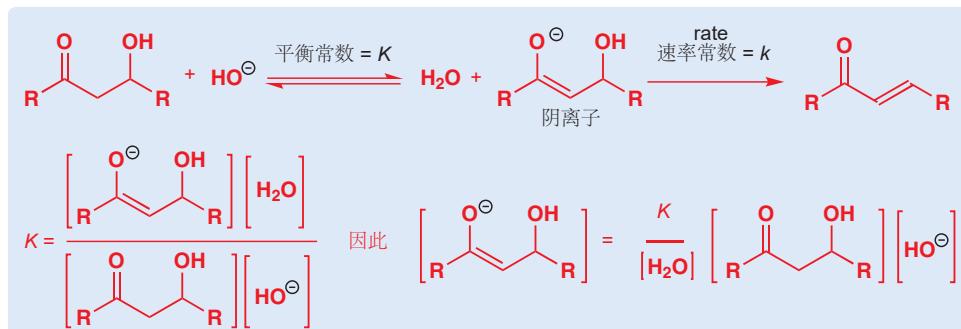


要夺去的质子有大约 25 的  $\text{pK}_a$ ，这是因为它的共轭碱是一个有芳香性的环戊二烯基阴离子 (我们在 Chapter 8 中讨论过)。在仲胺或者叔胺做碱的情况下，发生 E1cB 消除。随后消除产物还会自发地失去  $\text{CO}_2$ ，并得到胺，这是 Fmoc 保护基脱除的过程，我们会在 Chapter 23 讨论它的具体应用。



### E1cB 的速率方程

E1cB 反应的决速步，是单分子的消去过程，因此您可以想象，它会有一个一次的速率方程。事实上，速率也依赖碱的浓度，因为单分子消去过程包含的阴离子物种，其浓度在刚才我们所说的平衡中，是由碱的浓度决定的。在下面的常规 E1cB 反应中，阴离子的浓度可以被表示：



速率正比于阴离子的浓度，而我们知道其浓度的表达式。其中水分子的浓度效果上是恒定的，那么我们就可以将此类消除反应的速率方程简化为如下形式：

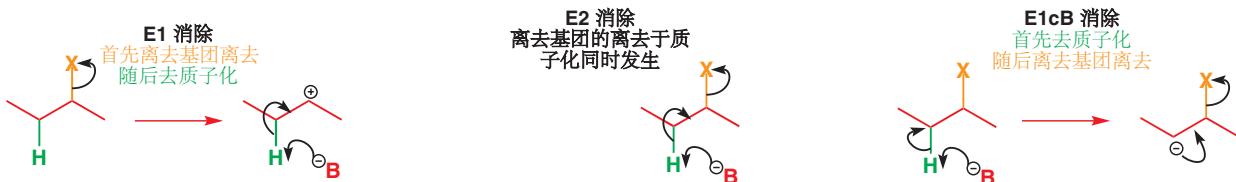
$$\text{rate} = k \frac{K}{[\text{H}_2\text{O}]} \left[ \text{起始物} \right] [\text{HO}^-] = \text{constant} \times \left[ \text{起始物} \right] [\text{HO}^-]$$

碱（氢氧根）仅仅是出现在了速率方程中，但这并不意味着它参与了决速步。碱浓度的增加，通过随之增加可用于消除的阴离子浓度，从而使反应加快。

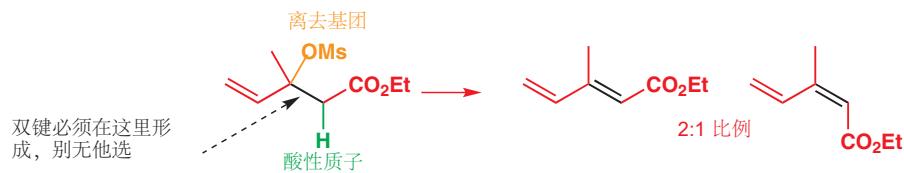
您在 Chapter 12 中三级速率方程的内容那里，曾遇到过这种思路。

### E1cB 消除的横向比较

我们可以将 E1cB 机理和其他消除机理，从离去基团和质子相对的离去时间的方面展开考虑。如果用三个刻度递变地表达这三种情况，那么 E1 就会在刻度的其中一侧：离去基团在第一步离去，而质子在第二步被夺去。在 E2 反应中，这两件事同时发生：质子的被夺去和离去基团的离去。而在 E1cB 反应中，质子在离去基团离去前被夺去。



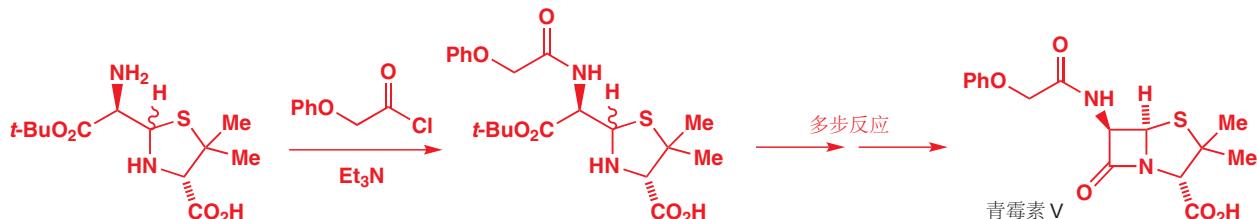
我们之前探讨过有关 E1 和 E2 反应的区域和立体选择性。对于 E1cB 反应，它的区域选择性非常直截了当：双键在 (a) 具有酸性的质子和 (b) 离去基团之间。



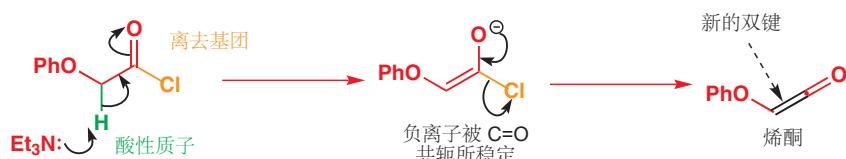
E1cB 反应也可能是立体选择性的——例如刚才的反应，主要得到的是 *E* 型烯烃 (*2:1* 与 *Z*)。中间体阴离子是平面型的，因此起始物的立体化学是无关紧要的，我们仅需要关心产物的位阻，较小的位阻是较好的 (通常是 *E* 型)。例如下面的双 E1cB 消除，仅得到 *E,E* 产物。



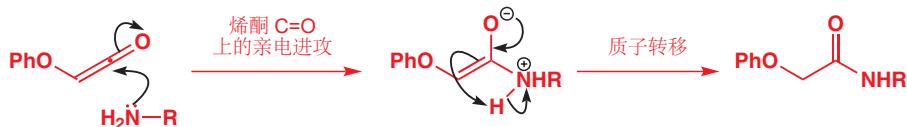
我们将向您介绍两个在意想不到的场合出现的 E1cB 消除，来完成这一章的内容。这两个不寻常的反应中，离去基团也是阴离子稳定基的一部分。首先，请尝试从青霉素 V (即盘尼西林 V, penicillin V) 首次全合成的路线中找到 E1cB 消除。



这个反应看似很简单——酰胺在碱性条件下形成——您或许期望机理如我们在 Chapter 10 中所说的一样进行。但事实上，酰氯的亲核取代是由 E1cB 消除所引起的一——无论什么时候，当您看到羧基邻位有质子的酰氯，并且有如三乙胺的碱存在时时，就应当先想到这种机理。



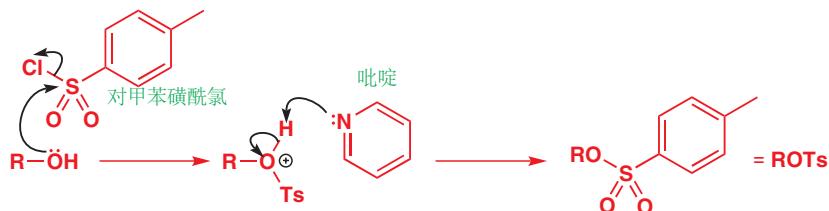
消除的产物是一个取代的烯酮——一个高反应性的物种，其父结构为您将在下下章遇到的  $\text{CH}_2=\text{C=O}$  分子。正是烯酮与胺反应，产生酰胺。



第二个“协同的” E1cB 消除在甲磺酰酯的形成反应中隐蔽地出现。我们在 Chapter 15 中就引入了磺酸酯，而在本章的 p. 391 又用到了它们，但我们一直避开（您可能会说，是一反常态的）对由磺酰氯制备它们的机理的解释。这是有意而为之的，因为  $\text{TsCl}$  与醇的反应按您之前可能预测过的机理进行，但  $\text{MsCl}$  与醇的反应则有消除的参与。

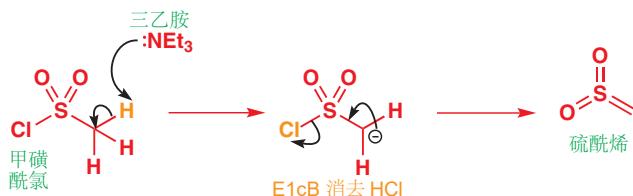
下面是由醇得到对甲苯磺酸酯的过程。醇作亲核试剂，进攻亲电的磺酰氯，而吡啶则负责移去质子以得到产物。

对甲苯磺酸酯的形成：试剂  $\text{ROH} + \text{TsCl} + \text{吡啶}$

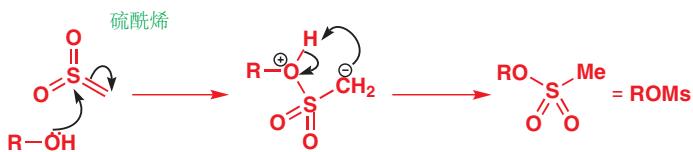


相比之下，甲磺酰氯与青霉素合成中的酰氯有一个共同的特征：都有一个相对酸性的质子，可以在碱的作用下被移去。去质子化过程后，发生氯离子的离去，这是甲磺酰酯生成的第一步，也是一个 E1cB 消除反应，其产物被称作硫酰烯 (sulfene)。

甲磺酸酯的形成: 试剂 ROH + MsCl + 三乙胺



硫酰烯的亲电性质和上面提到的烯酮稍稍有所区别: 醇做亲核试剂, 进攻硫并得到一个碳阴离子, 然后在经历质子转移得到甲磺酰酯。在硫的邻位形成阴离子并不罕见, 您会在 Chapter 27 再次看到。注意, 整个机理和上面我们提到的用酰氯进行酰化的机理是多么相似。



## 小结

我们将对本章讨论的三个重点进行梳理。

### 消除与取代的竞争

下面的表格总结了各种结构类型的卤代烃 (或对甲苯磺酸酯, 甲磺酸酯) 在具有代表性的几种亲核试剂 (也可能做碱) 下反应的一般模式。

		弱亲核试剂 (e.g. H <sub>2</sub> O, ROH)	弱碱性 亲核试剂 (e.g. I <sup>-</sup> , RS <sup>-</sup> )	强碱性 无空阻亲核试剂 (e.g. RO <sup>-</sup> )	强碱性 大空阻亲核试剂 (e.g. DBU, t-BuO <sup>-</sup> )
甲基	H <sub>3</sub> C-X	不反应	S <sub>N</sub> 2	S <sub>N</sub> 2	S <sub>N</sub> 2
伯碳 (无阻碍的)		不反应	S <sub>N</sub> 2	S <sub>N</sub> 2	E2
伯碳 (有阻碍的)		不反应	S <sub>N</sub> 2	E2	E2
仲碳		S <sub>N</sub> 1, E1 (慢)	S <sub>N</sub> 2	E2	E2
叔碳		E1 或 S <sub>N</sub> 1	S <sub>N</sub> 1, E1	E2	E2
阴离子稳定基的 β 位		E1cB	E1cB	E1cB	E1cB

表格中的一些要点:

- 甲基卤不能消除，因为相应位置上没有质子。
- 分支的增加有利于消除胜过有利于取代；强碱性的大空阻亲核试剂通常参与消除，除非像甲基卤那样除了取代别无选择。
- 除非底物是叔碳，好的亲核试剂经历  $S_N2$ ；叔碳生成阳离子中间体既可以通过  $E1$  消除，又可以作为通过  $S_N1$  取代。
- 高温通过增加反应自由能中的熵 ( $\Delta G = \Delta H - T\Delta S$ ) 以有利于消除反应。这在模棱两可的情况下确保进行  $E1$  的好方法。

## 烯烃的稳定性

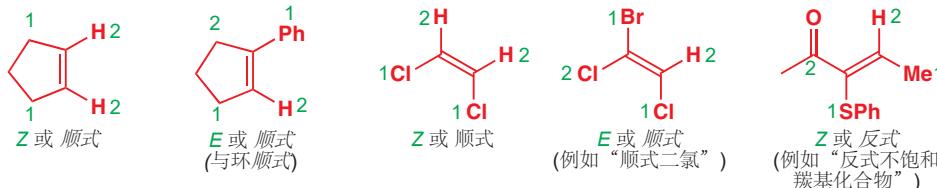
稳定化烯烃的因素：

- **共轭**——任何可以与烯烃共轭的事物都可以稳定它，包括羰基、腈、苯环、 $RO$ 、 $RNH$  或其他双键。这是最强的一类稳定因素，通常占主导地位。
- **取代基**——烷基通过弱的  $\sigma$ -共轭 稳定系统，因此更多烷基取代的烯烃更好——但要小心下一条。
- **空阻效应**——由于烯烃是平面型的、较大的，并且尤其是有带支链的取代基，和取代基 *syn* 排列时，烯烃变得不稳定，因此四取代烯烃通常比三取代烯烃不稳定。如果烯烃是一个稳定的环，这就不再适用了，因为环本身的其他部分与碳中心相连的两根键必须为 *syn* 型。

## 烯烃立体化学：术语的总结

对烯烃几何结构的正式描述方法是 *E* 和 *Z*. *Z* 来源于德语 “zusammen (在一起)”，意味着两个次序 (与 Chapter 14 中 *R* 和 *S* 命名时相同的次序规则) 最高的基团在烯烃的同侧。给反式烯烃标 *Z* 则是十分不幸的选择！*E* 来源于德语 “entgegen (相反)”，意味着两个次序最高的基团在异侧 (同样对于顺式烯烃是不幸的)。下面的结构上，双键每端的两个取代基都用绿色标注了相对次序，结构底端也有最终得到的几何结构的标记。

■ 这个术语只可以被用在烯烃上，也不能用于三维立体化学。



但谈论烯烃的几何结构时，*顺式*和*反式*仍可能是最常用的表达方法。通常说话者可以选择烯烃两侧最有意义，或参与正在讨论的反应的两个取代基，不考虑次序规则地说它们处于同侧（*顺式*）或异侧（*反式*）。这种表达方法更加灵活和用途广泛，可以配合画图，您只需要避免不出现歧义即可。

■ 我们在 p. 317 介绍的，用于表达相对立体化学的术语 *syn* 和 *anti* 也差不多。没有正式的定义，为了清晰也需要画图。

## 延伸阅读

取代和消除反应的对比, 请见: J. Keeler and P. Wothers, *Why Chemical Reactions Happen*, OUP, Oxford, 2003, chapter 11 和 F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry A, Structure and Mechanisms*, 5th edn, Springer 2007, chapter 5.

涉及对 DBU 和其他强碱的描述: T. Ishikawa, ed. *Superbases for organic synthesis: guanidines, amidines and phospha-zenes and related organocatalysts*, Wiley, Chichester, 2009. 关于保护基的描述: P. J. Kocienski, *Protecting Groups*, 3rd edn, Thieme, 2003.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 光谱分析综述

## 联系

### → 基础

- Mass spectrometry **ch3**
- Infrared spectroscopy **ch3**
- $^{13}\text{C}$  NMR **ch3**
- $^1\text{H}$  NMR **ch13**
- Stereochemistry **ch14**
- Conformation **ch16**
- Elimination **ch17**
- Carbonyl chemistry **ch10** and **ch12**

### 目标

- How spectroscopy explains the reactions of the C=O group
- How spectroscopy tells us about the reactivity of, and reaction products from, conjugated C=C and C=O bonds
- How spectroscopy tells us about the size of rings
- How spectroscopy solves the structure of unknown compounds
- Some guidelines for solving unknown structures

### → 展望

- A final review of spectroscopy, including what it tells us about the stereochemistry of molecules **ch31**
- Spectroscopy is an essential tool and will be referred to throughout the rest of the book

This is the first of two review chapters on spectroscopic methods taken as a whole. In Chapter 31 we shall tackle the complete identification of organic compounds, including the vital aspect of stereochemistry, introduced in Chapters 14 and 17. In this chapter we gather together some of the ideas introduced in previous chapters on spectroscopy and mechanism, and show how they are related. We shall explain the structure of the chapter as we go along.

## There are three reasons for this chapter

1. To review the methods of structure determination we met in Chapters 3 and 13, to extend them a little further, and to consider the relationships between them.
2. To show how these methods may be combined to determine the structure of unknown molecules.
3. To provide useful tables of data for you to use when you are attempting to determine unknown structures.

The main tables of data appear at the end of the chapter (pp. 423–425) so that they are easy to refer to when you are working on problems. You may also wish to look at them, along with the tables in the text, as you work through this chapter.

We shall deal with points 1 and 2 together, looking first at the interplay between the chemistry of the carbonyl group (as discussed in Chapters 10 and 11) and spectroscopy, solving some structural problems, then moving on to discuss, for example, NMR of more

than one element in the same compound, doing some more problems, and so on. We hope that the lessons from each section will help in your overall understanding of structure solving. The first section deals with the assignment of carbonyl compounds to their various classes.

## Spectroscopy and carbonyl chemistry

Chapters 10 and 11 completed our systematic survey of carbonyl chemistry, and we can now put together chemistry and spectroscopy on this most important of all functional groups.

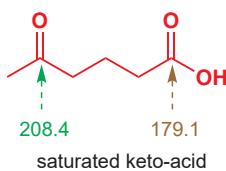
We have divided carbonyl compounds into two main groups:

1. aldehydes ( $\text{RCHO}$ ) and ketones ( $\text{R}^1\text{COR}^2$ )
2. acids ( $\text{RCO}_2\text{H}$ ) and their derivatives (in order of reactivity):
  - acid chlorides ( $\text{RCOCl}$ )
  - anhydrides ( $\text{RCO}_2\text{COR}$ )
  - esters ( $\text{R}^1\text{CO}_2\text{R}^2$ )
  - amides ( $\text{RCONH}_2$ ,  $\text{R}^1\text{CONMe}_2$ , etc.).

Which spectroscopic methods most reliably distinguish these two groups? Which help us to separate aldehydes from ketones? Which allow us to distinguish the various acid derivatives? Which offer the most reliable evidence on the chemistry of the carbonyl group? These are the questions we tackle in this section.

### Distinguishing aldehydes and ketones from acid derivatives

The most consistently reliable method for doing this is  $^{13}\text{C}$  NMR. It doesn't much matter whether the compounds are cyclic or unsaturated or have aromatic substituents, they all give carbonyl  $^{13}\text{C}$  shifts in about the same regions. There is a selection of examples on the facing page which we now discuss. First, look at the shifts arrowed into the carbonyl group on each structure. All the aldehydes and ketones fall between 191 and 208 ppm regardless of structure, whereas all the acid derivatives (and these are very varied indeed!) fall between 164 and 180 ppm. These two sets do not overlap and the distinction is easily made. Assigning the spectrum of the ketoacid in the margin, for example, is easy.

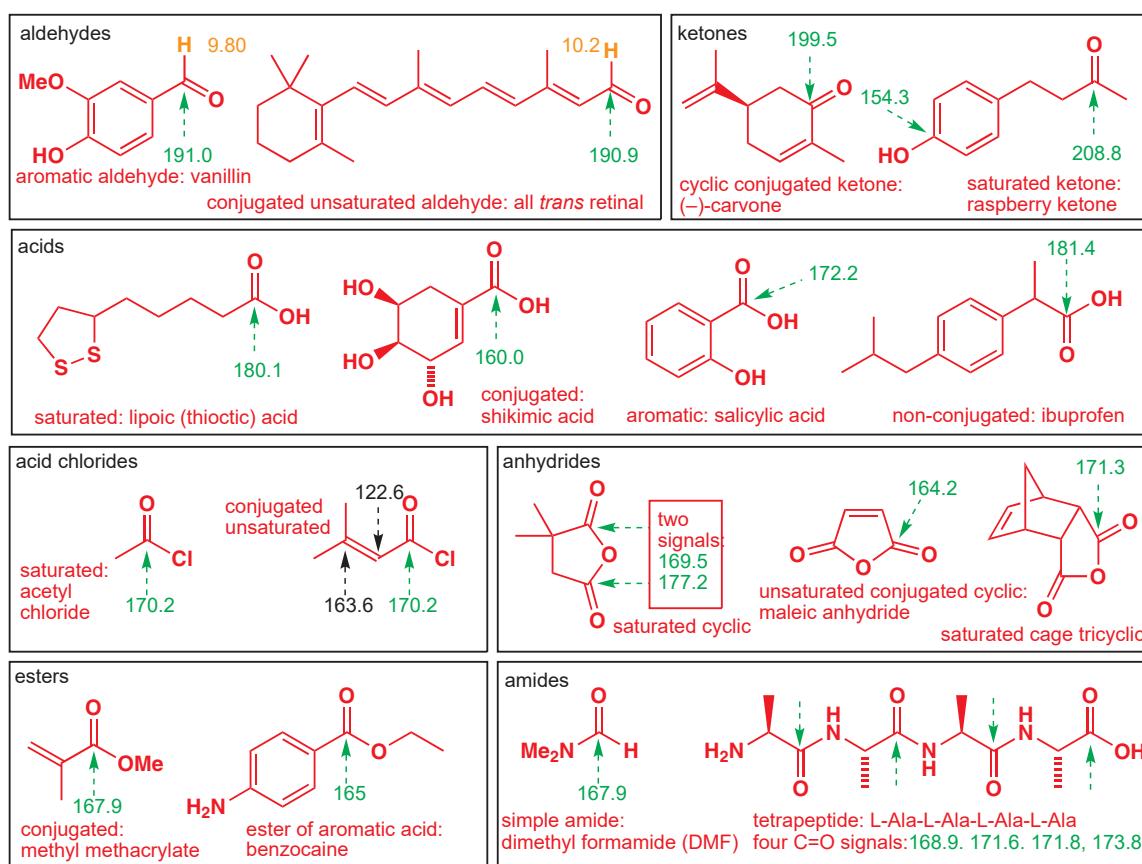


#### • $^{13}\text{C}$ NMR distinguishes acid derivatives from aldehydes and ketones

The carbonyl carbons of all aldehydes and ketones resonate at about 200 ppm, while acid derivatives usually resonate at about 175 ppm.

$^{13}\text{C}$  NMR shifts of carbonyl groups

Carbonyl group	$\delta_{\text{C}}$ , ppm
aldehydes	195–205
ketones	195–215
acids	170–185
acid chlorides	165–170
acid anhydrides	165–170
esters	165–175
amides	165–175



### More on these structures

#### Aldehydes and ketones

The first aldehyde is vanillin, which comes from the vanilla pod and gives the characteristic vanilla flavour in, for example, ice cream. Vanilla is the seed pod of a South American orchid. 'Vanilla essence' is made with synthetic vanillin and tastes slightly different because the vanilla pod contains other flavour components in small quantities. The second aldehyde is retinal. As you look at this structure your eyes use the light reaching them to interconvert *cis* and *trans* retinal in your retina to create nervous impulses (see also Chapter 27).

The two ketones are all flavour compounds too. The first, *(-)*-carvone, is the chief component (70%) of spearmint oil. Carvone is an interesting compound: in Chapter 14 you met the mirror-image isomers known as enantiomers, and *(-)*-carvone's mirror image, *(+)*-carvone, is the chief component (35%) of dill oil. Our taste can tell the difference, although an NMR machine can't and both carvones have *identical* NMR spectra. See Chapter 14 for more detail! The second ketone is 'raspberry ketone', which is largely responsible for the flavour of raspberries. It is entirely responsible for the flavour of some 'raspberry' foods. The signal for the aromatic carbon joined to OH is at 154.3 ppm (in the 100–150 ppm region because it is an unsaturated carbon atom joined to oxygen) and cannot possibly be confused with the ketone signal at 208.8 ppm. Both ketones have C=O shifts at about 200 ppm, and both lack any signals in the proton NMR of  $\delta > 8$ .

#### Acid derivatives

Lipoic acid uses its S–S bond in redox reactions (Chapter 42), while shikimic acid is an intermediate in the formation of compounds with benzene rings, such as phenylalanine, in living things (Chapter 42). Salicylic acid's acetate ester is aspirin, which is, of course, like the last example ibuprofen, a painkiller.

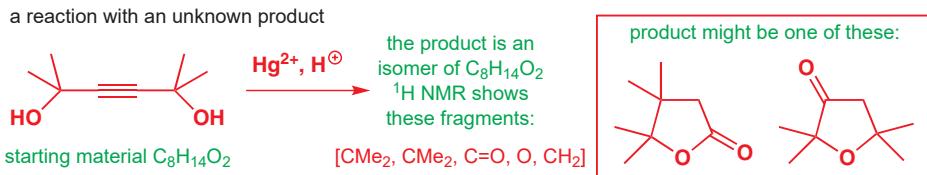
The first acid chloride is a popular reagent for the synthesis of acetate esters and you have seen its reactions in Chapter 10. We have chosen three cyclic anhydrides as examples because they are all related to an important reaction (the Diels–Alder reaction), which you will meet in Chapter 34.

The first ester, methyl methacrylate, is a bulk chemical. It is the monomer whose polymerization gives Perspex, the rigid transparent plastic used in windows and roofs. The second ester is an important local anaesthetic used for minor operations.

One amide is the now-familiar DMF, but the other is a tetrapeptide and so contains one carboxylic acid group at the end and three amide groups. Although the four amino acids in this peptide are identical (alanine, Ala for short), the carbon NMR faithfully picks up four different C=O signals, all made different by being different distances from the end of the chain.

The distinction can be vital in structural problems. The symmetrical alkyne diol below cyclizes in acid with Hg(II) catalysis to a compound having, by proton NMR, the structural fragments shown. The product is unsymmetrical in that the two  $\text{CMe}_2$  groups are still present, but they are now different. In addition, the chemical shift of the  $\text{CH}_2$  group shows that it is next to  $\text{C}=\text{O}$  but not next to oxygen. This leaves us with two possible structures. One is an ester and one a ketone. The  $\text{C}=\text{O}$  shift is 218.8 ppm and so there is no doubt that the second structure is correct.

You need not, at this stage, worry about *how* the reaction works. It is more important that you realize how spectroscopy enables us to work out *what has happened even before we have any idea how*. Nonetheless, it is true that the second structure here also makes more sense chemically as the carbon skeleton is the same as in the starting material.



### Distinguishing aldehydes from ketones is simple by proton NMR

Now look at the first two groups, the aldehydes and ketones. The two aldehydes have smaller carbonyl shifts than the two ketones, but they are too similar for this distinction to be reliable. What distinguishes the aldehydes very clearly is the characteristic proton signal for  $\text{CHO}$  at 9–10 ppm. So you should identify aldehydes and ketones by  $\text{C}=\text{O}$  shifts in carbon NMR and then separate the two by proton NMR.

#### ● Aldehyde protons are characteristic

A proton at 9–10 ppm indicates an aldehyde.

### Distinguishing acid derivatives by carbon NMR is difficult

Now examine the other panels on p. 409. The four carboxylic acids are all important biologically or medicinally. Their  $\text{C}=\text{O}$  shifts are very different *from each other* as well as from those of the aldehydes or ketones.

The next five compounds (two acid chlorides and three anhydrides) are all reactive acid derivatives, and the five esters and amides below them are all unreactive acid derivatives and yet the  $\text{C}=\text{O}$  shifts of all ten compounds fall in the same range. The  $\text{C}=\text{O}$  chemical shift is obviously *not* a good way to check on chemical reactivity.

What the carbon NMR fails to do is distinguish these types of acid derivative. There is more variation between the carboxylic acids on display than between the different classes of acid derivatives. This should be obvious if we show you some compounds containing two acid derivatives. Would you care to assign these signals?



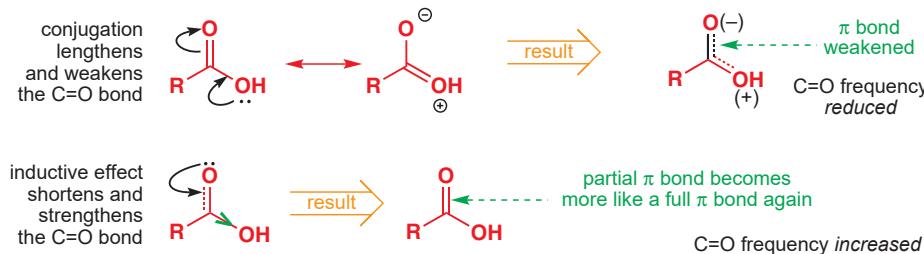
No, neither would we. In each case the difference between the carbonyl signals is only a few ppm. Although acid chlorides are extremely reactive in comparison with esters or amides, the electron deficiency at the carbon nucleus as measured by deshielding in the NMR spectrum evidently does not reflect this. Carbon NMR reliably distinguishes acid derivatives as a group from aldehydes and ketones as another group but it fails to distinguish even very reactive (for

example, acid chlorides) from very unreactive (for example, amides) acid derivatives. So how do we distinguish acid derivatives?

## Acid derivatives are best distinguished by infrared

A much better measure is the difference in IR stretching frequency of the C=O group. We discussed this in Chapter 10 (p. 206), where we noted a competition between conjugation by lone-pair electron donation *into* the carbonyl from OCOR, OR, or NH<sub>2</sub> and inductive withdrawal *from* the C=O group because of the electronegativity of the substituent. Conjugation donates electrons into the  $\pi^*$  orbital of the  $\pi$  bond and so lengthens and weakens it. The C=O bond becomes more like a single bond and its stretching frequency moves towards the single-bond region, that is, it goes *down*. The inductive effect removes electrons from the  $\pi$  orbital and so shortens and strengthens the  $\pi$  bond. It becomes more like a full double bond and moves *up* in frequency.

For a reminder of the distinction between conjugation and inductive effects, see Chapter 8, p. 176.



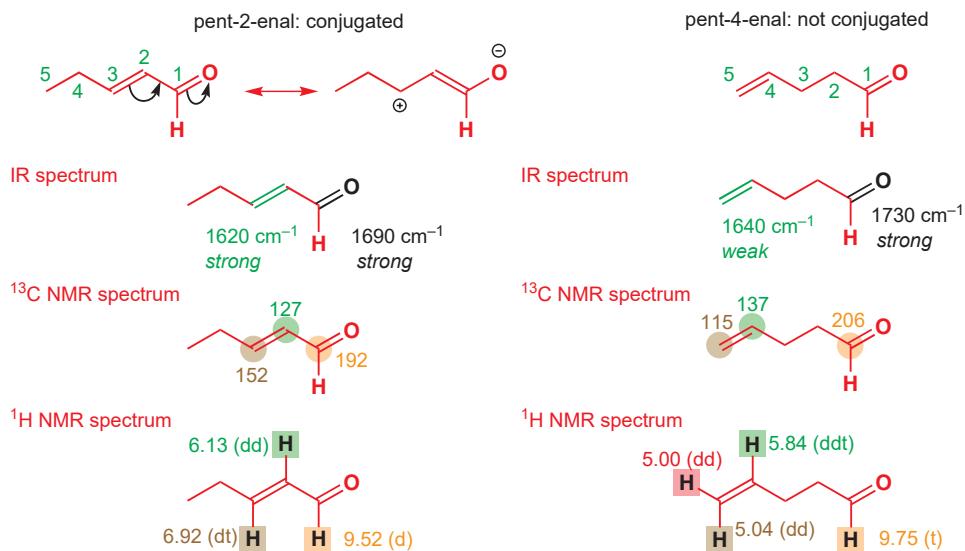
These effects are balanced in different ways according to the substituent. Chlorine is poor at lone-pair electron donation (its lone pair is in a large 3p orbital and overlaps badly with the 2p orbital on carbon) but strongly electron-withdrawing so acid chlorides absorb at high frequency, almost in the triple-bond region. Anhydrides have an oxygen atom between two carbonyl groups. Inductive withdrawal is still strong but conjugation is weak because the lone pairs are pulled both ways. Esters have a well-balanced combination with the inductive effect slightly stronger (oxygen donates from a compatible 2p orbital but is very electronegative and so withdraws electrons strongly as well). Finally, amides are dominated by conjugation as nitrogen is a much stronger electron donor than oxygen because it is less electronegative.

Acid chlorides	Anhydrides	Esters	Amides
inductive effect dominates $1815\text{ cm}^{-1}$	tug-of-war for lone pair: inductive effect dominates two peaks: $\sim 1790, 1810\text{ cm}^{-1}$	inductive effect slightly dominates $1745\text{ cm}^{-1}$	conjugation strongly dominates $\sim 1650\text{ cm}^{-1}$

The two peaks for anhydrides are the symmetrical and anti-symmetrical stretches for the two C=O groups; see Chapter 3, p. 70.

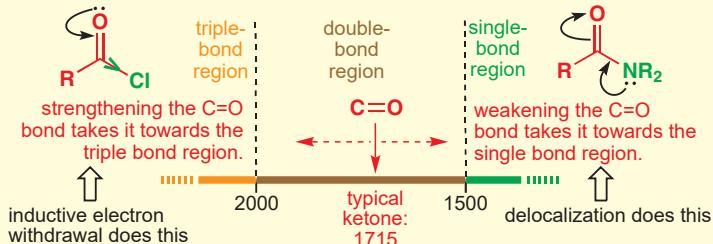
## Conjugation with $\pi$ electrons or lone pairs affects IR C=O stretches

We need to see how conjugation works when it is with a  $\pi$  bond rather than with a lone pair. This will make the concept more general as it will apply to aldehydes and ketones as well as to acid groups. How can we detect whether an unsaturated carbonyl compound is conjugated or not? Well, compare these two unsaturated aldehydes.



The key differences are the frequency of the  $\text{C}=\text{O}$  stretch (lowered by  $40\text{ cm}^{-1}$  by conjugation) and the strength (that is, the intensity) of the  $\text{C}=\text{C}$  stretch (increased by conjugation) in the IR. In the  $^{13}\text{C}$  NMR, C3 in the conjugated enal is moved out of the alkene region just into the carbonyl region, showing how electron-deficient this carbon atom must be. In the proton NMR there are many effects but the downfield shift of the protons on the alkene, especially C3 (again!), is probably the most helpful.

#### ● Summary of the effects of substituents on $\text{C}=\text{O}$ stretching frequency



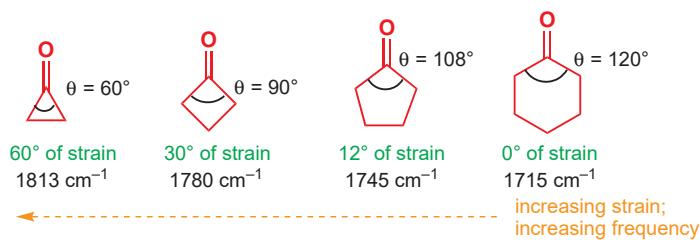
Because the infrared carbonyl frequencies follow such a predictable pattern, it is possible to make a simple list of correlations using just three factors. Two are the ones we have been discussing—conjugation (frequency-lowering) and the inductive effect (frequency-raising). The third is the effect of small rings and this we next need to consider in a broader context.

## Small rings introduce strain inside the ring and higher s character outside it

Cyclic ketones can achieve the perfect  $120^\circ$  angle at the carbonyl group only if the ring is at least six-membered. The smaller rings are ‘strained’ because the orbitals have to overlap at a less than ideal angle.

For a four-membered ring, the actual angle is  $90^\circ$ , so there is  $120^\circ - 90^\circ = 30^\circ$  of strain at the carbonyl group. The effects of this strain on five-, four-, and three-membered rings are shown here.

■ The three-membered ring is, of course, flat. The others are not. Even the four-membered ring is slightly puckered, the five and especially the six-membered rings more so. This is all discussed, along with analysis of ring strain, in Chapter 16.

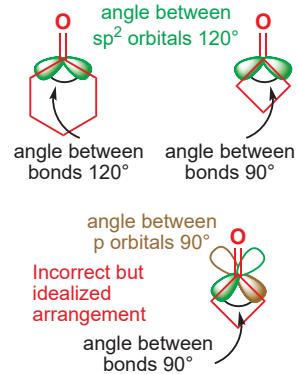
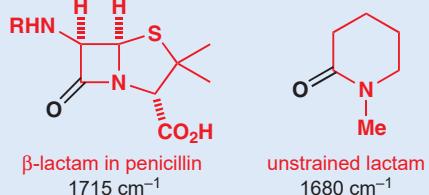


But why should strain raise the frequency of a carbonyl group? It is evidently shortening and strengthening the C=O bond as it moves it towards the triple-bond region (higher frequency), not towards the single-bond region (lower frequency). In a six-membered ring, the  $sp^2$  orbitals forming the  $\sigma$  framework around the carbonyl group can overlap perfectly with the  $sp^3$  orbitals on neighbouring carbon atoms because the orbital angle and the bond angle are the same. In a four-membered ring the orbitals do not point towards those on the neighbouring carbon atoms, but point too far out, effectively forcing the bonds to be bent and lowering the degree of overlap.

Ideally, we should like the orbitals to have an angle of 90° as this would make the orbital angle the same as the bond angle. In theory it *would* be possible to have a bond angle of 90° if we used pure p orbitals instead of  $sp^2$  hybrid orbitals. The diagram in the margin shows this hypothetical situation. If we did this, we should leave a pure s orbital for the  $\sigma$  bond to oxygen. This extreme is not possible, but a compromise is. *Some* more p character goes into the ring bonds—maybe they become  $s^{0.8}p^{3.2}$ —so that they can approach the 90° angle needed, and the same amount of extra s character goes into the  $\sigma$  bond to oxygen. The more s character there is in the orbital, the shorter it gets as s orbitals are much smaller than p orbitals.

### Lactam C=O stretching frequencies

A further good example is the difference between C=O stretching frequencies in cyclic amides, or lactams. The penicillin class of antibiotics all contain a four-membered ring amide known as a  $\beta$ -lactam. The carbonyl stretching frequency in these compounds is way above the 1680 cm<sup>-1</sup> of the six-membered lactam, which is what you might expect for an unstrained amide.



## Simple calculations of C=O stretching frequencies in IR spectra

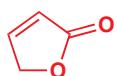
The best way is to relate all our carbonyl frequencies to those for saturated ketones (1715 cm<sup>-1</sup>). We can summarize what we have just learned in a table.

Notice in this simple table (for full details you should refer as usual to a specialist book) that the adjustment '30 cm<sup>-1</sup>' appears quite a lot (~30 cm<sup>-1</sup> for both alkene and aryl, for example), that the increment for small rings is 35 cm<sup>-1</sup> each time (30 to 65 cm<sup>-1</sup> and then 65 to 100 cm<sup>-1</sup>), and that the extreme effects of Cl and NH<sub>2</sub> are +85 and -85 cm<sup>-1</sup>, respectively. These effects are additive. If you want to estimate the C=O frequency of a proposed structure, just add or subtract all the adjustments to 1715 cm<sup>-1</sup> and you will get a reasonable result.

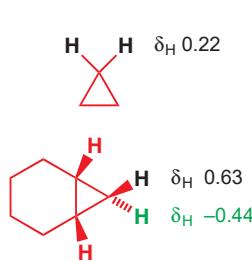
Effects of substituents on IR carbonyl frequencies

Effect	Group	C=O stretch, cm <sup>-1</sup>	Frequency change <sup>a</sup> , cm <sup>-1</sup>
inductive effect	Cl	1800	+ 85
	OCOR	1765, 1815	+ 50, +100
	OR	1745	+ 30
	H	1730	+ 15
conjugation	C=C	1685	-30
	aryl	1685	-30
	NH <sub>2</sub>	1630	-85
ring strain	five-membered ring	1745	+ 30
	four-membered ring	1780	+ 65
	three-membered ring	1815	+ 100

<sup>a</sup>Difference between stretching frequency of C=O and stretching frequency of a typical saturated ketone (1715 cm<sup>-1</sup>).



Try this out with the five-membered unsaturated (and conjugated) lactone (cyclic ester) in the margin. We must add  $30\text{ cm}^{-1}$  for the ester, subtract  $30\text{ cm}^{-1}$  for the double bond, and add  $30\text{ cm}^{-1}$  for the five-membered ring. Two of those cancel out, leaving just  $1715 + 30 = 1745\text{ cm}^{-1}$ . These compounds absorb at  $1740\text{--}1760\text{ cm}^{-1}$ . Not bad!



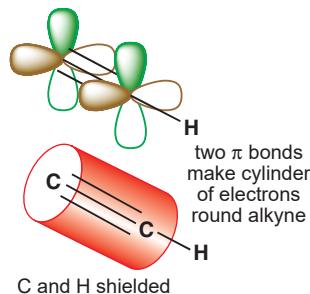
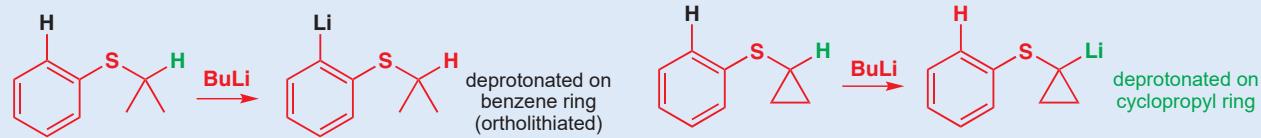
## NMR spectra of alkynes and small rings

This idea that small rings have more p character in the ring and more s character outside the ring also explains the effects of small rings on proton NMR shifts. These hydrogens, particularly on three-membered rings, resonate at unusually high fields, between 0 and 1 ppm in cyclopropanes instead of the 1.3 ppm expected for  $\text{CH}_2$  groups, and may even appear at negative  $\delta$  values. High p character in the framework of small rings also means high s character in C–H bonds outside the ring and this will mean shorter bonds, greater shielding, and small  $\delta$  values.

### Three-membered rings and alkynes

You have also seen the same argument used in Chapter 8 to justify the unusual acidity of C–H protons on triple bonds (such as alkynes and HCN), and alluded to in Chapter 3 to explain the stretching frequency of the same C–H bonds. Like alkynes, three-membered rings are also unusually easy to deprotonate in base.

Here is an example where deprotonation occurs at a different site in two compounds identical except for a C–C bond closing a three-membered ring. The first is an ortholithiation of the type discussed in Chapter 24.

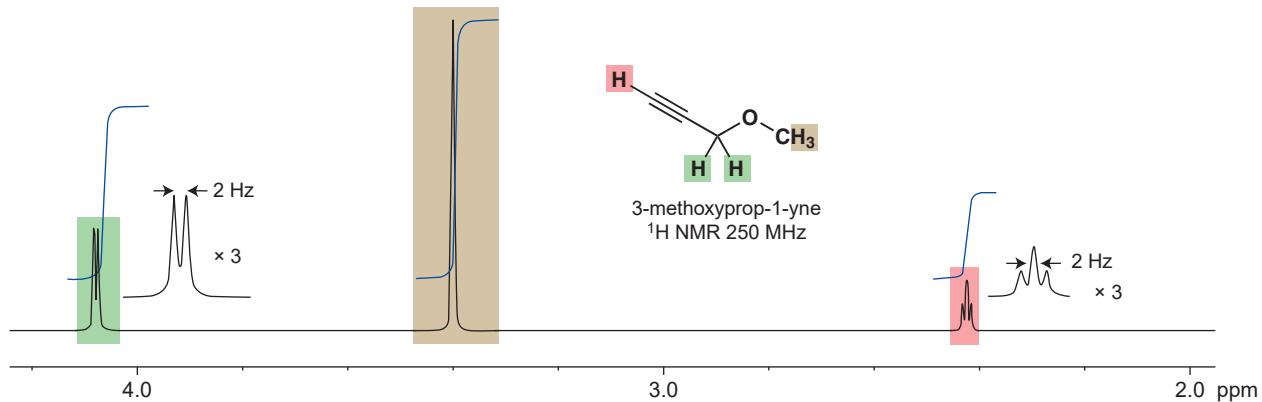


Now what about the NMR spectra of alkynes? By the same argument, protons on alkynes ought to appear in the NMR at quite high field because the C atom is sp hybridized, so it makes its  $\sigma$  bonds with sp orbitals (i.e. 50% s character). Protons on a typical alkene have  $\delta_H$  about 5.5 ppm, while the proton on an alkyne comes right in the middle of the protons on saturated carbons at about  $\delta_H$  2–2.5 ppm. This is rather a large effect just for increased s character and some of it is probably due to better shielding by the triple bond, which surrounds the linear alkyne with  $\pi$  bonds without a nodal plane.

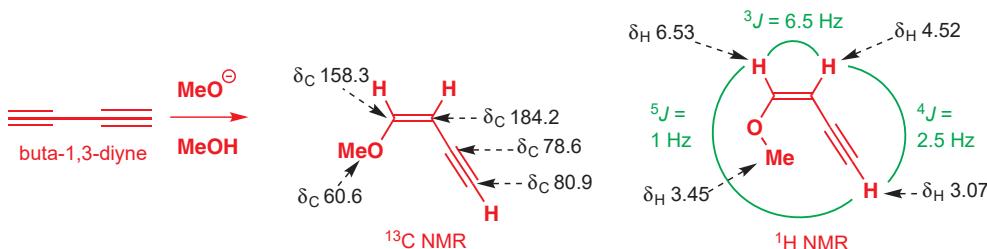
This means that the carbon atoms also appear at higher field than expected, not in the alkene region but from about  $\delta_C$  60–80 ppm. The s character argument is important, however, because shielding can't affect IR stretching frequencies, yet  $\text{C}\equiv\text{C}-\text{H}$  stretches are strong and at about  $3300\text{ cm}^{-1}$ , just right for a strong C–H bond.

A simple example is the ether 3-methoxyprop-1-yne. Integration alone allows us to assign the spectrum and the  $^1\text{H}$  signal at 2.42 ppm, the highest field signal, is clearly the alkyne proton. Notice also that it is a triplet and that the  $\text{OCH}_2$  group is a doublet. This  $^4J_{\text{HH}}$  is small (about 2 Hz) and, although there is nothing like a letter 'W' in the arrangement of the bonds, coupling of this kind is often found in alkynes.

► In Chapter 13, p. 296, you saw that bonds aligned in a 'W' arrangement can give rise to a small  $^4J_{\text{HH}}$  coupling.



A more interesting example comes from the base-catalysed addition of methanol to buta-1,3-diyne (diacetylene). The compound formed has one double and one triple bond and the  $^{13}\text{C}$  NMR shows clearly the greater deshielding of the double bond.

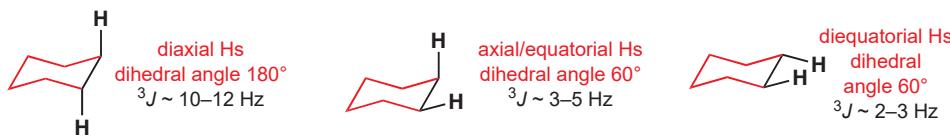


You may have noticed that we have drawn the double bond with the *cis* (Z) configuration. We know that this is true because of the proton NMR, which shows a 6.5 Hz coupling between the two alkene protons (much too small for a *trans* coupling; see p. 295). There is also the longer-range coupling ( $^4\text{J} = 2.5$  Hz) just described and even a small very long-range coupling ( $^5\text{J} = 1$  Hz) between the alkyne proton and the terminal alkene proton.

## Proton NMR distinguishes axial and equatorial protons in cyclohexanes

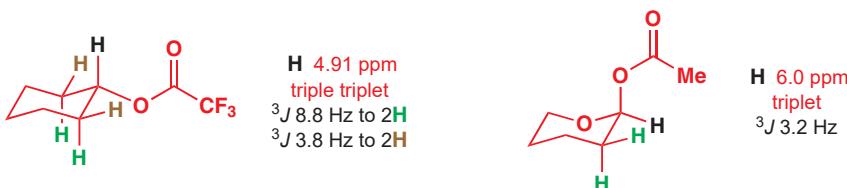
Coupling is a through-bond phenomenon, as we know from the couplings in *cis* and *trans* alkenes, where *trans* alkenes have much larger coupling constants as their orbitals are perfectly parallel. Another case of perfectly parallel orbitals occurs with *trans*-diaxial protons in cyclohexanes. Typical coupling constants are 10–12 Hz for *trans*-diaxial protons, but much smaller (2–5 Hz) for axial/equatorial and equatorial/equatorial protons.

► Coupling in alkenes is explained on p. 295.



This makes assignment of conformation easy. The simple ester below has a triplet for the black H, with two large coupling constants (8.8 Hz) that must be to axial protons (green) and two small coupling constants (3.8 Hz) that must be to equatorial Hs (brown). This is possible only if the black H is axial and the ester group must therefore be equatorial. The acetal ester on the right is very different: it is a simple triplet with two small coupling constants (3.2 Hz), which is too small for an axial/axial coupling. The only possibility therefore is that the black proton is equatorial, and one of the 3.2 Hz couplings is to its equatorial neighbour, and the other to its axial neighbour. The ester group must be axial in this compound.

► Proton–proton coupling in alkenes is discussed in Chapter 13 and the conformation of cyclohexanes is discussed in Chapter 16. The Karplus relationship, explaining precisely what affects the couplings in cyclohexanes, is discussed in Chapter 31.

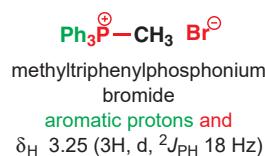


► You will see in Chapter 31 why the ester group might prefer to be axial in this compound.

## Interactions between different nuclei can give enormous coupling constants

We have looked at coupling between hydrogen atoms and you may have wondered why we have ignored coupling between other NMR active nuclei. Why does  $^{13}\text{C}$  not cause similar couplings? In this section we are going to consider not only couplings between the same kind of nuclei,

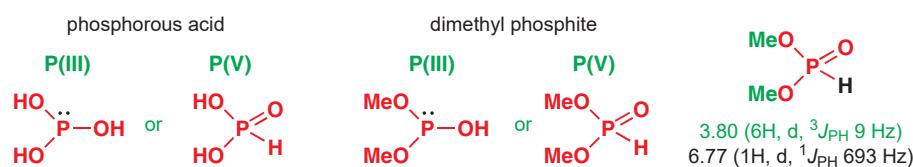
■ Note that these spectra with heteronuclear couplings provide the only cases where we can see one doublet in the proton NMR. Normally, if there is one doublet, there must be another signal with at least this complexity as all coupling appears twice (A couples to B and so B also couples to A!). If the coupling is to another element (here phosphorus) then the coupling appears once in each spectrum. The Wittig reagent has an  $A_3P$  ( $\text{CH}_3P$ ) system: proton A appears as a doublet, while the phosphorus atom appears as a quartet in the *phosphorus* spectrum at a completely different frequency, but with the same coupling constant measured in Hz.



such as two protons, called **homonuclear coupling**, but also coupling between different nuclei, such as a proton and a fluorine atom or  $^{13}\text{C}$  and  $^{31}\text{P}$ , called **heteronuclear coupling**.

Two nuclei are particularly important,  $^{19}\text{F}$  and  $^{31}\text{P}$ , since many organic compounds contain these elements and both are at essentially 100% natural abundance and have spin  $I = 1/2$ . We shall start with organic compounds that have just one of these nuclei and see what happens to both the  $^1\text{H}$  and the  $^{13}\text{C}$  spectra. In fact, it is easy to find a  $^{19}\text{F}$  or a  $^{31}\text{P}$  atom in a molecule because these elements couple to all nearby carbon and hydrogen atoms. Since they can be directly bonded to either,  $^1J$  coupling constants such as  $^1J_{\text{CF}}$  or  $^1J_{\text{PH}}$  become possible, as well as the more ‘normal’ couplings such as  $^2J_{\text{CF}}$  or  $^3J_{\text{PH}}$ , and these  $^1J$  coupling constants can be enormous.

We shall start with a simple phosphorus compound, the dimethyl ester of phosphorous acid ( $\text{H}_3\text{PO}_3$ ). There is an uncertainty about the structure of both the acid and its esters. They could exist as P(III) compounds with a lone pair of electrons on phosphorus, or as P(V) compounds with a P=O double bond.

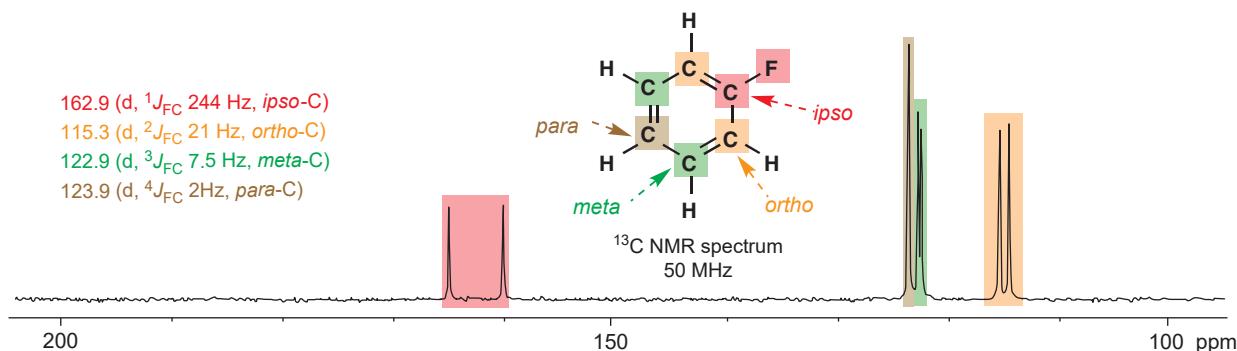


In fact, dimethyl phosphite has a  $^1\text{H}$  doublet with the amazing coupling constant of 693 Hz: on a 250 MHz machine the two lines are over 2 ppm apart and it is easy to miss that they are two halves of the same doublet. This can only be a  $^1J_{\text{PH}}$  as it is so enormous. The compound has to have a P–H bond and the P(V) structure is correct. The coupling to the protons of the methyl group is much smaller but still large for a three-bond coupling ( $^3J_{\text{PC}}$  of 18 Hz).

Next, consider the phosphonium salt you met at the end of Chapter 11 for use in the Wittig reaction, turning aldehydes and ketones to alkenes. It has a  $^2J_{\text{PH}}$  of 18 Hz. There is no doubt about this structure—it is just an illustration of coupling to phosphorus. There is coupling to phosphorus in the carbon spectrum too: the methyl group appears at  $\delta_{\text{C}}$  10.6 ppm with a  $^1J_{\text{PC}}$  of 57 Hz, somewhat smaller than typical  $^1J_{\text{PH}}$ . We haven’t yet talked about couplings to  $^{13}\text{C}$ : we shall now do so.

### Coupling in carbon NMR spectra

We shall use coupling with fluorine to introduce this section. Fluorobenzenes are good examples because they have a number of different carbon atoms all coupled to the fluorine atom.

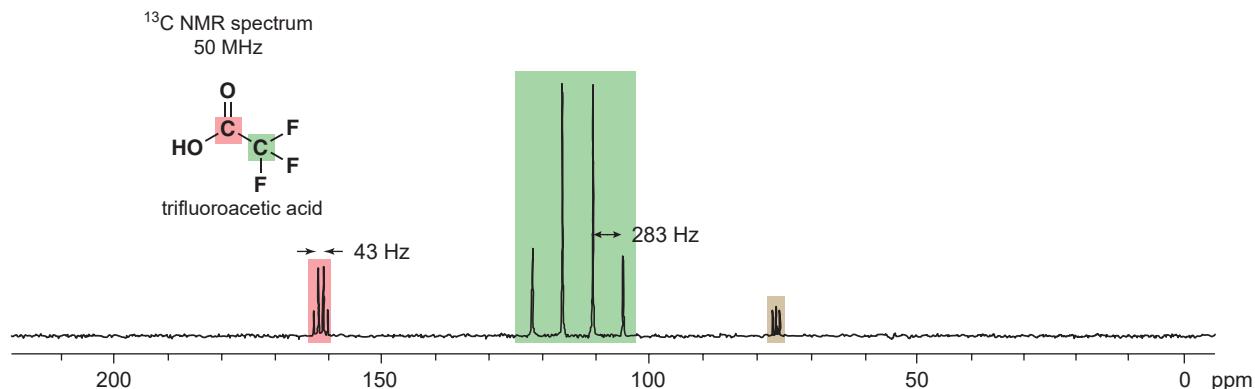


■ *Ipso* can join the list (*ortho*, *meta*, *para*) of trivial names for positions on a substituted benzene ring. The *ipso* carbon is the one directly attached to a substituent.

The carbon directly joined to fluorine (the *ipso* carbon) has a very large  $^1J_{\text{CF}}$  value of about 250 Hz. More distant coupling is evident too: all the carbons in the ring couple to the fluorine in PhF with steadily diminishing  $J$  values as the carbons become more distant.

Trifluoroacetic acid is an important strong organic acid (Chapter 8) and a good solvent for  $^1\text{H}$  NMR. The carbon atom of the  $\text{CF}_3$  group is coupled equally to all the three fluorines and so appears as a quartet with a large  $^1J_{\text{CF}}$  of 283 Hz, about the same as in PhF. Even the carbonyl

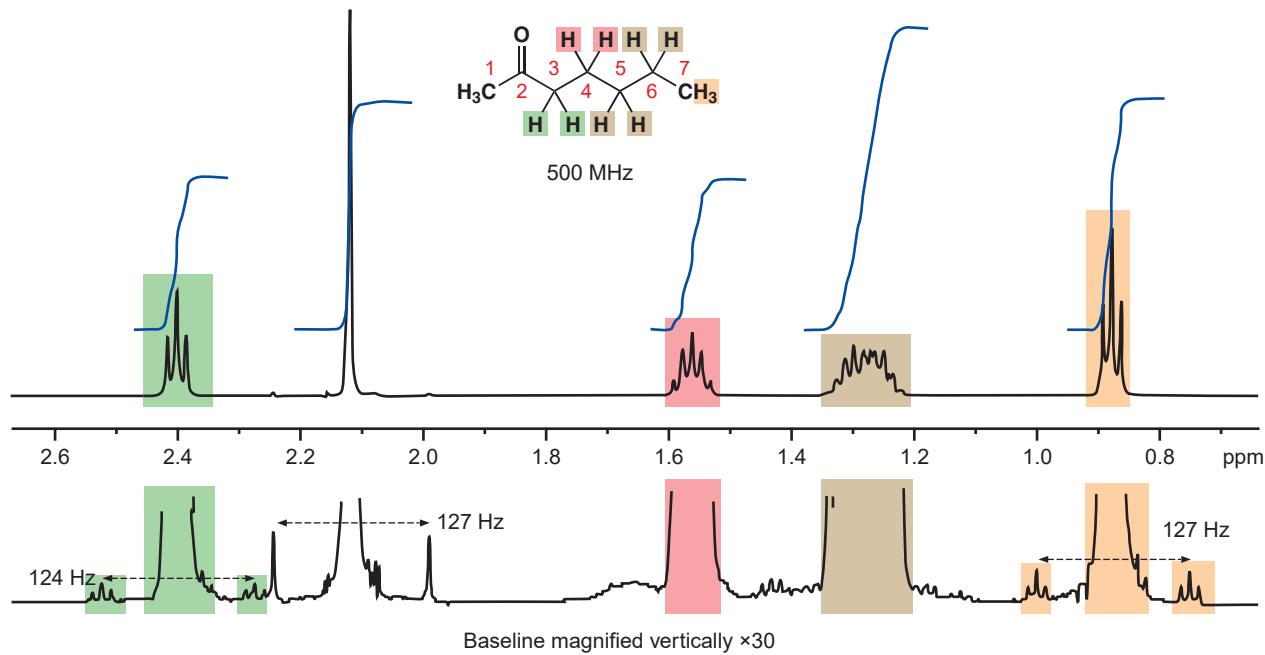
group is also a quartet, although the coupling constant is much smaller ( $^2J_{\text{CF}}$  is 43 Hz). Notice too how far downfield the  $\text{CF}_3$  carbon atom is!



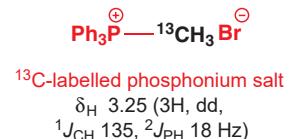
### Coupling between protons and $^{13}\text{C}$

In view of all this, you may ask why we don't apparently see couplings between  $^{13}\text{C}$  and  $^1\text{H}$  in either carbon or proton spectra. In proton spectra the answer is simple: we don't see coupling to  $^{13}\text{C}$  because of the low abundance (1.1%) of  $^{13}\text{C}$ . Most protons are bonded to  $^{12}\text{C}$ : only 1.1% of protons are bonded to  $^{13}\text{C}$ . If you look closely at proton spectra with very flat baselines, you may see small peaks either side of strong peaks at about 0.5% peak height. These are the  $^{13}\text{C}$  'satellites' for those protons that are bonded to  $^{13}\text{C}$  atoms.

As an example, look again at the 500 MHz  $^1\text{H}$  NMR spectrum of heptan-2-one that we saw on p. 294. When the baseline of this spectrum is vertically expanded, the  $^{13}\text{C}$  satellites may be seen. The singlet due to the methyl protons is actually in the centre of a tiny doublet due to the 1% of protons coupling to  $^{13}\text{C}$ . Similarly, each of the triplets in the spectrum is flanked by two tiny triplets. The two tiny triplets on either side make up a doublet of triplets with a large  $^1J$  coupling constant to the  $^{13}\text{C}$  (around 130 Hz) and smaller  $^3J$  coupling to the two equivalent protons.



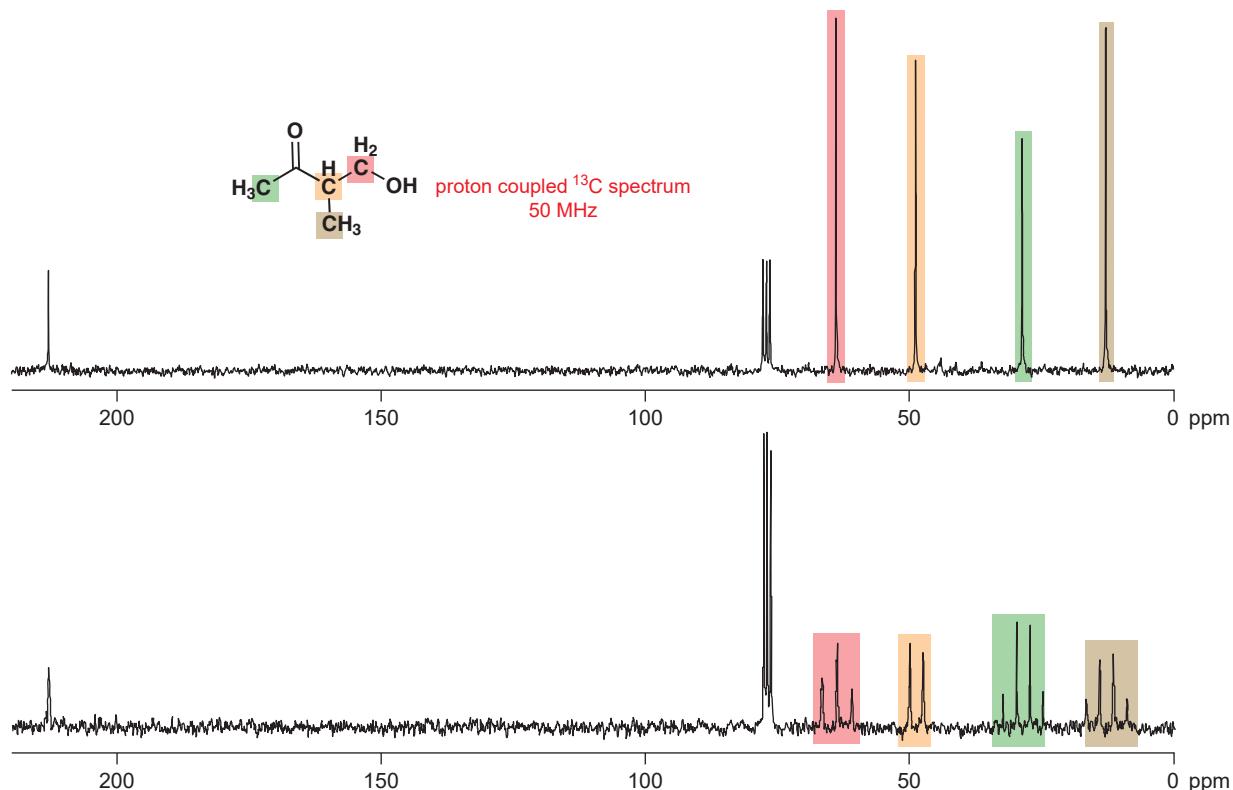
$^{13}\text{C}$  satellites are usually lost in the background noise of the spectrum and need concern us no further. You do, however, see coupling in the  $^1\text{H}$  NMR spectrum with compounds deliberately labelled with  $^{13}\text{C}$  because the  $^{13}\text{C}$  abundance can then approach 100%. The same Wittig reagent we saw a moment ago shows a 3H doublet of doublets with the typically enormous  $^1J_{\text{CH}}$  of 135 Hz when labelled with pure  $^{13}\text{C}$  in the methyl group.



But this begs the question—where is the 135 Hz coupling in the  $^{13}\text{C}$  NMR? Surely we should see this coupling to the protons in the  $^{13}\text{C}$  NMR spectrum too?

### Why is there no coupling to protons in normal $^{13}\text{C}$ NMR spectra?

We get the singlets consistently seen in carbon spectra because of the way we record the spectra. The values of  $^1J_{\text{CH}}$  are so large that, if we recorded  $^{13}\text{C}$  spectra with all the coupling constants, we would get a mass of overlapping peaks. When run on the same spectrometer, the frequency at which  $^{13}\text{C}$  nuclei resonate turns out to be about a quarter of that of the protons. Thus a ‘400 MHz machine’ (remember that the magnet strength is usually described by the frequency at which the protons resonate) gives  $^{13}\text{C}$  spectra at 100 MHz. Coupling constants ( $^1J_{\text{CH}}$ ) of 100–250 Hz would cover 2–5 ppm and a  $\text{CH}_3$  group with  $^1J_{\text{CH}}$  of about 125 Hz would give a quartet covering nearly 8 ppm (see the example on the previous page).



Since the proton-coupled  $^{13}\text{C}$  spectrum can so easily help us to distinguish  $\text{CH}_3$ ,  $\text{CH}_2$ ,  $\text{CH}$ , and quaternary carbons, you might wonder why they are not used more. The above example was chosen very carefully to illustrate proton-coupled spectra at their best. Unfortunately, this is not a typical example. More usually, the confusion from overlapping peaks makes this just not worthwhile. So  $^{13}\text{C}$  NMR spectra are recorded while the whole 10 ppm proton spectrum is being irradiated with a secondary radio frequency source. The proton energy levels are equalized by this process and all coupling disappears. Hence the singlets we are used to seeing.

For the rest of this chapter we shall not be introducing new theory or new concepts; we shall be applying what we have told you to a series of examples where spectroscopy enables chemists to identify compounds.

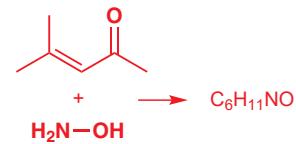
## Identifying products spectroscopically

### An ambiguous reaction product

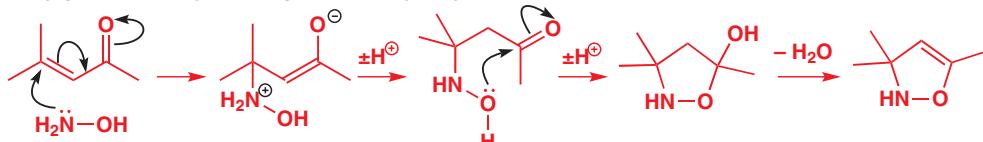
► This was the case of diazonamide A (p. 45).

In Chapter 3 we gave an example of a compound which was misidentified because an O atom and an N atom were mistaken for one another, even in the X-ray crystal structure.

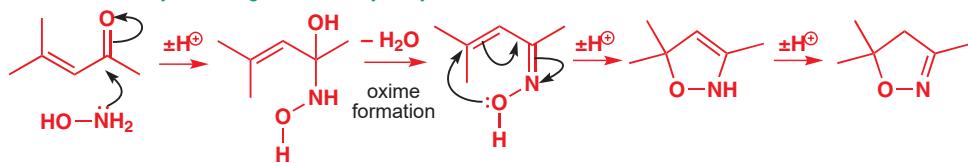
Another famous case of ambiguity between structures containing O or N arises in the identification of the product of addition of hydroxylamine ( $\text{NH}_2\text{OH}$ ) to a simple enone. This condensation reaction gives a compound with the formula  $\text{C}_6\text{H}_{11}\text{NO}$ . But what is its structure? We can first of all think about what we expect to happen: it is not always necessary to do this in order to identify a structure, but it can help. Nitrogen is more nucleophilic than oxygen so we might expect it to add first. But will it add directly to the carbonyl group or in the conjugate fashion we shall describe in Chapter 22? Either way, an intermediate will be formed that can cyclize.



#### conjugate addition by the nitrogen atom of hydroxylamine



#### direct addition by the nitrogen atom of hydroxylamine



The two possible isomeric products were once the subject of a long-running controversy, but with IR and proton NMR spectra of the product, doubt vanished. The IR showed no NH stretch. The NMR showed no alkene proton but did have a  $\text{CH}_2$  group at 2.63 ppm. Only the second structure is possible.

We need to look now at a selection of problems of different kinds to show how the various spectroscopic methods can cooperate in structure determination.

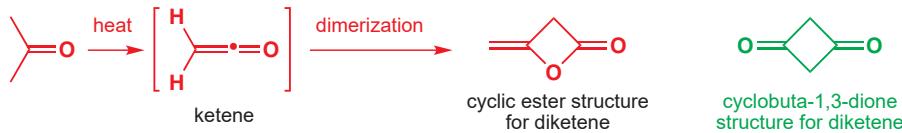
Do not be concerned about the details of the mechanisms: note that we have used the ' $\pm \text{H}^+$ ' shorthand introduced in Chapter 11, and have abbreviated the mechanism where water is eliminated and the oxime formed—the full mechanism of imine (and oxime) formation can be found in Chapter 11, p. 229. In this chapter, we are much more concerned just with the structure of the products.

## Reactive intermediates can be detected by spectroscopy

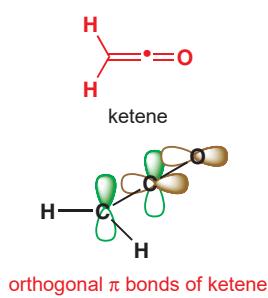
Some intermediates proposed in reaction mechanisms look so unlikely that it is comforting if they can be isolated and their structure determined. We feel more confident in proposing an intermediate if we are sure that it can really be made. Of course, this is not necessarily evidence that the intermediate is actually formed during reactions and it certainly does *not* follow that the failure to isolate a given intermediate disproves its involvement in a reaction. We shall use ketene as an example.

Ketene looks pretty unlikely! It is  $\text{CH}_2=\text{C=O}$  with two  $\pi$  bonds ( $\text{C=C}$  and  $\text{C=O}$ ) to the same carbon atom. The orbitals for these  $\pi$  bonds must be orthogonal because the central carbon atom is sp hybridized with two linear  $\sigma$  bonds and two p orbitals at right angles both to the  $\sigma$  bonds and to each other. Can such a molecule exist? When acetone vapour is heated to very high temperatures ( $700\text{--}750^\circ\text{C}$ ) methane is given off and ketene is supposed to be the other product. What is isolated is a ketene dimer ( $\text{C}_4\text{H}_4\text{O}_2$ ) and even the structure of this is in doubt as two reasonable structures can be written.

We used this logic in Chapter 15: carbocations were proposed as intermediates in  $\text{S}_{\text{N}}1$  reactions long before they were observed spectroscopically, but it was reassuring to be able to see them by NMR once appropriate conditions were devised (see p. 335).



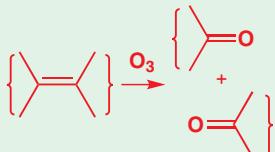
The spectra fit the ester structure well, but not the more symmetrical diketone structure at all. There are *three* types of proton (cyclobuta-1,3-dione would have just *one*), with allylic coupling between one of the protons on the double bond and the  $\text{CH}_2$  group in the ring. The carbonyl group has the shift (185 ppm) of an acid derivative (not that of a ketone, which would be about 200 ppm) and all four carbons are different.



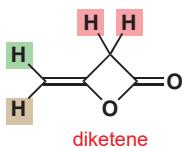
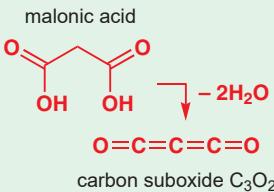
The structure of ketene is analogous to that of *allene*, discussed in Chapter 7, p. 146. Ketene is isoelectronic (p. 354) with  $\text{CO}_2$  and azide,  $\text{N}_3^-$ .

■ **Ozonolysis or ozonation**

is the cleavage of an alkene by ozone ( $O_3$ ). The reaction and its mechanism are discussed in Chapters 19 and 34: the only point to note now is that ozone is a powerful oxidant and cleaves the alkene to make two carbonyl compounds. Again, in this chapter we are concerned only with the structure of the products and how these can be determined.



■ Malonic anhydride cannot be made directly from malonic acid because attempted dehydration of the acid leads to the exotic molecule carbon suboxide  $C_3O_2$ .

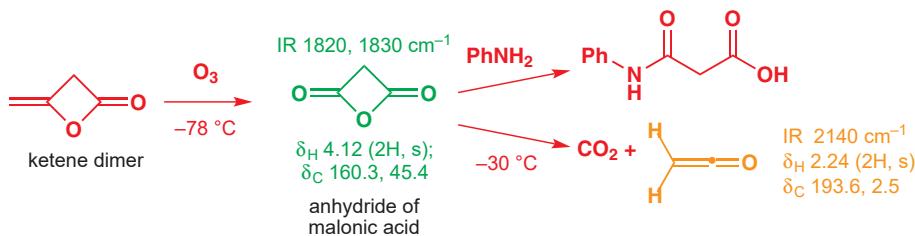


$^1H$  NMR spectrum:  
4.85 (1H, narrow t,  $J \sim 1$ )  
4.51 (1H, s)  
3.90 (2H, d,  $J \sim 1$ )

$^{13}C$  NMR spectrum:  
185.1, 147.7, 67.0, 42.4

Ozonolysis of ketene dimer gives a very unstable compound that can be observed only at low temperatures ( $-78^\circ C$  or below). It has two carbonyl bands in the IR and reacts with amines to give amides, so it looks like an anhydride (Chapter 10). Can it be the previously unknown cyclic anhydride of malonic acid?

The two carbonyl bands are of high frequency, as would be expected for a four-membered ring—using the table on p. 413 we estimate  $1715 + 50\text{ cm}^{-1}$  (for the anhydride) +  $65\text{ cm}^{-1}$  (for the four-membered ring) =  $1830\text{ cm}^{-1}$ . Both the proton and the carbon NMR are very simple: just a 2H singlet at 4.12 ppm, shifted downfield by two carbonyls, a C=O group at 160 ppm, right for an acid derivative, and a saturated carbon shifted downfield but not as much as a  $\text{CH}_2\text{O}$  group.



All this is reasonably convincing, and is confirmed by allowing the anhydride to warm to  $-30^\circ C$ , at which temperature it loses  $\text{CO}_2$  (detected by the  $^{13}\text{C}$  peak at 124.5 ppm) and gives another unstable compound with the strange IR frequency of  $2140\text{ cm}^{-1}$ . Could this be monomeric ketene? It's certainly not either of the possible ketene dimers as we know what their spectra are like, and this is quite different: just a 2H singlet at 2.24 ppm and  $^{13}\text{C}$  peaks at 194.0 and, remarkably, 2.5 ppm. It is indeed monomeric ketene.

### Squares and cubes: molecules with unusual structures

Some structures are interesting because we believe they can tell us something fundamental about the nature of bonding while others are a challenge because many people argue that they cannot be made. What do you think are the prospects of making cyclobutadiene, a conjugated four-membered ring, or the hydrocarbons tetrahedrane and cubane, which have, respectively, the shapes of the perfectly symmetrical Euclidean solids, the tetrahedron and the cube?

With four electrons, cyclobutadiene is anti-aromatic—it has  $4n$  instead of  $4n + 2$  electrons. You saw in Chapter 7 that cyclic conjugated systems with  $4n$  electrons (cyclooctatetraene, for example) avoid being conjugated by puckering into a tub shape. Cyclobutadiene cannot do this: it must be more or less planar, and so we expect it to be very unstable. Tetrahedrane has four fused three-membered rings. Although the molecule is tetrahedral in shape, each carbon atom is nowhere near a tetrahedron, with three bond angles of  $60^\circ$ . Cubane has six fused four-membered rings and is again highly strained.

In fact, cubane has been made, cyclobutadiene has a fleeting existence but can be isolated as an iron complex, and a few substituted versions of tetrahedrane have been made. The most convincing evidence that you have made any of these three compounds would be the extreme simplicity of the spectra. Each has only one kind of hydrogen and only one kind of carbon. They all belong to the family  $(\text{CH})_n$ .

Cubane has a molecular ion in the mass spectrum at 104, correct for  $\text{C}_8\text{H}_8$ , only CH stretches in the IR at  $3000\text{ cm}^{-1}$ , a singlet in the proton NMR at 4.0 ppm, and a single line in the carbon



cyclobutadiene



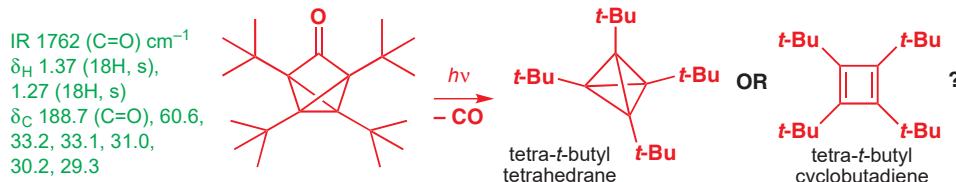
tetrahedrane



cubane

NMR at 47.3 ppm. It is a very symmetrical molecule and a stable one in spite of all those four-membered rings.

Stable compounds with a cyclobutadiene and a tetrahedrane core can be made if each hydrogen atom is replaced by a *t*-butyl group. The very large groups round the edge of the molecule repel each other and hold the inner core tightly together. Now another difficulty arises—it is rather hard to tell the compounds apart. They both have four identical carbon atoms in the core and four identical *t*-butyl groups round the edge. The starting material for a successful synthesis of both was the tricyclic ketone below identified by its strained C=O stretch and partly symmetrical NMR spectra. When this ketone was irradiated with UV light (indicated by '*hv*' in the scheme), carbon monoxide was evolved and a highly symmetrical compound (*t*-BuC)<sub>4</sub> was formed. But which compound was it?



► You can read more about the synthesis of cubane in Chapter 36, when we discuss the rearrangement reactions that were used to make it.

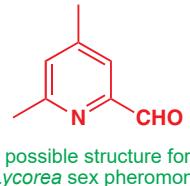
The story is made more complicated (but in the end easier!) by the discovery that this compound on heating turned into another very similar compound. There are only two possible structures for (*t*-BuC)<sub>4</sub>, so clearly one compound must be the tetrahedrane and one the cyclobutadiene. The problem simplifies with this discovery because it is easier to distinguish two possibilities when you can make comparisons between two sets of spectra. Here both compounds gave a molecular ion in the mass spectrum, neither had any interesting absorptions in the IR, and the proton NMRs could belong to either compound as they simply showed four identical *t*-Bu groups. So did the carbon NMR, of course, but it showed the core too. The first product had only saturated carbon atoms, while the second had a signal at 152.7 ppm for the unsaturated carbons. The tetrahedrane is formed from the tricyclic ketone on irradiation but it isomerizes to the cyclobutadiene on heating.

### Identifying compounds from nature

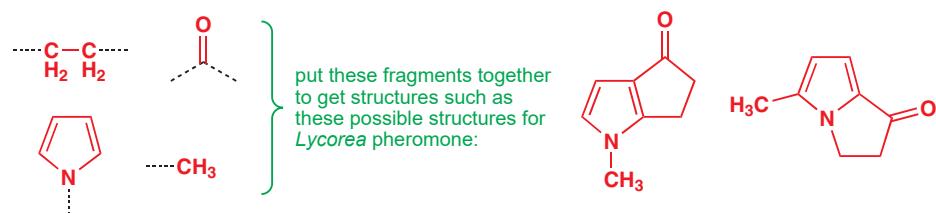
The next molecules we need to know how to identify are those discovered from nature—natural products. These often have biological activity and many useful medicines have been discovered this way. We shall look at a few examples from different fields. The first is the sex pheromone of the Trinidad butterfly *Lycorea ceres ceres*. The male butterflies start courtship by emitting a tiny quantity of a volatile compound. Identification of this type of compound is very difficult because of the minute amounts available but this compound was crystallized and gave enough for a mass spectrum and an IR. The highest peak in the mass spectrum was at 135. This is an odd number so we might have one nitrogen atom and a possible composition of C<sub>8</sub>H<sub>9</sub>ON. The IR showed a carbonyl peak at 1680  $\text{cm}^{-1}$ . With only this meagre information, the first proposals were for a pyridine aldehyde.

Eventually a little more compound (6 mg!) was available and a proton NMR spectrum was run. This showed at once that this structure was wrong. There was no aldehyde proton and only one methyl group. More positive information was the pair of triplets showing a  $-\text{CH}_2\text{CH}_2-$  unit between two electron-withdrawing groups (N and C=O?) and the pair of doublets for neighbouring protons on an aromatic ring, although the chemical shift and the coupling constant are both rather small for a benzene ring.

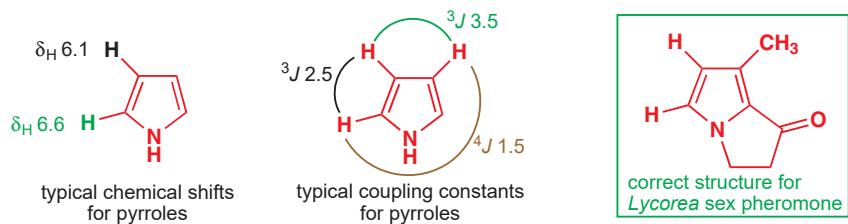
If we look at what we have got so far, we see that we have accounted for four carbon atoms in the methyl and carbonyl groups and the  $-\text{CH}_2\text{CH}_2-$  unit. This leaves only four carbon atoms for the aromatic ring. We must use nitrogen too as the only possibility is a pyrrole ring. Our fragments are now those shown below (the black dotted lines show joins to another fragment). These account for all the atoms in the molecule and suggest structures such as these.



► Pyrrole was introduced in Chapter 7, p. 162.



Now we need to use the known chemical shifts and coupling constants for these sorts of molecules. An N–Me group would normally have a larger chemical shift than 2.2 ppm so we prefer the methyl group on a carbon atom of the pyrrole ring. Typical shifts and coupling constants around pyrroles are shown below. Chemists do not, of course, remember these numbers; we look them up in tables. Our data, with chemical shifts of 6.09 and 6.69 ppm and a coupling constant of 2.5 Hz, clearly favour hydrogen atoms in the 2 and 3 positions, and suggest this structure for the sex pheromone, which was confirmed by synthesis and is now accepted as correct.



## Tables

The final section of this chapter contains some tables of NMR data, which we hope you will find useful in solving problems. In Chapter 13 there were a few guides to chemical shift—summaries of patterns that you might reasonably be expected to remember. But we have left the main selections of hard numbers—tables that *you are not expected to remember*—until now. There are a few comments to explain the tables, but you will probably want to use this section as reference rather than bedtime reading. The first four tables give detailed values for various kinds of compounds and the final table gives a simple summary. We hope that you will find this last table particularly useful.

### Effects of electronegativity

This table shows how the electronegativity of the atom attached directly to a methyl group affects the shifts of the  $\text{CH}_3$  protons ( $\delta_{\text{H}}$ ) and the  $\text{CH}_3$  carbon atom ( $\delta_{\text{C}}$ ) in their NMR spectra.

Chemical shifts of methyl groups attached to different atoms

Element	Electronegativity	Compound	$\delta_{\text{H}}$ , ppm	$\delta_{\text{C}}$ , ppm
Li	1.0	$\text{CH}_3\text{—Li}$	-1.94	-14.0
Si	1.9	$\text{CH}_3\text{—SiMe}_3$	0.0	0.0
I	2.7	$\text{CH}_3\text{—I}$	2.15	-23.2
S	2.6	$\text{CH}_3\text{—SMe}$	2.13	18.1
N	3.1	$\text{CH}_3\text{—NH}_2$	2.41	26.9
Cl	3.2	$\text{CH}_3\text{—Cl}$	3.06	24.9
O	3.4	$\text{CH}_3\text{—OH}$	3.50	50.3
F	4.0	$\text{CH}_3\text{—F}$	4.27	75.2

## Effects of functional groups

Many substituents are more complicated than just a single atom and electronegativity is only part of the story. We need to look at all the common substituents and see what shifts they cause relative to the CH skeleton of the molecule. Our zero really ought to be at about 0.9 ppm for protons and at 8.4 ppm for carbon, that is, where ethane ( $\text{CH}_3\text{—CH}_3$ ) resonates, and not at the arbitrary zero allocated to  $\text{Me}_4\text{Si}$ . In the table below we give such a list. The reason for this is that the shifts (from  $\text{Me}_4\text{Si}$ ) themselves are not additive but the shift differences (from 0.9 or 8.4 ppm) are.

Chemical shifts of methyl groups bonded to functional groups

	Functional group	Compound	$\delta_{\text{H}}$ , ppm	$\delta_{\text{H}} - 0.9$ , ppm	$\delta_{\text{C}}$ , ppm	$\delta_{\text{C}} - 8.4$ , ppm
1	silane	$\text{Me}_4\text{Si}$	0.0	-0.9	0.0	-8.4
2	alkane	$\text{Me—Me}$	0.86	0.0	8.4	0.0
3	alkene	$\text{Me}_2\text{C}=\text{CMe}_2$	1.74	0.84	20.4	12.0
4	benzene	$\text{Me—Ph}$	2.32	1.32	21.4	13.0
5	alkyne	$\text{Me—C}=\text{C—R}^{\text{a}}$	1.86	0.96		
6	nitrile	$\text{Me—CN}$	2.04	1.14	1.8	-6.6
7	acid	$\text{Me—CO}_2\text{H}$	2.10	1.20	20.9	11.5
8	ester	$\text{Me—CO}_2\text{Me}$	2.08	1.18	20.6	11.2
9	amide	$\text{Me—CONHMe}$	2.00	1.10	22.3	13.9
10	ketone	$\text{Me}_2\text{C=O}$	2.20	1.30	30.8	21.4
11	aldehyde	$\text{Me—CHO}$	2.22	1.32	30.9	21.5
12	sulfide	$\text{Me}_2\text{S}$	2.13	1.23	18.1	9.7
13	sulfoxide	$\text{Me}_2\text{S=O}$	2.71	1.81	41.0	32.6
14	sulfone	$\text{Me}_2\text{SO}_2$	3.14	2.24	44.4	36.0
15	amine	$\text{Me—NH}_2$	2.41	1.51	26.9	18.5
16	amide	$\text{MeCONH—Me}$	2.79	1.89	26.3	17.9
17	nitro	$\text{Me—NO}_2$	4.33	3.43	62.5	53.1
18	ammonium salt	$\text{Me}_4\text{N}^+\text{Cl}^-$	3.20	2.10	58.0	49.6
19	alcohol	$\text{Me—OH}$	3.50	2.60	50.3	44.3
20	ether	$\text{Me—OBu}$	3.32	2.42	58.5	50.1
21	enol ether	$\text{Me—OPh}$	3.78	2.88	55.1	46.7
22	ester	$\text{Me—CO}_2\text{Me}$	3.78	2.88	51.5	47.1
23	phosphonium salt	$\text{Ph}_3\text{P}^+—\text{Me}$	3.22	2.32	11.0	2.2

<sup>a</sup>R=CH<sub>2</sub>OH; compound is but-2-yn-1-ol.

The effects of groups based on carbon (the methyl group is joined directly to another carbon atom) appear in entries 2 to 11. All the electron-withdrawing groups based on carbonyl and cyanide have about the same effect (1.1–1.3 ppm downfield shift from 0.9 ppm). Groups based on nitrogen (Me—N bond) show a similar progression through amine, ammonium salt, amide, and nitro compound (entries 15–18). Finally, all the oxygen-based groups (Me—O bond) show large shifts (entries 19–22).

### Effects of substituents on CH<sub>2</sub> groups

It is more difficult to give a definitive list for CH<sub>2</sub> groups as they have two substituents. In the table below we set one substituent as phenyl (Ph) just because so many compounds of this kind are available, and give the actual shifts relative to PhCH<sub>2</sub>CH<sub>3</sub> for protons (2.64 ppm) and PhCH<sub>2</sub>CH<sub>3</sub> for carbon (28.9 ppm), again comparing the substituent with the CH skeleton.

If you compare the shifts caused on a CH<sub>2</sub> group by each functional group in the table below with the shifts caused on a CH<sub>3</sub> group by the same functional group in the table on p. 423 you will see that they are broadly the same.

Chemical shifts of CH<sub>2</sub> groups bonded to phenyl and functional groups

	Functional group	Compound	$\delta_H$ , ppm	$\delta_H - 2.64$ , ppm	$\delta_C$ , ppm	$\delta_C - 28.9$ , ppm
1	silane	PhCH <sub>2</sub> —SiMe <sub>3</sub>	?	?	27.5	-1.4
2	hydrogen	PhCH <sub>2</sub> —H	2.32	-0.32	21.4	-7.5
3	alkane	PhCH <sub>2</sub> —CH <sub>3</sub>	2.64	0.00	28.9	0.0
4	benzene	PhCH <sub>2</sub> —Ph	3.95	1.31	41.9	13.0
5	alkene	PhCH <sub>2</sub> —CH=CH <sub>2</sub>	3.38	0.74	41.2	12.3
6	nitrile	PhCH <sub>2</sub> —CN	3.70	1.06	23.5	-5.4
7	acid	PhCH <sub>2</sub> —CO <sub>2</sub> H	3.71	1.07	41.1	12.2
8	ester	PhCH <sub>2</sub> —CO <sub>2</sub> Me	3.73	1.09	41.1	12.2
9	amide	PhCH <sub>2</sub> —CONEt <sub>2</sub>	3.70	1.06	?	?
10	ketone	(PhCH <sub>2</sub> ) <sub>2</sub> C=O	3.70	1.06	49.1	20.2
11	thiol	PhCH <sub>2</sub> —SH	3.69	1.05	28.9	0.0
12	sulfide	(PhCH <sub>2</sub> ) <sub>2</sub> S	3.58	0.94	35.5	6.6
13	sulfoxide	(PhCH <sub>2</sub> ) <sub>2</sub> S=O	3.88	1.24	57.2	28.3
14	sulfone	(PhCH <sub>2</sub> ) <sub>2</sub> SO <sub>2</sub>	4.11	1.47	57.9	29.0
15	amine	PhCH <sub>2</sub> —NH <sub>2</sub>	3.82	1.18	46.5	17.6
16	amide	HCONH—CH <sub>2</sub> Ph	4.40	1.76	42.0	13.1
17	nitro <sup>a</sup>	PhCH <sub>2</sub> —NO <sub>2</sub>	5.20	2.56	81.0	52.1
18	ammonium salt	PhCH <sub>2</sub> —NMe <sub>3</sub> <sup>+</sup>	4.5/4.9		55.1	26.2
19	alcohol	PhCH <sub>2</sub> —OH	4.54	1.80	65.3	36.4
20	ether	(PhCH <sub>2</sub> ) <sub>2</sub> O	4.52	1.78	72.1	43.2
21	enol ether	PhCH <sub>2</sub> —OAr <sup>a</sup>	5.02	2.38	69.9	41.0
22	ester	MeCO <sub>2</sub> —CH <sub>2</sub> Ph	5.10	2.46	68.2	39.3
23	phosphonium salt	Ph <sub>3</sub> P <sup>+</sup> —CH <sub>2</sub> Ph	5.39	2.75	30.6	1.7
24	chloride	PhCH <sub>2</sub> —Cl	4.53	1.79	46.2	17.3
25	bromide	PhCH <sub>2</sub> —Br	4.45	1.81	33.5	4.6

<sup>a</sup> Compound is (4-chloromethylphenoxyethyl)benzene.

### Shifts of a CH group

We can do the same with a CH group, and in the left-hand side of the table below we take a series of isopropyl compounds, comparing the measured shifts with those for the central proton ( $\text{CHMe}_2$ ) or carbon ( $\text{CHMe}_2$ ) of 2-methylpropane. We set two of the substituents as methyl groups and just vary the third. Yet again the shifts for the same substituent are broadly the same.

Effects of  $\alpha$  and  $\beta$  substitution on  $^1\text{H}$  and  $^{13}\text{C}$  NMR shifts in  $\text{Me}_2\text{CHX}^\text{a}$

X	Effects on $\text{C}_\alpha$ ( $\text{Me}_2\text{CH}-\text{X}$ ), ppm				Effects on $\text{C}_\beta$ ( $\text{Me}_2\text{CH}-\text{X}$ ), ppm			
	$\delta_\text{H}$	$\delta_\text{H} - 1.68$	$\delta_\text{C}$	$\delta_\text{C} - 25.0$	$\delta_\text{H}$	$\delta_\text{H} - 0.9$	$\delta_\text{C}$	$\delta_\text{C} - 8.4$
Li			10.2	-14.8			23.7	17.3
H	1.33	-0.35	15.9	-9.1	0.91	0.0	16.3	7.9
Me	1.68	0.00	25.0	0.0	0.89	0.0	24.6	16.2
$\text{CH}=\text{CH}_2$	2.28	0.60	32.0	7.0	0.99	0.09	22.0	13.6
Ph	2.90	1.22	34.1	9.1	1.24	0.34	24.0	15.6
CHO	2.42	0.74	41.0	16.0	1.12	0.22	15.5	7.1
COMe	2.58	0.90	41.7	16.7	1.11	0.21	27.4	19.0
$\text{CO}_2\text{H}$	2.58	0.90	34.0	4.0	1.20	0.30	18.8	10.4
$\text{CO}_2\text{Me}$	2.55	0.87	33.9	8.9	1.18	0.28	19.1	10.7
$\text{CONH}_2$	2.40	0.72	34.0	9.0	1.08	0.18	19.5	11.1
CN	2.71	1.03	20.0	-5.0	1.33	0.43	19.8	11.4
$\text{NH}_2$	3.11	1.43	42.8	17.8	1.08	0.18	26.2	17.8
$\text{NO}_2$	4.68	3.00	78.7	53.7	1.56	0.66	20.8	12.4
SH	3.13	1.45	30.6	5.6	1.33	0.43	27.6	19.2
$\text{Si-Pr}$	3.00	1.32	33.5	8.5	1.27	0.37	23.7	15.3
OH	4.01	2.33	64.2	39.2	1.20	0.30	25.3	16.9
$\text{O-i-Pr}$	3.65	1.97	68.4	43.4	0.22	0.22	22.9	14.5
$\text{O}_2\text{CMe}$	5.00	3.32	67.6	42.6	1.22	0.32	21.4(8)	17.(0/4)
Cl	4.19	2.51	53.9	28.9	1.52	0.62	27.3	18.9
Br	4.29	2.61	45.4	20.4	1.71	0.81	28.5	20.1
I	4.32	2.36	31.2	6.2	1.90	1.00	21.4	13.0

<sup>a</sup> There is coupling between the CH and the  $\text{Me}_2$  groups in the proton NMR.

### Shifts in proton NMR are easier to calculate and more informative than those in carbon NMR

This final table, on p. 426, helps to explain something we have avoided so far. Correlations of shifts caused by substituents in proton NMR really work very well. Those in  $^{13}\text{C}$  NMR work much less well and more complicated equations are needed. More strikingly, the proton shifts often seem to fit better with our understanding of the chemistry of the compounds. There are two main reasons for this.

First, the carbon atom is much closer to the substituent than the proton. In the compounds in the table on p. 423 the methyl carbon atom is directly bonded to the substituent, while the protons are separated from it by the carbon atom of the methyl group. If the functional group is based on a large electron-withdrawing atom like sulfur, the protons will experience a simple inductive electron withdrawal and have a proportional downfield shift. The carbon atom is close enough to the sulfur atom to be shielded as well by the lone-pair electrons in the large  $3\text{sp}^3$  orbitals. The proton shift caused by S in  $\text{Me}_2\text{S}$  is about the same (1.23 ppm) as that caused by a set of more or less equally strong electron-withdrawing groups like CN (1.14 ppm) or ester (1.18 ppm). The carbon shift (9.7 ppm) is less than that caused by an ester (11.2 ppm) but much *more* than that caused by CN, which actually shifts the carbon upfield (-6.6 ppm) relative to the effect of a methyl group.

Approximate additive functional group (X) shifts in  $^1\text{H}$  NMR spectra

Entry	Functional group X	$^1\text{H}$ NMR shift difference <sup>a</sup> , ppm
1	alkene ( $-\text{C}=\text{C}-$ )	1.0
2	alkyne ( $-\text{C}\equiv\text{C}-$ )	1.0
3	phenyl ( $-\text{Ph}$ )	1.3
4	nitrile ( $-\text{C}\equiv\text{N}$ )	1.0
5	aldehyde ( $-\text{CHO}$ )	1.0
6	ketone ( $-\text{COR}$ )	1.0
7	acid ( $-\text{CO}_2\text{H}$ )	1.0
8	ester ( $-\text{CO}_2\text{R}$ )	1.0
9	amide ( $-\text{CONH}_2$ )	1.0
10	amine ( $-\text{NH}_2$ )	1.5
11	amide ( $-\text{NHCOR}$ )	2.0
12	nitro ( $-\text{NO}_2$ )	3.0
13	thiol ( $-\text{SH}$ )	1.0
14	sulfide ( $-\text{SR}$ )	1.0
15	sulfoxide ( $-\text{SOR}$ )	1.5
16	sulfone ( $-\text{SO}_2\text{R}$ )	2.0
17	alcohol ( $-\text{OH}$ )	2.0
18	ether ( $-\text{OR}$ )	2.0
19	aryl ether ( $-\text{OAr}$ )	2.5
20	ester ( $-\text{O}_2\text{CR}$ )	3.0
21	fluoride ( $-\text{F}$ )	3.0
22	chloride ( $-\text{Cl}$ )	2.0
23	bromide ( $-\text{Br}$ )	2.0
24	iodide ( $-\text{I}$ )	2.0

<sup>a</sup> To be added to 0.9 ppm for  $\text{MeX}$ , 1.3 ppm for  $\text{CH}_2\text{X}$ , or 1.7 ppm for  $\text{CHX}$ .

Second, the carbon shift is strongly affected not only by what is directly joined to that atom ( $\alpha$  position), but also by what comes next ( $\beta$  position). The right-hand half of the table on p. 424 shows what happens to methyl shifts when substituents are placed on the next carbon atom. There is very little effect on the proton spectrum: all the values are much less than the shifts caused by the same substituent on a methyl group in the table on p. 423. Carbonyls give a down-field shift of about 1.2 ppm when directly joined to a methyl group, but only of about 0.2 ppm when one atom further away. By contrast, the shifts in the carbon spectrum are of the same order of magnitude in the two tables, and the  $\beta$  shift may even be greater than the  $\alpha$  shift! The CN group shifts a directly bonded methyl group upfield (-6.6 ppm) when directly bonded, but downfield (14.4 ppm) when one atom further away. This is an exaggerated example, but the point is that these carbon shifts must *not* be used to suggest that the CN group is electron-donating in the  $\alpha$  position and electron-withdrawing in the  $\beta$  position. The carbon shifts are erratic but the proton shifts give us useful information and are worth understanding as a guide to both structure determination and the chemistry of the compound.

When you use this table and are trying to interpret, say, a methyl group at 4.0 ppm then you have no problem. Only one group is attached to a methyl group so you need a single shift value—it might be a methyl ester, for example. But when you have a  $\text{CH}_2$  group at 4.5 ppm and you are interpreting a downfield shift of 3.2 ppm you must beware. There are *two* groups attached to each  $\text{CH}_2$  group and you might need a single shift of about 3 ppm (say, an ester again) or two shifts of 1.5 ppm, and so on. The shifts are additive.

## 延伸阅读

A reminder: you will find it an advantage to have one of the short books on spectroscopic analysis to hand as they give explanations, comprehensive tables of data, and problems. We recommend *Spectroscopic Methods in Organic Chemistry* by D. H. Williams and Ian Fleming, McGraw-Hill, London, 6th edn, 2007.

Other books include R. M. Silverstein, F. X. Webster, and D. J. Kiemle, *Spectrometric Identification of Organic Compounds*,

Wiley, 2005 and a book of problems: L. D. Field, S. Sternhell, and J. R. Kalman, *Organic Structures from Spectra*, 3rd edn, Wiley, 2003.

The  $^{13}\text{C}$  NMR of ketene was reported by J. Firl and W. Runger, *Angew. Chem. Int. Ed.*, 1973, **12**, 668, the tetrahedrane/cyclobutadiene story is expounded by G. Maier in *Angew. Chem. Int. Ed.*, 1988, **27**, 309, and the *Lycorea* sex pheromone story by G. Meinwald and team, *Science*, 1968, **164**, 1174.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 19

## 烯烃的亲电加成

### 联系

#### ► 基础

- 形成烯烃的消除反应 ch17
- 碳阳离子的稳定性，它们在  $S_N1$  中的反应 ch15

#### 目标

- 简单、未共轭烯烃与亲电试剂的反应
- 将  $C=C$  双键用亲电加成转化为其他官能团
- 如何预测不对称烯烃在哪一端与亲电试剂反应
- 烯烃的立体选择性、立体专一性、区域选择性反应
- 如何通过亲电加成反应制备卤代烷、环氧、醇和醚
- 如何将烯烃断裂为两个羰基化合物

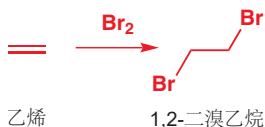
#### ► 展望

- 对带有氧取代基的烯烃(烯醇和烯醇盐)的亲电加成 ch20
- 对芳环的亲电加成 ch21
- 对缺电子烯烃的亲核加成 ch22
- 烯烃的周环反应 ch34
- 重排反应 ch36

## 烯烃与溴反应

溴( $Br_2$ )是棕色的，也是烯烃的经典检验方法之一，烯烃会使棕色的溴的水溶液转变为无色。烯烃使溴水褪色：烯烃与溴发生反应。这个反应的产物是二溴烷烃，右侧的反应展示了最简单的烯烃，乙烯的情况。

为了理解这个反应，乙基本章中您会遇到的其他类似反应，您需要像我们在 Chapter 5 中那样思考，从亲核试剂、亲电试剂的角度考察反应性。每当您遇到一个新的反应，您应该立刻忖度，“哪个试剂是亲核试剂，那个试剂是亲电试剂？”很明显，烯烃和溴都不带电，但  $Br_2$  有一个低能的空轨道( $Br-Br \sigma^*$ )，并因此是亲电试剂。 $Br-Br$  键格外脆弱，溴与很多亲核试剂按如下方式反应。



在与乙烯的反应中，烯烃一定是亲核试剂，它的 HOMO 是  $C=C \pi$  键。其他简单烯烃也类似地富电子，通常作为亲核试剂来进攻亲电试剂。

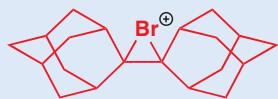
- 简单的非共轭烯烃是亲核试剂，并与亲电试剂反应。

当它与  $\text{Br}_2$  反应时，烯烃充满的  $\pi$  轨道 (HOMO) 会与溴空的  $\sigma^*$  轨道反应，给出产物。那么产物会是什么样的？首先请考察涉及到的轨道。



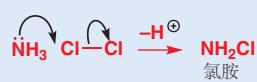
### 我们怎么知道溴𬭩离子的存在？

空阻大的烯烃形成的溴𬭩离子对亲核进攻有抗性。  
在下面这个大空阻的锂资质，溴𬭩离子足够稳定，可以被 X-射线晶体学表征。



### 氯胺

您有没有对普遍观点（和厂商的商标上）关于不能将两种不同类型的清洁剂混合的警告存疑？这种危险源于亲核试剂对氯单质（亲电试剂）的进攻。一些清洁溶液包含氯单质（漂白剂，用于杀死霉和细菌，通常用于浴室），还有的清洁剂含有氨（溶解脂类沉淀，通常用于厨房）。氨是亲核的，氯是亲电的，它们的产物是高毒且易爆的氯胺（chloramines）， $\text{NH}_2\text{Cl}$ ,  $\text{NHCl}_2$ , 和  $\text{NCl}_3$ 。



Interactive mechanism for reaction of ethylene with bromine

▶ 将第二步与亲核试剂进攻环氧的方式对比，Chapter 15, p. 354.

$\pi$  轨道最高的电子密度就分布在两个碳原子之间，因此这是我们预料的溴会进攻的位置。 $\pi$  HOMO 能与  $\sigma^*$  LUMO 唯一的成键相互作用方式是  $\text{Br}_2$  以其一端接近——这是产物形成的方式。对称的三元环产物被称作溴𬭩离子（溴离子，bromonium ion）。



我们如何绘制溴𬭩离子形成的机理？我们有两种选择。最简单的方式是表现  $\pi$  键的中间进攻  $\text{Br}-\text{Br}$ ，以反映我们在轨道上观察到的变化。

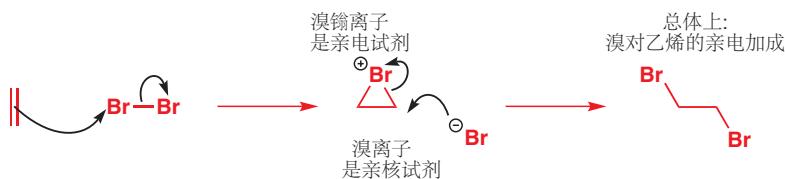


但这种表示方式有一个问题：由于只有一对电子发生转移，我们又是如何形成两根新的 C–Br 键的呢？因此我们需要将 C–Br 键都表示成半键。但溴𬭩离子是一个带有两根真正 C–Br 键的中间体（侧边的文字框提供了证据）。因此一种可替代的表述方式包含溴的孤对电子所发起的箭头。



我们认为，第一种表示方法更准确地涉及了关键的轨道相互作用，因此我们会使用第一种，而第二种也是可接受的。

当然，这个反应的最终产物并不是溴𬭩离子。这个反应的第一步会马上发生：溴𬭩离子本身作为亲电试剂，与溴单质加成步骤中失去的溴离子反应。我们现在可以画出整个反应正确的机理，它被称作对双键的亲电加成 (electrophilic addition)，因为溴单质 ( $\text{Br}_2$ ) 是一个亲电试剂。总体上，溴分子添加到了烯烃的双键上。



$\text{Br}^-$  对溴𬭩离子的进攻是一个常规的  $S_{\text{N}}2$  取代反应——关键的轨道包括溴离子的 HOMO 和有张力的三元环中其中一根 碳–溴 键的  $\sigma^*$ 。和所有  $S_{\text{N}}2$  反应一样，亲核试剂通过从离去基团的正后方接近，以保持与  $\sigma^*$  的最大重叠，并使受进攻的碳上发生构型翻转。更复杂的反应（后文讨论）的立体化学结果是这种机理的一个重要证据。

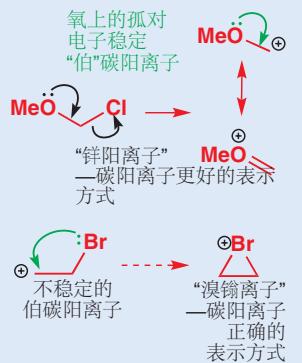
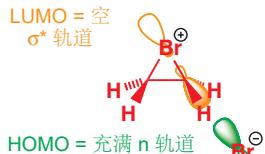
您可能不解，为什么溴进攻溴𬭩离子中一个碳原子，而不是带有正电荷的溴原子。事实上，它可以这样做，但这样只会重新生成溴单质和烯烃：即反应的第一步是可逆的。

### 另一种思考溴𬭩离子的方式

您可以将溴𬭩离子想象为被与临近的溴原子的相互作用所稳定的碳阳离子。您已经看到过，氧对碳阳离子有相似的作用——例如氯化 MOM 的  $S_{\text{N}}1$  取代中的锌离子中间体，p. 338, Chapter 15。

溴原子的距离较远，且三元环存在环张力，但由于溴在周期表中周期数较高，并含有较分散的孤对电子，它于是也可有相似的稳定化效应。

这两种类型的稳定化不是等价的：碳阳离子与溴𬭩离子是两种不同的分子，形状也不同；而锌离子与其碳阳离子只是同一分子的两种表示方式。杂原子对其邻位阳离子中心，通过用至少一对孤电子形成三元环中间体的稳定化作用，不局限于溴或其他卤素，在氧、硫、硒化合物的化学中也是一个重要的方面，您会在 Chapter 27 中看到它们。

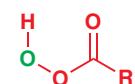


## 烯烃氧化生成环氧

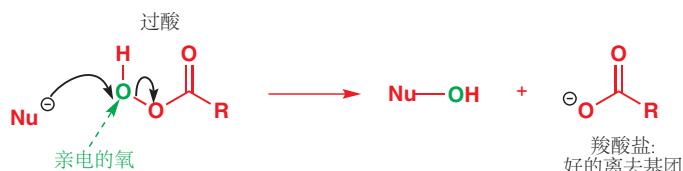
溴对烯烃的亲电加成是一个氧化反应。开始的烯烃的氧化程度 (oxidation level) 与醇相同，而产物则有两个与醇的氧化程度相同的碳原子——况且二溴代物的消除给出的是炔烃 (Chapter 17, p. 398)。有大量的其他氧化剂，包含亲电的氧原子，可以与亲核的烯烃反应，产出环氧 epoxides (氧丙环, oxiranes)。您可以将环氧视作溴𬭩离子的氧类似物，但和溴𬭩离子不同的是，它们还算稳定。



这个反应最常用的  
氧化剂是过羧酸:



最简单的环氧，环氧乙烷 (ethylene oxide, 或 oxirane 本身)，可以由乙烯与氧在高温，银催化下的直接氧化，以吨量级生产。这些条件很难适合一般实验室采用，而实验室最常用的环氧化试剂是过羧酸 peroxy-acids (或称过酸 peracids)，过酸中羧基与酸性氢间有一个额外的氧原子——它们是过氧化氢 ( $\text{H}_2\text{O}_2$ ) 的酯。它们的酸性比羧酸弱，因为它们的共轭碱不再能因到羧基上的离域而稳定。但它的氧原子 (绿色所示的) 是亲电的，因为亲核试剂的进攻会取代羧基，一个好的离去基团。过酸的 LUMO 是弱的 O–O 键的  $\sigma^*$  轨道。

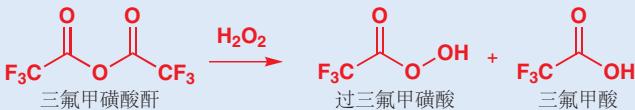


■ 您已经见过，环氧可通过分子内取代反应形成，但烯烃的环氧化是更加重要的方式。环氧的另一种名称 (氧丙环, oxirane)，来源于环的系统命名方法：“ox (氧/𫫇)”表示 O 原子，“ir”表示三元环，而 “ane” 表示饱和。您可能会遇到氧丁环 oxetane (记得 Wittig 反应中的氧磷丁环, Chapter 11, p. 238)，而 THF 从不被称作氧戊环/𫫇戊环 (oxolane), 二氧戊环 (dioxolane) 是五元环状缩醛的另一个名称。

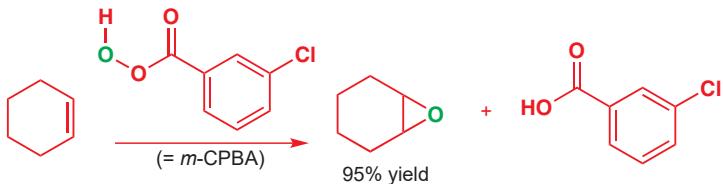


### 制备过酸

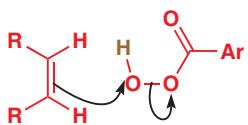
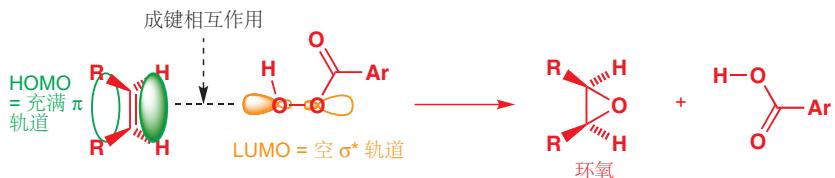
过酸是由其相应的酸酐和高浓度的过氧化氢制备的。通常，过酸的母体酸酸性越强（酸根离子离去性越好），过酸的氧化性就越强：最强氧化性的过酸之一是过三氟甲磺酸 (peroxy-trifluoroacetic acid)。过氧化氢，在很高浓度下(> 80%)，潜在易爆，并难以运输，



最常用的过酸被称作 *m*-CPBA, 或*间*氯代过氧苯甲酸(*meta*-chloroperoxybenzoic acid). *m*-CPBA是一种安全的结晶固体。下面是它与环己烯反应以 95% 产率给出环氧的过程。

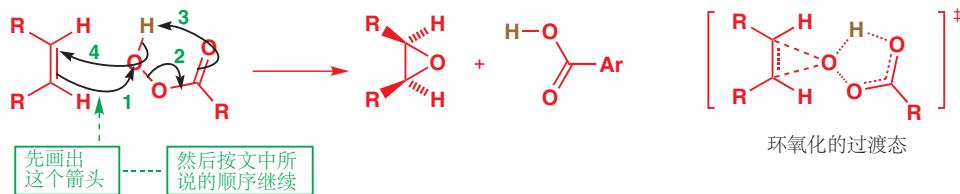


如您所料，亲核性的烯烃从其 HOMO，即  $\pi$  轨道的中心进攻过酸。首先，所涉及的轨道如是。



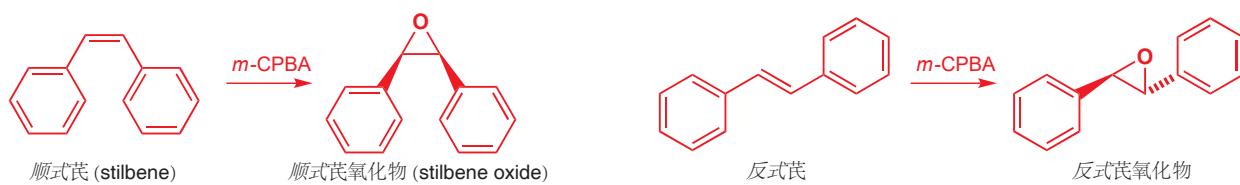
下面是弯曲箭头的机理。机理的本质是烯烃的  $\pi$  轨道对弱的、极化的、亲电的 O–O 键的进攻，我们可以像侧边栏中所示的那样画得更简单。但在真实的反应中，有一个质子（棕色所示）从环氧转移到羧酸副产物中。小心地绘制弯曲箭头，您可以将它们在一步中表示。由亲核的  $\pi$  键出发：将电子送至氧，断裂 O–O 键，在原来的羰基中的电子去夺质子时形成新的羰基键，并用旧的 O–H 键的电子形成环氧中的第二根 C–O 键。不要对意大利面式的外观 (spaghetti effect) 感到为难——当您思考过程的机理时，每个箭头都很合乎逻辑。这个反应的过渡态将成键和断键过程显示得更清晰。

 Interactive mechanism for epoxidation of ethylene



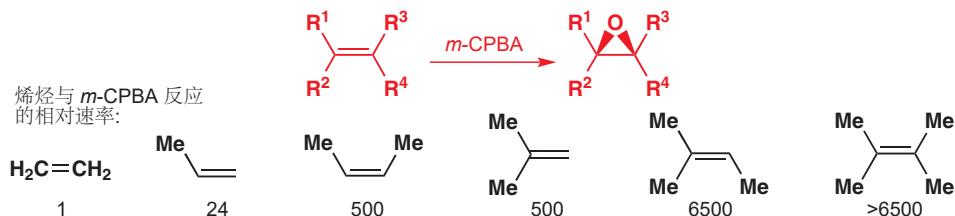
环氧化是立体专一性的

由于环氧中两根新的 C–O 都在烯烃  $\pi$  键的同一面形成，烯烃的几何结构会在环氧的立体化学中得以反映。这个反应因此是立体选择性的。下面是两个展现这一特点的例子：其中顺式烯烃给出顺式环氧，而反式烯烃给出反式环氧。

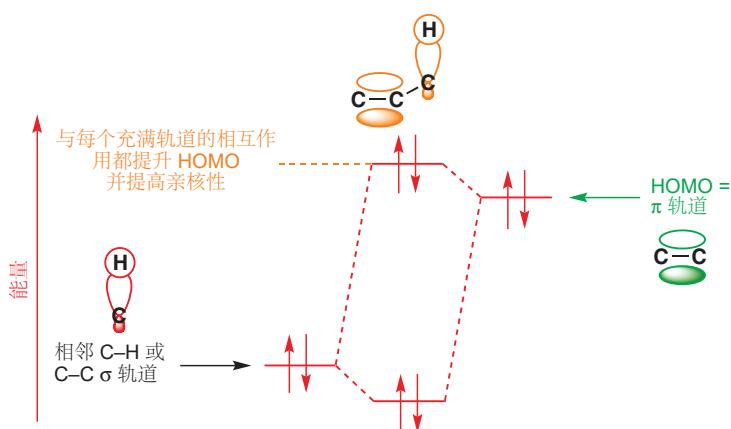


### 多取代的烯烃环氧化进行得快

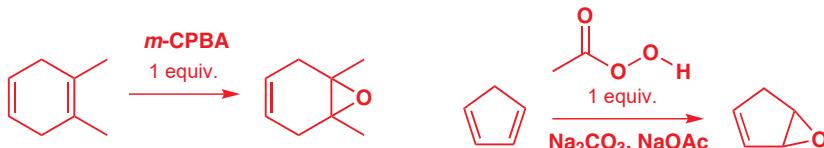
过酸可以与带有任何取代模式的烯烃 (除去与吸电子基团共轭的，它们需要另一种试剂：Chapter 22) 给出环氧，而下方的数据显示，根据双键上取代基数目不同，环氧化的速率多种多样。



现在，不仅多取代的烯烃更加稳定 (Chapter 17)，而且多取代的烯烃也更加亲核。我们在 Chapter 15 中向您介绍，烷基是给电子的，因为它们能稳定碳阳离子。相同的给电子效应提升了双键 HOMO 的能量，使之更加亲核。您可以用这种方式思考：每根允许其  $\sigma$  轨道和烯烃的  $\pi$  轨道相互作用的 C–C 或 C–H 键都会稍稍提高烯烃的 HOMO，如下能级图所示。烯烃取代得越多，能量上升得也就越多。



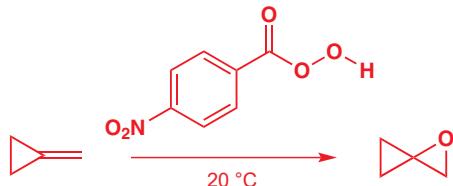
烯烃不同取代模式反应性的差异，可以通过用限量的氧化剂，仅在一对烯烃中更高活性的一个上环氧化以得到利用。在下面的第一个例子中，一个四取代的烯烃优先于另一个顺式二取代烯烃反应。当两个烯烃取代数相同时，其中一个发生的环氧化会减弱另一个的亲核性（新的氧原子是吸电子的，并且双烯烃通常也比烯烃更加亲核：后文）。环戊烯的单环氧化是一个有用的中间体，可以在有保障的条件下由双烯直接环氧化制备。



■ 此处的碳酸钠/乙酸钠用作缓冲，以阻止反应混合物太过酸性——记得，环氧化反应有羧酸作为副产物。一些环氧在酸中是不稳定的，我们稍后会见到。

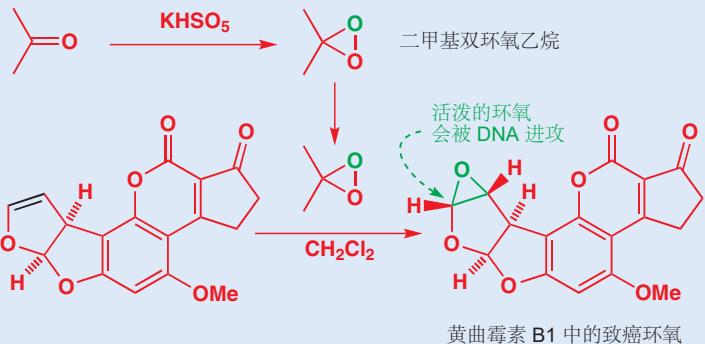
对硝基过苯甲酸是危险而易爆的，它的活性足以生产这种引人注目的高张力螺环环氧 (氧杂螺戊环 oxaspiropentane)，生产它是为了研究它与亲核试剂的反应。

■ 螺环化合物是有两个环以一个原子连接的化合物。与 **稠环** (两个相邻原子连接的) 和 **桥环** (两个不相连原子连接的) 对比 (见 p. 653)。

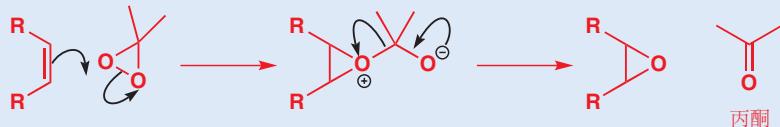


### 二甲基双环氧乙烷和致癌的过氧化物

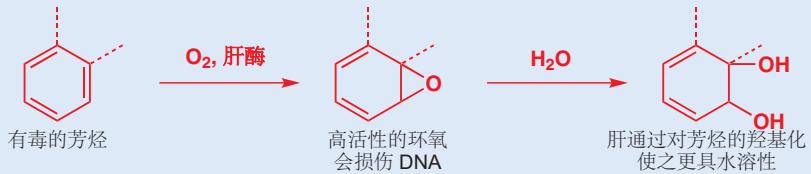
某些真菌，尤其是曲霉菌种 *Aspergillus* sp. (在潮湿谷物上生长的一种)，会生产一类人类已知的最致癌的物质，黄曲霉素 (aflatoxins)，其中一种 (当然，完全天然的) 在人体中会代谢为如下所示的环氧。一些美国化学家决定合成这种环氧，以调查它与 DNA 的反应，并希望能确切地了解它们导致癌症的原理。这种环氧太过活泼，不能通过过酸制备 (由于酸性副产物)，它们使用了一种称为二甲基双环氧乙烷 (二甲基过氧化酮, dimethyldioxirane) 的试剂制备。



二甲基双环氧乙烷由丙酮被 KHSO<sub>5</sub> 氧化得到，但它太过活泼，因此不能在溶液中储存超过很短的一个周期。在环氧化步骤中转移了一个氧原子后，剩下的只是无害的丙酮，如下机理所示。

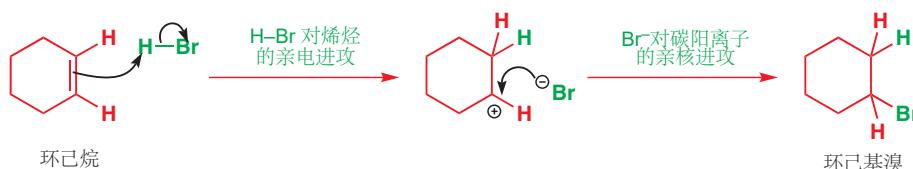


肝是各种进行氧化反应的酶的场所——其目的是通过添加羟基，使不想要的非水溶性分子变得更加极性，以使之溶于水。不幸的是，氧化过程的一些中间体是高活性的环氧，会损伤 DNA。这也是芳香碳氢化物可能导致癌症的原因。注意，用化学 (而不是生物) 方法氧化芳烃是十分困难的。



## 不对称烯烃的亲电加成是区域选择性的

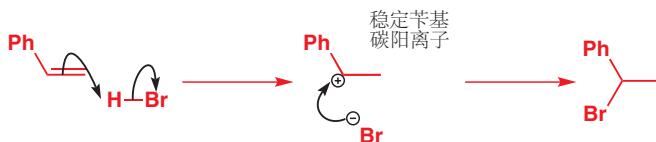
在环氧化反应、溴单质的亲电加成反应中，烯烃的两端都添加了同类的原子 (Br 或 O)。但在对其他亲电试剂，例如 H–Br 的亲电加成反应中，就会出现选择：哪个碳得到 H，哪个又得到 Br？您将需要预测和解释不对称烯烃和 HBr 的反应的能力，但我们的考察应该从一种对称烯烃开始——环己烯。下面是发生的变化。当 H–Br 作为亲电试剂时，被进攻的是 H，失去 Br<sup>-</sup>。与溴原子不同的是，氢原子不能形成三元环阳离子——它没有可用的孤对电子。因此一个质子（加成的实质是质子）加成到烯烃上所给出的产物，最好表示为一个碳阳离子。这个碳阳离子迅速地与刚形成的溴离子反应。总体上，H–Br 加入到了烯烃上。这是制备简单溴代烃的一个使用方法。



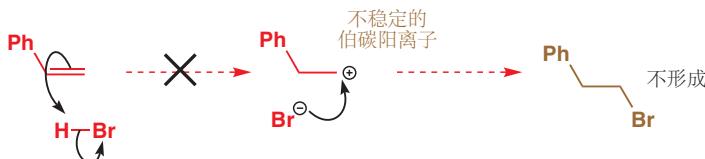
下面是另两个溴代烃的合成，而这时，由于烯烃是不对称的（两端有不同的取代基），我们就需要问了，烯烃的哪段被进攻呢。首先，结果如下。



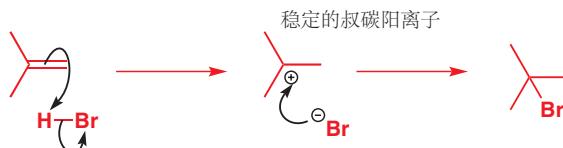
每种情况下，溴原子都结束于较多取代的碳原子，如下的机理解释了原因。苯乙烯 (styrene) 有两种被 HBr 质子化的结构，即使您不知道反应的结果，您也应该能立刻找到，哪个结构是有利的。在一端得质子化给出一个稳定的苄基阳离子，其正电荷离域在苯环中。



在另一端的质子化会给出一个高度不稳定的伯阳离子，因此这个过程不会发生。



在异丁烯那里，您也能得到相同的结果：较稳定的叔碳阳离子导向产物；另一种伯碳阳离子则不会形成。

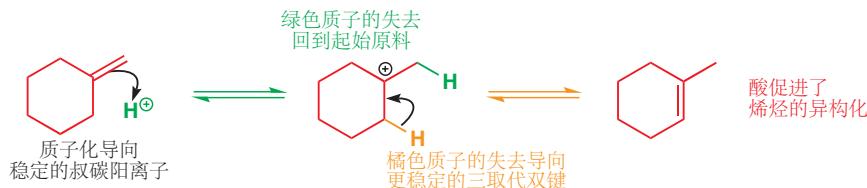


### 马氏规则 (马尔科夫尼科夫规则, Markovnikov's rule)

对于 H-X 对烯烃的亲电加成，有一个传统的准则被称作马氏规则，它这样规定：“质子最终连接在原来双键有较多氢的一侧的碳原子上（氢加氢多）。”虽然这个规则会被人谈起，但我们不建议您去背它。因为就像所有的“规则”一样，理解其背后的原因远比背诵重要得多。例如，您可以预测下面反应的产物；但恕我直言，马尔科夫尼科夫却不能。



烯烃的质子化得到碳阳离子是无庸赘述的。碳阳离子可能如您所见，捕获一个亲核试剂；它们也可以失去一个质子并重新得到烯烃。与之相同的说法是，质子化是可逆的。但失去的不必是相同的质子，可能通过与所得不同的质子的失去得到一个更稳定的烯烃。这意味着，酸，可以催化烯烃的异构化——包括 Z 和 E 之间的几何异构体，以及区域异构体。

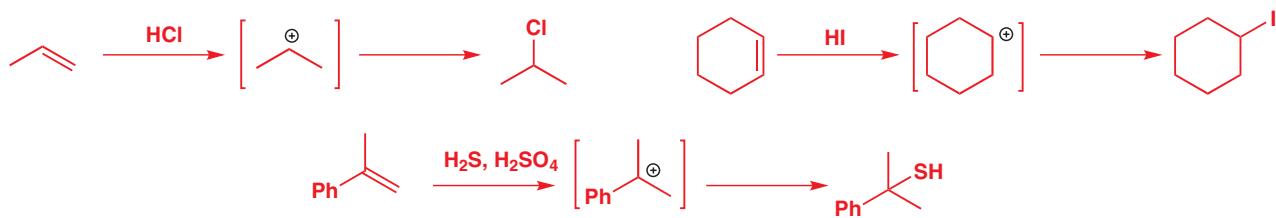


### E1 和异构化

烯烃在酸中的异构化可能是酸性下的 E1 消除通常给出 E 型烯烃的很大一部分原因。在 Chapter 17 中，我们阐释了动力学控制条件是如何导向 E 型烯烃的：在反应条件下，E 和 Z 型烯烃会互相转化，使热力学产物占据上风。同样在 Chapter 12 中也有讨论。

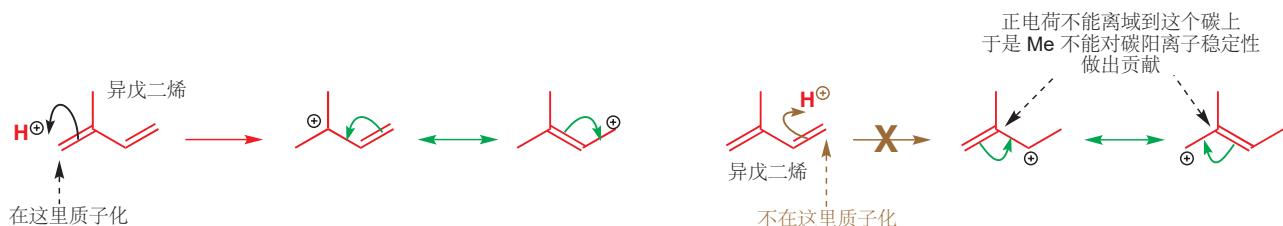


其他亲核试剂也可拦截碳阳离子，例如用 HCl 处理烯烃给出氯代烃，用 HI 则给出碘代烃，用 H<sub>2</sub>S 则给出硫醇。



## 双烯的亲电加成

本章的前文内容中，您见到双烯/二烯 (diene) 的环氧化给出单环氧：只有其中一根双键反应。这是一个很常见的观察结果：双烯要比孤立烯烃更加亲核。这很容易通过对烯烃、双烯 HOMO 相对能量的考察给出解释——在 p. 148, Chapter 7 的讨论。双烯烃因此对在酸中质子化给出阳离子很敏感。下面是用酸处理 2-甲基-1,3-丁二烯 (异戊二烯 isoprene) 时其发生的变化。质子化给出一个稳定的离域烯丙基阳离子。



为什么在左侧双键质子化而非右侧？两侧的双键质子化的产物都是烯丙基阳离子，但在右侧质子化得到的阳离子不能从甲基附加的稳定化作用中收益，因为正电荷不能离域到带有甲基的碳上。

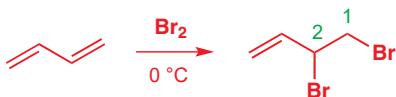
如果酸是  $\text{HBr}$ ，那么  $\text{Br}$  对阳离子的亲核进攻紧随其后。阳离子在空阻最小的一端被进攻，得到一种重要的化合物异戊烯基 (prenyl) 溴。这很像您在 Chapter 15 中遇到的反应——在烯丙基化合物上的  $\text{S}_{\text{N}}1$  取代反应的后半部分。



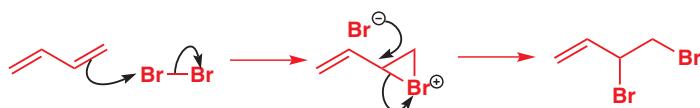
整体上看， $\text{H}$  和  $\text{Br}$  加入到了双烯体系的两端。用  $\text{Br}_2$  溴化双烯，也会发生相同的变化。



稍稍改变反应条件则会给出不同的结果。如果反应在低温下完成，溴仅仅会加入其中一根双键，并给出一种 1,2-二溴代物。



这个化合物是溴化反应的动力学产物。1,4-二溴代物 只在反应被加热时才生成，是热力学产物。对于反应机理，先是在双烯上的亲电加成，给出一个溴𬭩离子，然后溴离子使之开环，并得到二溴代物。下图所展示的，溴离子进攻的是溴𬭩离子较多取代的一端——这是下一节的内容，我们目前还不能确定(因为在哪一端的进攻都给出相同的产物)。



如果您需要回顾动力学和热力学控制，请回到 p. 264, Chapter 12.

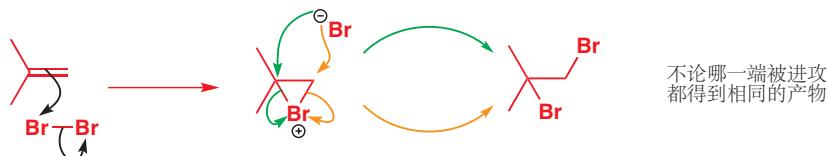
这个 1,2-二溴代物 仍可以通过亲核取代，继续反应。溴离子是一个好的亲核试剂，也是一个好的离去基团，有如此的烯丙基体系，可以发生亲核试剂和离去基团都是溴离子的  $S_N1$  反应。中间体是一个阳离子，由于溴的孤对电子可以帮助稳定正电荷，该碳阳离子伪装成了溴𬭩离子。一个伪装成溴𬭩离子的碳阳离子。溴离去后，溴又可以进攻，在原位进攻返回产物，而在烯丙基体系的较远端进攻则给出 1,4-二溴代物。这些步骤在高温下都是可逆的，因此 1,4-二溴代物 在这些条件下得以生成的事实，就意味着它比 1,2-二溴代物 更稳定。其原因不难看出：双键的取代基更多，且两个较大的溴原子相距较远。



Interactive mechanism for bromination of butadiene

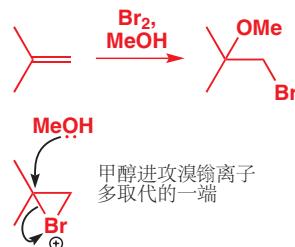
## 不对称溴𬭩区域选择性地开环

我们在讨论烯烃的溴化反应时，忽略了烯烃在对称性上的问题，因为即使是不对称的烯烃，溴离子以任何方式进攻溴𬭩，都会给出相同的 1,2-二溴代物。



但当溴化反应在亲核性的溶剂——例如水或甲醇——中完成时，溶剂分子会与溴离子竞争对溴𬭩的开环。如您所知醇是比溴差很多的亲核试剂，但由于溶剂的浓度很高（记得——水体系中，水本身的浓度是 55 M），大多数时候溶剂都会抢在前面。当用乙醇中的溴处理异丁烯时，甲醇仅会进攻溴𬭩离子多取代的一端以得到一种醚。当一个官能团可以在不止一处反应，对反应位点的选择被称作反应的区域选择性 (regioselectivity)。我们会在 Chapter 24 中回到这一概念。

我们在 Chapter 8 中推出了这个数字。



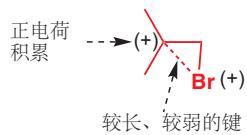
甲醇进攻的是溴𬭩离子空阻最大的位点，因此必然有一些比空阻更强有力的效果影响着它。看问题的一个角度是重新考虑我们对于溴𬭩离子开环为  $S_N2$  过程的假设。这个情况下，它看起来并不像  $S_N2$ ；我们有一个叔中心，您自然料到是  $S_N1$ ，并因此经历如下的阳离子。但我们已经说过，这个阳离子通过三元环溴𬭩离子的形成而稳定，但如果形成了三元环，则我们必须进攻溴𬭩离子，这使我们回到开始的地方：一个  $S_N2$  机理！

两种在溴𬭩离子上取代的极限机理



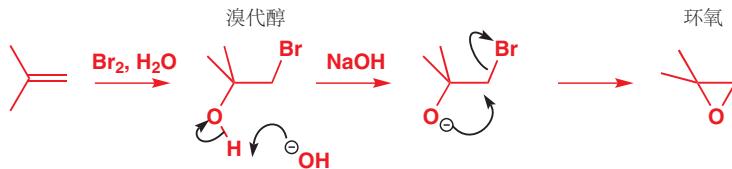
这个难题的答案是，这个取代反应往往并不是纯  $S_N1$  或纯  $S_N2$  机理：有时，机理是二者之中的某个位置。也许在离去基团开始离开时，在碳上形成了一个部分正电荷，并被亲核试剂拦截。这对所发生的变化提供了一个很好的解释。溴开始离开，而与此同时一个部分电荷在碳上积累。溴在叔端上的离开比在伯端上的离开发展得更好，因为前者能够稳定逐渐积累的正电荷。对溴𬭩离子更好的表达方式位于边栏，一根 C–Br 键比另一根长，也比另一根更加极化。

亲核试剂现在有了选择：进攻更容易接近的溴𬭩离子的伯端，还是电荷更多，C–Br 键更脆弱的叔端呢？后者显然是更快的反应。过渡态中，碳上有相当大的正电荷，也被称为一个松散的 (loose)  $S_N2$  过渡态。



Interactive mechanism for regioselective addition to unsymmetrical alkenes

在水中溴化（注：即次溴酸化）的产物为溴代醇（bromohydrins）。用碱处理它们，可以在醇上去质子，并立竿见影地发生分子内  $S_N2$  反应：溴作为离去基团被逐出，并生成一个环氧。这是避免使用过酸的环氧合成有用的一种替代方法。



### 烯烃溴化的速率

烯烃与过酸发生环氧化时，取代基越多反应越快，这种模式同样适用于溴化。溴𬭩离子是一个活泼的中间体，因此溴化反应的决速步是溴单质的进攻。下图显示了当取代基由无（乙烯）增加至四个的过程中，对其在与甲醇中的溴反应的速率的影响。每增加一

个取代基，速率上都会产生极大的影响。取代基内部带支链的程度（Me 与 *n*-Bu 与 *t*-Bu 的对照）产生较小的负面影响；几何结构 (*E* 与 *Z* 对照) 和取代模式 (1,1-二取代与 1,2-二取代对照) 也有较小的影响；这两点也许来源于空阻因素。

各种烯烃与甲醇中溴反应的相对速率

	$\text{H}_2\text{C}=\text{CH}_2$	$t\text{-Bu}-\text{CH}_2$	$n\text{-Bu}-\text{CH}_2$						
速率 最慢 → 最快	1	27	100	1750	2700	5700	13000	1900000	

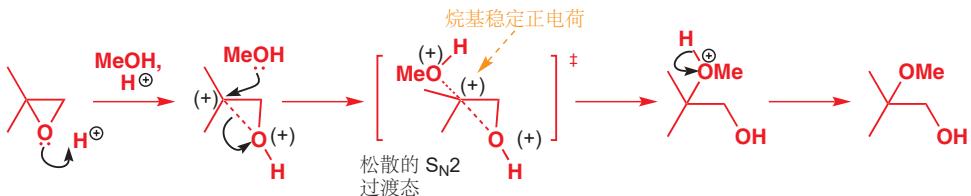
### 环氧开环的区域选择性可以取决于反应条件

■ 烷氧基阴离子绝不是  $S_N2$  反应中的离去基团：环氧的活性（与溴𬭩离子相比）仅因环张力而产生。

虽然环氧同溴𬭩离子一样，带有含张力的三元环，但它们的反应若想进行得好，则要么需要酸催化化，要么需要强大的亲核试剂。对比如下的两个与 1,1,2-三取代环氧 的反应。它们是与我们在 Chapter 15 (p. 352) 中引入的反应有关的亲核取代反应，但在那一章，我们小心避开了对不对称类环氧的讨论。在这个例子中，区域化学随着反应性的变化而彻底改变。这是为什么？

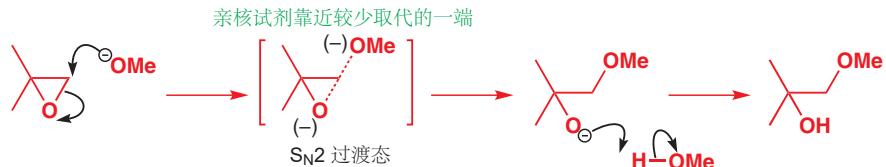


我们将由酸催化反应开始，因为这与我们刚刚讨论的例子更加相似——在多取代的一端开环。酸的质子化产生了一个带正电的中间体，与对应的溴𬭩离子具有相似性。两个烷基使质子化的环氧在叔端碳上积累正电荷，于是甲醇进攻这里，就像是进攻溴𬭩离子一样。甲醇原本活性很低，但您可以这样想，质子化的离去基团将其“拉”来参与反应。

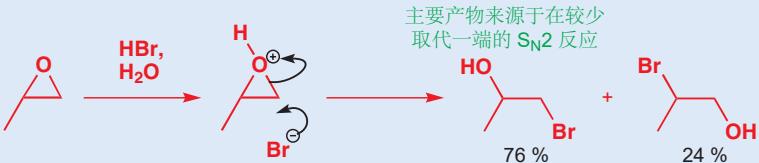


■ 记得， $S_N1$  只在离去基团较好时发生得快 (Chapter 15)。

在碱中，环氧氧化物不能质子化，也不能积累正电荷。而没有质子化的情况下，环氧氧原子是一个差的离去基团，只在当强的亲核试剂“推”着其反应时才可反应：这个反应变成了纯  $S_N2$ 。空阻也成为了控制因素，甲氧基阴离子只进攻环氧的伯端。



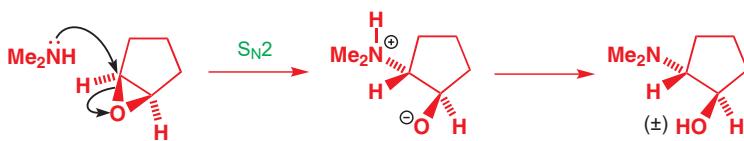
上述例子让问题看似很明确。但环氧开环的区域选择性并不像所属的那样简单，因为即使是用酸催化剂，在伯中心上的  $S_N2$  取代仍是快的。例如， $\text{Br}^-$  在酸性下进攻如下的环氧较少取代的一端，只有 24% 的产物来源于“被稳定的阳离子”的路径。推翻有一端未取代的环氧在该端的反应偏好，而使之在另一端反应是很困难的。



对于大多数环氧的取代反应，如果您屈服于它在较少一端的反应偏好，给予其碱性条件与强的亲核试剂，那么区域选择性会大大提高。

## 烯烃的亲电加成可以是立体专一性的

(烯烃亲电加成的立体专一性建立在溴𬭩离子中间体的立体专一性上。)下面有几个环氧开环的例子，它们本应属于 Chapter 15 的范畴，但它们与溴𬭩离子的反应性十分相似。而本节我们则需要类比，以考察溴𬭩离子反应的立体化学的另一方面。首先是下面的几个例子，帮您回忆 Chapter 15 有关环氧的内容。



环氧的开环是立体专一性的： $S_N2$  反应，并且经历翻转。环氧若在环的顶面，那么氨基就需要从底面进攻，两个基团最终在环上处于 *anti* 构型。用环戊烯和 *m*-CPBA 可制备环氧，而如下的两步反应则可以让您在双键上加入一个 OH 基和一个  $\text{Me}_2\text{N}$  基，并且它们处于 *anti* 构型。



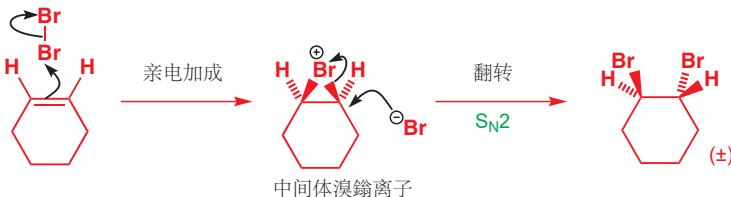
现在我们可以着眼于烯烃亲电加成的立体化学了。

### 对烯烃的亲电加成可产生立体异构体

当用溴的四氯化碳溶液处理环己烯时，得到的产物完全是外消旋的 *anti*-1,2-二溴环己烷



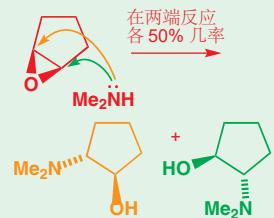
结果处于意想之中，首先形成溴𬭩离子，然后是经历构型翻转的  $S_N2$  反应。



烯烃的溴化是立体专一性的，因为起始烯烃的几何结构决定了产物的立体化学。我们不能通过环己烯论证这一结论，因为六元环中仅能存在 *Z* 双键。而 *Z* 和 *E*-2-丁烯在乙酸中的溴化和氯化，产生的都是单一产物，每种情形都发生 *Anti* 加成——溴𬭩离子做中间体的又一证据。

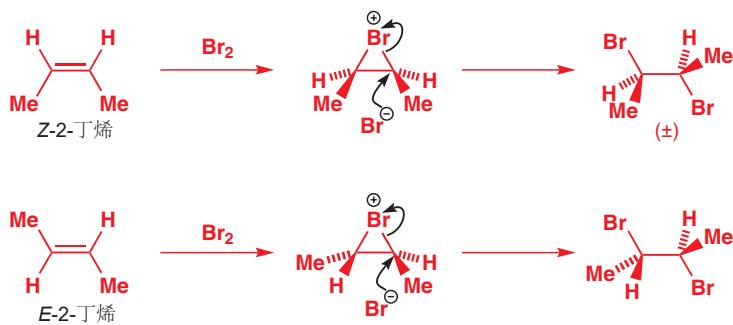
■ 立体专一性，指的是这个反应的结果的立体化学取决于环氧本身的立体化学。 $S_N2$  反应别无选择，必须经历构型翻转。我们在 p. 396 讨论了“立体专一性”和“立体选择性”的术语。

■ 注意产物下方的  $(\pm)$  符号。如我们在 Chapter 14 所讨论，它们仅是单一的非对映体，而不可避免地以对映体的外消旋混合物形成。您可以用下面的方式看这个问题： $\text{Me}_2\text{NH}$  会以相同的可能性进攻环氧等价的两端。每种都给出相同的非对映体，但会给出相反的对映体。两种对映体会恰恰以相同数量形成。

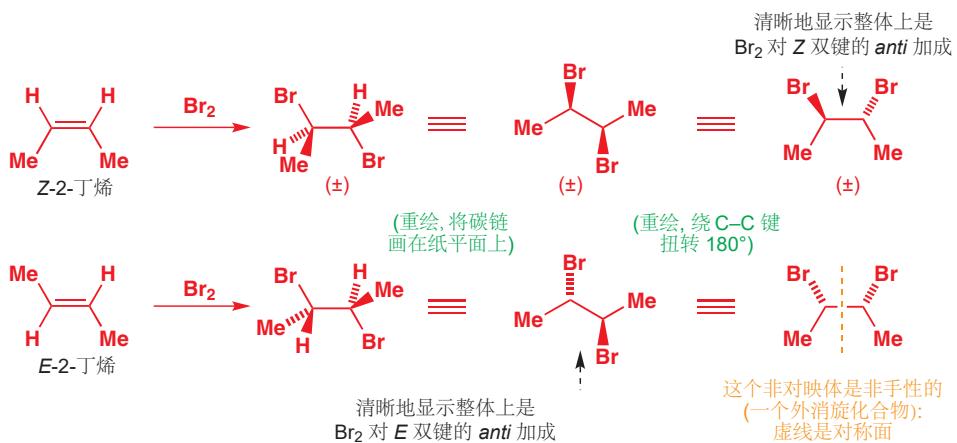


■ 右边这种“不生成”的结构不需要标  $(\pm)$ ，因为它是非手性结构——它包含一个对称面，因此是内消旋化合物(见 p. 317)。

Interactive mechanism for reaction of cyclohexene with bromine



如果我们重新画这两种产物，它们的立体化学就会呈现得更加清晰，如下图中，两个反应的产物都以两种不同方式画出。第一种画法（构象）中的产物通过旋转，使碳链位于纸平面上：您可以从中很清晰地看出对  $E$  双键的 *anti* 型加成。第二种，则是将中心键扭转  $180^\circ$  并给出一个（不现实的）重叠式构象；展示这种构象有两个原因：首先您可以清晰地看出对  $Z$  双键的 *anti* 型加成，其次，从中观察到  $E$ -丁烯溴化产物的非手性也相当容易，这就是为什么我们没有在  $E$  烯烃的产物标注  $(\pm)$ 。



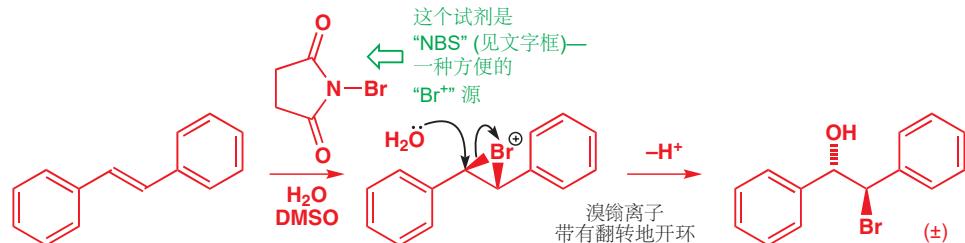
Interactive mechanism for stereospecific *anti* addition to alkenes

注意，每个产物的三种不同视角都表达的是相同的立体异构体；在构型上没有改变，仅仅是通过构想上的改变，帮您理解所发生的变化。如果您没跟上“重绘”的步骤，就请制作模型。通过实践，您将很快能在头脑中构建模型，并能思考出键旋转时取代基发生的变化。不要让它们掩盖了更重要、更简单的结论：

● 溴对烯烃经历 *anti* 加成。

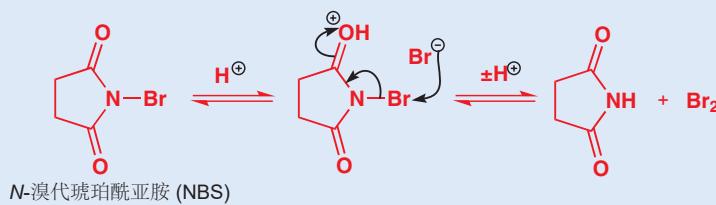
## 立体选择性合成中的溴𬭩离子中间体

意想之中，其他您在本章中见过的可拦截溴𬭩离子的亲核试剂（水和醇）也会立体专一性地反应。下面的反应可大规模地应用，水分子带有构型翻转地给溴𬭩离子开环，以生产一种简单的非对映体产物（当然是外消旋的）。

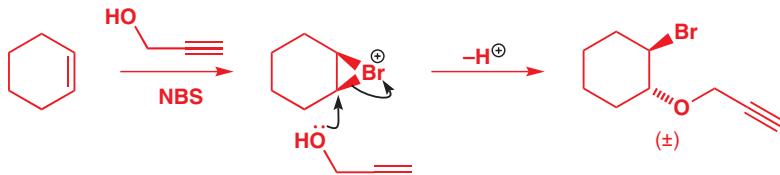


### N-溴代琥珀酰亚胺, NBS

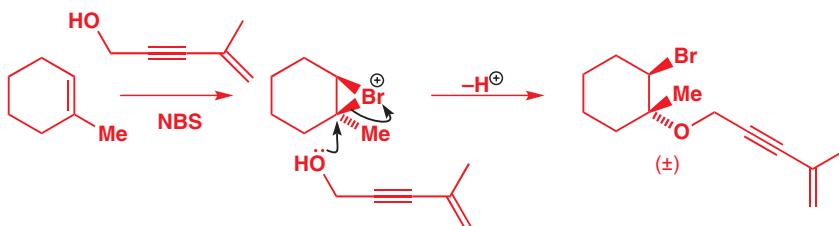
这里用于形成溴𬭩离子的试剂称为 *N*-溴代琥珀酰亚胺 (*N*-溴代丁二酰亚胺, *N*-bromosuccinimide), 简写作 NBS。与有毒的液溴不同的是, NBS 是一个很容易处理的晶体, 并且在您不打算让  $\text{Br}^-$  来开环时可以得到很完美的使用。它通过在溶液中产生很少浓度的  $\text{Br}_2$  起作用: 小量的  $\text{HBr}$  就足够使反应进行, 而此后每次加成反应都产生另一分子的  $\text{HBr}$ , 于是便从 NBS 中释放更多的  $\text{Br}_2$ 。在某种意义上, NBS 是一种 “ $\text{Br}^+$ ” 源。用作  $\text{Br}_2$  源是其家喻户晓的用途, 这是因为低浓度下 NBS 和  $\text{Br}_2$  的反应是等同的。



试剂 NBS 只生成低浓度的  $\text{Br}_2$ , 因此  $\text{Br}^-$  的浓度往往很低; 于是, 即使醇不作溶剂, 也有能力与  $\text{Br}^-$  竞争给溴𬭩开环。在下个例子中, 所用醇是 “炔丙基 (propargyl) 醇”, 2-炔-1-丙醇。它与环己烯和 NBS 反应给出预料中的 *anti*-二取代产物。

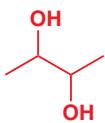


当 1-甲基环己烯作为起始原料时, 还另有区域选择性的问题。醇进攻溴𬭩离子较多取代的一侧——在 “松散的  $S_N2$ ” 过渡态中部分正电荷稳定性最佳的一种(见 p. 437). 这个反应的确说明了机理介于  $S_N1$  和  $S_N2$  之间的结论。构型翻转, 暗示  $S_N2$  反应了; 而在叔碳上反应, 则会让您想到  $S_N1$ .



■ 注意(本例中)溴单质只与最富电子的三取代烯烃反应, 而不在乎二取代烯烃和炔烃。

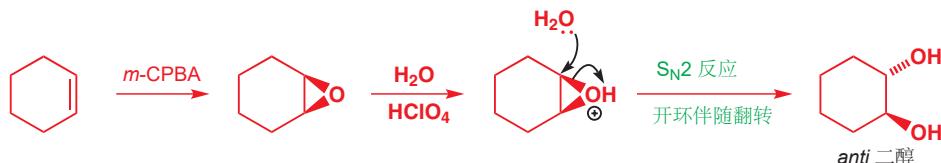
## 添加两个羟基: 双羟基化反应



一个 1,2-二醇

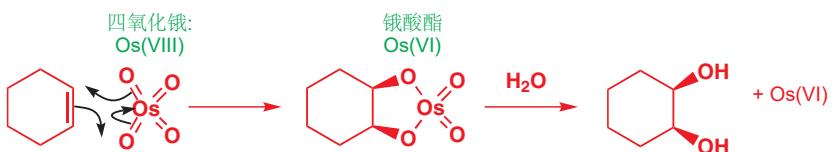
很多重要的化合物——例如碳氢化合物——都含有在相邻碳原子上的两个羟基。它们被称作 1,2-二醇(邻二醇)。制备 1,2-二醇的方法是在双键的两侧加入两个羟基。这件事可以用两种方式完成，并且这两种方法给出的产物是不同的非对映体。

第一种方法用到的都是您已学过的内容。当亲核试剂进攻环氧时，就会生成醇。而如果亲核试剂是水，则产物为二醇。环氧的开环是一个  $S_N2$  反应，伴随立体化学翻转；因此在这个例子中，两个羟基在六元环的不同侧：产物是一个 *anti* 二醇。环氧开环可以在酸或碱中完成。

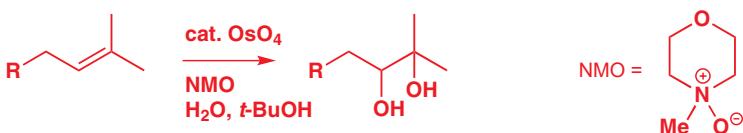


Interactive mechanism for dihydroxylation of alkenes

■ 这个反应的机理中，箭头呈环状，并结束于它们的出发点；这样的机理叫做周环(*pericyclic*)机理：我们会在 Chapter 34 详细讨论。

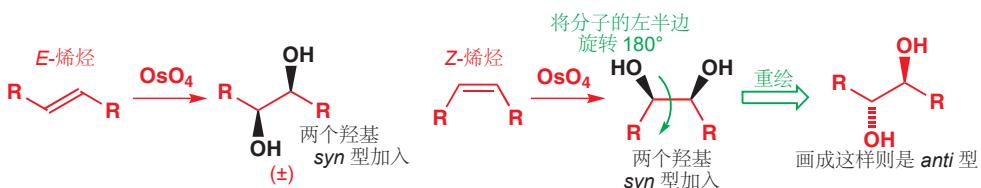


因为反应中生成了  $Os(VI)$ ，而添加一个简单的氧化过程则可以将其复原为  $Os(VIII)$ ，这个反应最有效的版本是利用仅催化量的  $Os(VIII)$  以及化学计量的再氧化剂(氧化助剂, reoxidant)，通常是化合物 NMO，即 *N*-甲基吗啉-*N*-氧化物。在下面的例子中，只有一个新的手性中心，因此不存在非对映体。



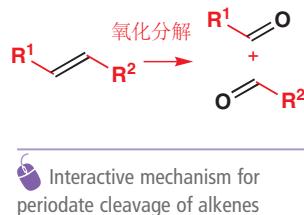
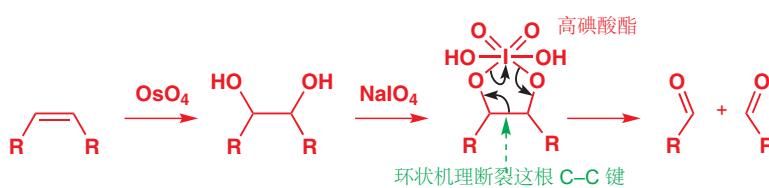
■ 这种思路在 p. 440 关于烯烃溴化的内容中有更多的讨论。想象这两种产物的手性也是值得的：第一种是手性的，没有对称面(符号 (±))提醒您我们没有必要画出第二种对映体，因为必然是外消旋的)；第二种是非手性的，在所示的第一种构象中有一个对称面，第二种中则有一个对称中心。如果您感到不清楚，请回到 Chapter 15。

因为  $OsO_4$  *syn* 型地给烯烃添加两个羟基，全过程的产物取决于起始原料烯烃的几何结构：它是立体专一性的。这方面与溴化反应类似(p. 439)，溴化反应是一个 *anti* 加成。下面的两个例子，是不同的烯烃产生两种不同的非对映体的过程：机理上讲，双羟基化都是 *syn* 型的，但将 *Z* 烯烃画作它更伸展的形式，则呈现出 *anti* 立体化学。



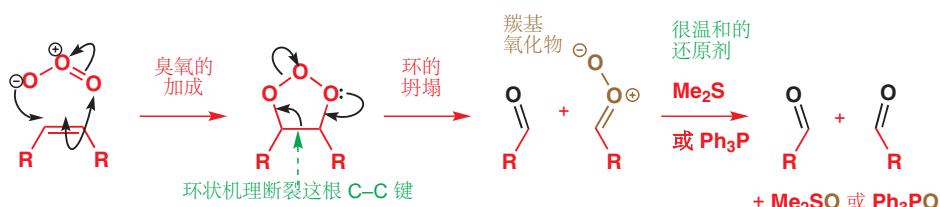
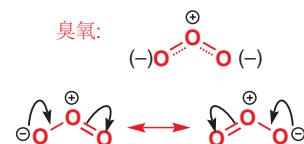
## 彻底断裂双键: 高碘酸解和臭氧解

有时, 我们有必要彻底地断裂烯烃双键, 换句话说就是不仅氧化其  $\pi$  键 (如您所见, 用  $\text{Br}_2$  或  $\text{OsO}_4$ ), 而且也氧化其  $\sigma$  键, 如侧边栏所示。这可以通过  $\text{OsO}_4$  连同高碘酸钠,  $\text{NaIO}_4$  引发的两步反应完成。邻二醇产物生成一个高碘酸酯, 随后以与  $\text{OsO}_4$  步骤相似的环状机理分解, 形成两个醛。 $\text{NaIO}_4$  也可以将 Os(VI) 重新氧化为 Os(VIII), 因此仅需要催化量的 Os.



这个过程由两个成功的氧化反应连续发生而完成——第一个是  $\pi$  键的, 第二个是  $\sigma$  键——试剂不同 (既可以在一步中, 也可以在两步中加入——您可以使用  $\text{NaIO}_4$  断裂任何邻二醇, 无论是不是用  $\text{OsO}_4$  制备的). 但还有另一个试剂, 可以在一步中完成这两个氧化反应: 那就是臭氧 (ozone).

臭氧是一个对称的弯曲分子, 居中是一个带正电的氧原子, 两端则是两个分享负电荷的氧原子。臭氧是不稳定的, 可在反应前由氧制备 (用一种称为“臭氧发生器 ozonizer”的设备), 并立即通入反应混合物。像  $\text{OsO}_4$  一样, 它通过一个环状机理加入烯烃: 产物是一个含有三个氧原子的五元环。它非常不稳定, 通过一根弱的 O–O 键和一根 C–C  $\sigma$  键的断裂迅速坍塌 (collapse), 过程中获得两根强的 C=O 键。

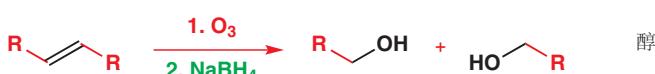
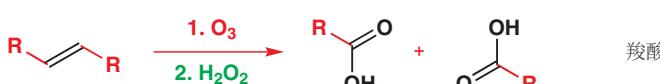
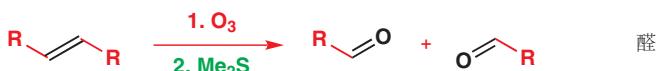


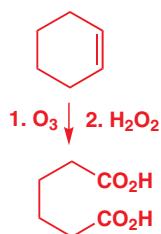
中间体产物是一个简单的醛 (左侧) 和一个新的, 看起来相当不稳定的分子, 被称作羧基氧化物 *carbonyl oxide* (右侧)。用非常温和的还原剂, 如二甲硫醚,  $\text{Me}_2\text{S}$ , 或三苯基磷,  $\text{Ph}_3\text{P}$ , 都可以移去“空余的”氧, 以得到两分子醛。

烯烃在臭氧下的分解反应是一个重要的反应, 被称作臭氧解 (*ozonolysis*)。臭氧解不仅可用于生成去醛, 还可用于其他官能团。用氧化剂, 如  $\text{H}_2\text{O}_2$  来竞争反应, 则给出羧酸; 更强的还原剂, 如  $\text{NaBH}_4$  则会给出醇。下面给出了总反应变化:

■ 羧基氧化物被还原的机理比此处所展示的更复杂, 我们会在 Chapter 34 中考察。

烯烃臭氧解...





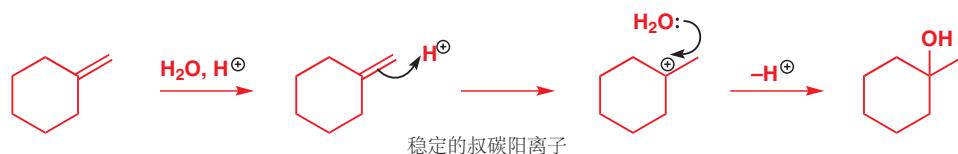
环己烯的臭氧解是尤其有用的，它给出 1,6-二羧基化合物，其他方法很难制备。最简单的情形中，我们得到的是 1,6-己二酸 (肥酸 adipic acid)，批量生产尼龙的一种单体。



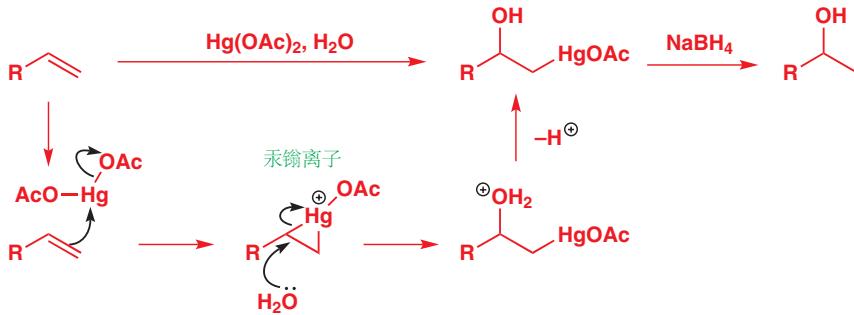
## 添加一个羟基：如何在双键上加水

在 Chapter 17 中您已见到，烯烃可以通过醇的 E1 消除——酸催化下脱水——制备。而本节，我们要问的问题是：如何使消除逆向进行呢——换句话说，如何使双键水化呢？

偶尔，简单地用酸的水溶液就可以完成。这个反应仅在烯烃的质子化可给出一个稳定的叔阳离子时可工作。这个阳离子然后被溶剂水捕获。



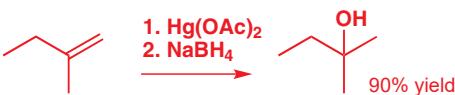
不过，通常很难预测酸的水溶液会水化烯烃，还是给醇脱水。我们即将要展现给您的是另一种更可靠的方法。关键在于用过渡金属帮您解决困境。烯烃是软的亲核试剂 (p. 357) 并可以很好地与软的亲电试剂，例如过渡金属阳离子相互作用。例如侧边栏所示的是烯烃与 **汞(II)** 阳离子形成的配合物。这个配合物应当让您回忆起溴𬭩离子，因为它们的反应也是相似的。即使是相对无力的亲核试剂，例如水、醇，用作溶剂时，也可以给“汞𬭩 (mercurinium)” 离子开环，以生成醇、醚。下面的方案中，**汞(II)** 由醋酸汞(II),  $\text{Hg(OAc)}_2$  提供，我们可以用两根共价的  $\text{Hg}-\text{O}$  键表示它。不出所料的，水进攻带正电的汞𬭩离子多取代的一侧。



■ 脱汞的步骤包含自由基化学，会在 Chapter 37 中讨论。您会在 Chapter 40 中学习更多有机金属和它们的反应。

我们在烯烃上加入了  $\text{OH}$  和  $\text{Hg(II)}$ ，此反应也被称作“羟汞化 (oxymercuration)”。但仍遗留一个问题：如何赶走金属。 $\text{C}-\text{Hg}$  键很弱，最简单的办法是将  $\text{Hg}$  用  $\text{H}$  代替，即使用还原剂： $\text{NaBH}_4$  能不错地工作。

下面是一个羟汞化-脱汞 (oxymercuration–demercuration) 反应工作的例子。汞化合物中间体不经分离。

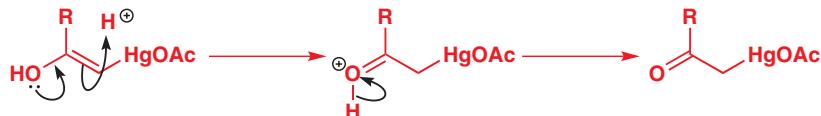


## 炔烃的水化

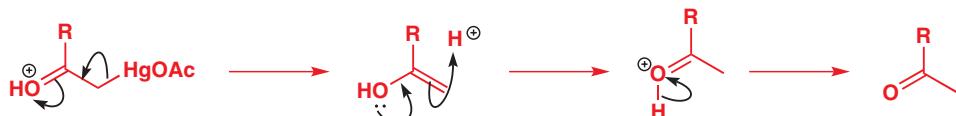
羟汞化对于炔烃工作得尤其好。与烯烃的羟汞化类比，可以得到如下条件、产物，产物为最右侧的分子。



但从炔烃羟汞化体系中分离出的产物事实上是一个酮。如果您允许初期产物上的一个质子，从氧转移至碳上——先在 C 上质子化，然后在 O 上去质子——那么您就能看到其原因。C=O 键比 C=C 键强，这个简单的反应也进行得快。



我们现在有了一个酮，但我们仍旧含有汞。相邻的羰基并不构成麻烦，因为此时任何弱的亲核试剂都可以在酸的存在下去除汞，如下所示。最后，另一个质子转移 (再次由 O 到 C) 给出反应的实际产物：一个酮。



这是一个制备甲基酮非常有用的方法，而末端炔烃可用 Chapter 9 中的方法制备 (炔基金属对亲核试剂的加成)。



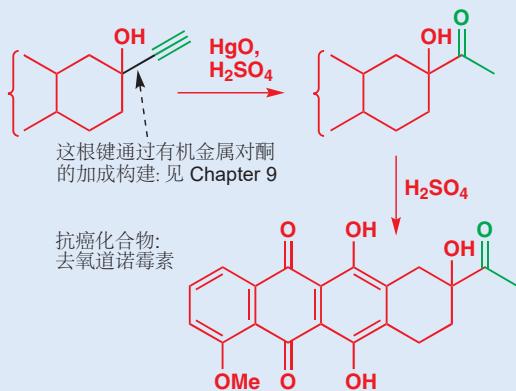
## 烯醇

这种带有羟基的烯烃被称为烯醇 enols (ene + ol)，它们是化学上最重要的中间体之一。这个反应凑巧包含了它们，因此我们向您简短地介绍了，但在下一章及今后，您会遇到更多烯醇 (和它们的去质子姊妹，烯醇盐) 在化学上发挥的深远意义。



## 抗癌化合物

蒽环类 (anthracycline class) 抗癌药物 (包括道诺霉素 daunomycin 和阿霉素 adriamycin) 可以用汞(II)催的炔烃水化生产。所用的炔烃通过您在 Chapter 9 中所学的方法，即炔基金属对酮的加成合成。下面是抗癌化合物去氧道诺霉素 (deoxydaunomycinone) 合成的最后一步：炔通过  $\text{Hg}^{2+}$  在稀硫酸中水化，给出最终产物。



## 硼氢化



上述对双键或三键的加水方法，都涉及阳离子中间体，新的羟基往往结束于更能稳定正电荷的一边（见 p. 433，即马氏规则加水）。但如果我们恰恰想反过来加水呢（反马氏规则加水）？例如，您该如何合成侧边栏中的分子呢？

答案是利用另一种元素：硼。硼烷（Boranes），包括  $\text{BH}_3$  本身和带有一个或两个烃基的类似物， $\text{HBR}_2$ （侧边栏展示了一个重要的例子），可通过可写作如下形式的机理，加入烯烃形成一根新的 C–H 键和一根新的 C–B 键。烯烃将电子推向硼的空 p 轨道，与此同时硼上的氢迁移移到烯烃上。



■ 为什么 B 结束于较少取代的碳上？部分地因为电子效应——这个反应由烯烃  $\pi$  电子对硼原子上空 p 轨道的给电子过程驱动，因此硼加在烯烃堆积正电荷（叫多取代）的另一端；还部分地因为空间效应—— $\text{BR}_2$  比  $\text{H}$  大，因此它加在较小空阻的一端，上方的 9-BBN 会被选用的原因，就是因为其中的 B 原子被双环体系变得更大。

重要的是，如果烯烃是不对称的，硼倾向于加在少取代的碳原子上。这个反应可以多次发生，因此如果您用烯烃和  $\text{BH}_3$  开始反应，最后得到的会使三烃基硼烷。

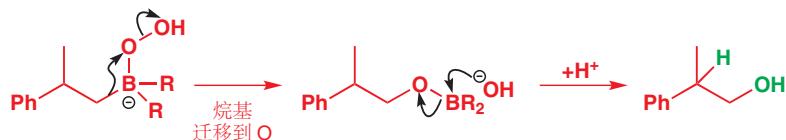


如果您想制备的是硼烷的话，那么目前为止都很好；但本节我们向自己提出的问题是，如何在双键上加水。这时需要的是硼化学中一个古怪的知识。我们刚刚构建的 C–B 键可以被  $\text{NaOH}$  和  $\text{H}_2\text{O}_2$  的混合物氧化为 C–O。混合物会生成过氧氢根阴离子  $\text{HO}^-\text{O}^-$ ，会加入硼上重要的空 p 轨道。产物是一个带负电的结构，如下所示。

过氧氢根阴离子



这个产物不稳定，会通过一个您应当仔细观察的机理分解。您对这个反应并不熟悉，但如果用心想想，就会觉得它有道理。 $\text{O}-\text{O}$  键很弱，断开时失去  $\text{HO}^-$ ；与此同时，硼上其中一个烷基可以由 B 迁移到 O，以解除硼原子上的负电荷，给出如下所示的结构。



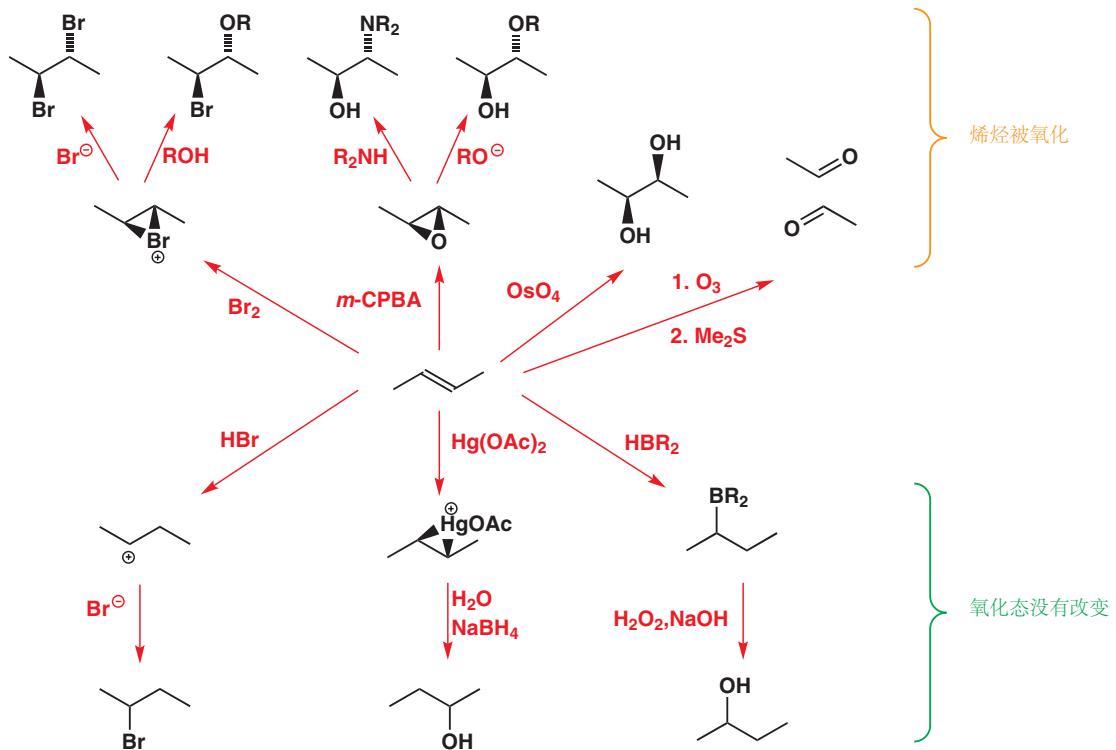
### Interactive mechanism of hydroboration

► 这个机理，C–B 键转化为 C–X 键的过程，是硼的典型反应性。它也与 Baeyer–Villiger 氧化，Chapter 36 有一些相似性。

我们现在有了我们想要的 C–O 键，唯一需要的就是氢氧根卷土重来，从醇产物中移去 B。产物经质子化即为我们的醇。我们如何确保迁移的 R 基是正确的呢？嗯，如果我们用  $\text{BH}_3$ ，那么我们会得到三个取代基相同的三烃基硼烷，三根 C–B 键可以依次被氧化；如果我们用  $\text{HBR}_2$  试剂 9-BBN，那么也只有硼氢化反应中新生成的非环状取代基可迁移，选择性地得到我们想要的产物。

## 小结...亲电加成反应概述

$\text{Br}_2$ ,  $\text{Hg}^{2+}$ , 以及过酸对烯烃的亲电加给出三元环中间体(与过酸给出的稳定的三元环, 环氧化). 这三类三元环都可与亲核试剂反应给出 1,2-双官能团产物; 开环过程受(1)区域选择性、(2)立体专一性的控制。双键的质子化得到一个阳离子, 可捕获亲核试剂, 这个反应用于制备卤代烷。一些您可以通过本章的方法制备的化合物种类如下所示。



## 延伸阅读

本章对轨道的论述, 也在 *Molecular Orbitals and Organic Chemical Reactions: Student Edition* by Ian Fleming, Wiley, Chichester, 2009 中有所涉及。F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry A, Structure and Mechanisms*, 5th

edn, Springer, 2007, chapter 5, 中处理了消除和加成反应的内容。  
p. 428 页所展示的稳定溴𬭩离子的表征: R. S. Brown et al., *J. Am. Chem. Soc.*, 1994, 116, 2448.

## Check your understanding

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To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 20

## 烯醇和烯醇盐的形成和反应

### 联系

#### → 基础

- 羰基化学 ch6, ch9, ch10, & ch11
- 对烯烃的亲电加成 ch19

#### 目标

- 羰基如何与另一种被称为烯醇的异构体处于平衡存在
- 酸和碱如何促进烯醇及其共轭碱，烯醇盐的形成
- 烯醇和烯醇盐有固有的亲核反应性
- 利用这种反应性可以在羰基旁边引入官能团
- 烯醇硅醚和烯醇锂可用作稳定烯醇盐等价物

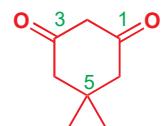
#### → 展望

- 芳香化合物作为亲核试剂 ch21
- 烯醇盐在 C-C 键构筑上的用途 ch25 & ch26
- 烯醇盐化学在化学家用以制备分子的方法中处于的中心位置 ch28

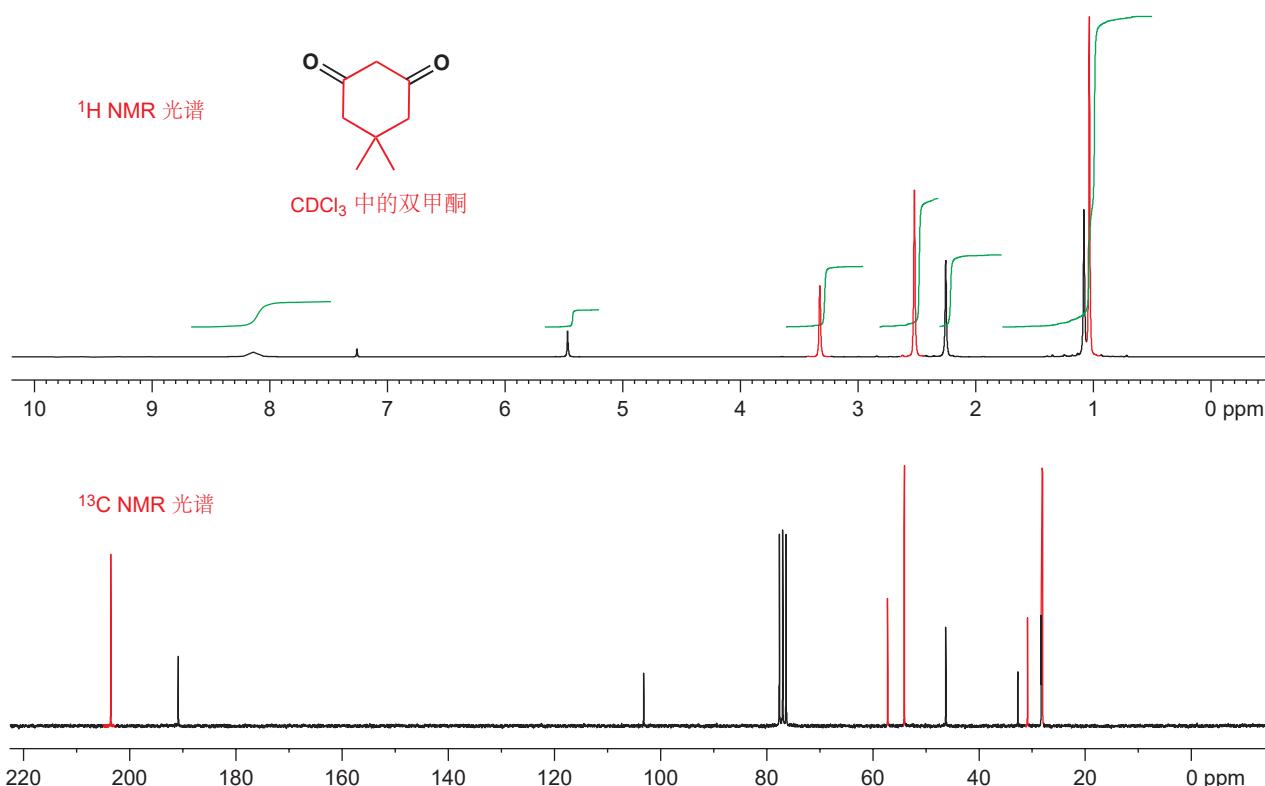
我们在羰基化学上花费了悬河泻水之篇幅，但我们认为这是值得的。您在 Chapter 6 中遇到了本书中的第一类反应，即羰基上的亲核加成。然后在 Chapters 9, 10, 和 11 中我们考虑了对羰基亲核进攻的各个方面。这两类反应中，羰基化合物都体现亲电性，但事实上，它们还有与之对立的另一性质，亲核性：对醛、酮和羧酸衍生物的亲电进攻也是使用的反应。但相同的一类化合物，是怎么接受亲核、亲电两类进攻的呢？本章要所要解决的矛盾就要于此，我们将会看到大多数羰基化合物，可以以两种形式存在——一种亲电的和一种亲核的。羰基化合物的亲电形式就是它们本身，而亲核形式被称作 **烯醇 (enol)**。

### 化合物的混合也能算做是纯净物吗？

您可以从化学品供应商那里买到双甲酮 (5,5-二甲基-1,3-环己二酮)。当您买到任何一种化合物的时候，明智的做法都是通过 NMR 光谱来检验这个化合物的纯度。我们对新买的双甲酮也做了在 CDCl<sub>3</sub> 溶液中的 1H 和 13C NMR 光谱，下一页图中红色的峰为二酮。光谱很清晰地告诉我们，我们买到的是两种化合物的混合物，如果是您，可能很倾向于退货。



“双甲酮 (dimedone)”  
5,5-二甲基-1,3-环己二酮



记得要忽略 CDCl<sub>3</sub> 溶剂的峰: δ<sub>H</sub> 7.25 和 δ<sub>C</sub> 77.

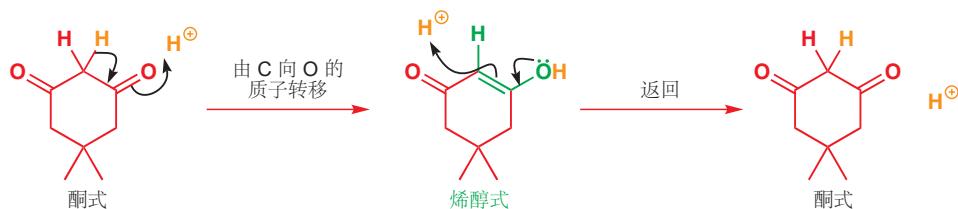
样品的绝大部分确实都是 5,5-二甲基-1,3-戊二酮。但剩下的是什么呢？剩下的一种化合物与双甲酮的光谱很像，结构上也很像：它有 CMe<sub>2</sub> 的 6H 单峰，也有环两侧的两个 CH<sub>2</sub>；在 <sup>13</sup>C NMR 光谱中有五个信号。其不同之处在于：在 δ<sub>H</sub> 8.15 处有一个宽信号，看上去像 OH 基，更重要的是在 δ<sub>H</sub> 5.5 处，双键区域内，出现尖锐的峰。它有两个不同的 sp<sup>2</sup> 碳原子。这都与下方所示的烯醇 (enol) 结构匹配。

如果您需要回忆有关化学位移，和 <sup>1</sup>H NMR 中不同种类的质子的内容，可以翻回 Chapter 13, p. 272.



## 互变异构现象：烯醇通过质子转移生成

烯醇正如其名所指：烯-醇 (ene-ol)；即有一个 C=C 双键，双键上又有一个 OH 基取代。刚刚的情形中，烯醇式的双甲酮由酮式位于中间的 CH<sub>2</sub> 向其羰基氧的质子转移得到，这一反应被称作烯醇化 (enolization).



注意，烯醇化的反应在 pH 上没有变化——质子被碳失去，又被氧获得。这是个仅发生微小变化的奇怪反应：唯一的变化是质子的转移，和双键的转移。这样的互相转变被称为互变异构现象 (ta-

utomerism).

### 互变异构现象 (Tautomerism)

任何仅包含分子内质子转移的反应，都被称作互变异构现象。下面有两个例子。



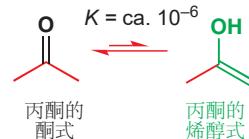
我们在 Chapter 8 曾讨论过这类反应，其中原子的酸性和碱性是主要考虑因素。在第一个例子中，两个互变体 (互变异构体, tautomers) 是完全相同的，平衡常数是确切的 1 (而混合比例也是 50:50)。而在第二个例子中 (含咪唑化合物在 p. 178 出现)，平衡则会偏向一侧，这取决于 R 的性质。

### 为什么简单的醛和酮不以烯醇式存在呢？

Chapters 13 和 18 中，我们也观察了一些羰基化合物，但并没有在 IR 或 NMR 光谱中发现烯醇的信号，双甲酮的现象十分罕见 (我们稍后会讨论)。虽然任何邻位有质子的羰基化合物都能发生烯醇化，但像环己酮、丙酮这类简单的羰基化合物，在通常条件下都只有痕量的烯醇式存在。这平衡完全趋向于酮式的形成 (丙酮烯醇化的平衡常数 K 大约为  $10^{-6}$ )。

这是因为 C=C 双键和 O–H 单键的结合要 (稍稍) 比 C=O 双键和 C–H 单键的结合不稳定。右侧显示了这些键的平均键能。烯醇式中 O–H 键比酮式中 C–H 键强得多。

一般情况下的一般酮，溶液中烯醇式的含量都为酮式的  $10^5$  分之一。那我们为什么还认为它们那么重要呢？这是因为烯醇化只是电子转移的过程，即使我们不能检测烯醇式微小的占比，它仍然在每时每刻发生着。接下来我们将讨论这一说法的证据。



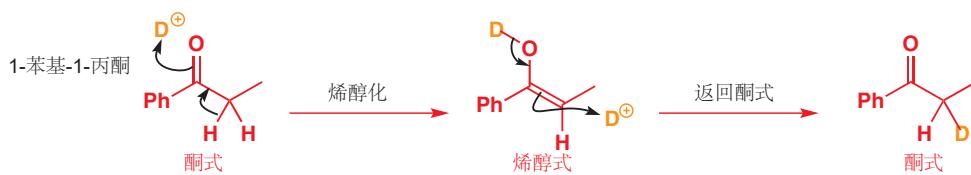
酮式和烯醇式中具代表性的键能 ( $\text{kJ mol}^{-1}$ )

	与 H 的键	$\pi$ 键	和
酮式	440 (C–H)	720 (C=O)	1160
烯醇式	500 (O–H)	620 (C=C)	1120

### 羰基化合物与烯醇平衡的证据

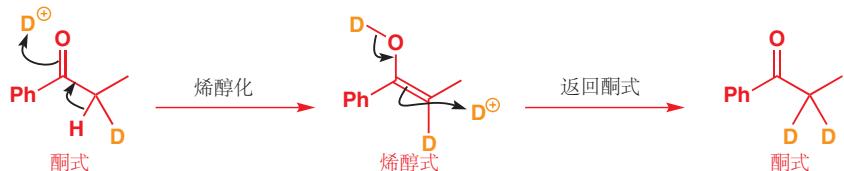
如果您将简单的羰基化合物 (如 1-苯基-1-丙酮，“苯丙酮 propiophenone”) 溶于  $\text{D}_2\text{O}$ ，并使  ${}^1\text{H}$  NMR 光谱运行一段时间，您会发现与羰基毗邻的质子的信号会非常缓慢地消失。如果随后又将这个化合物分离出来，质谱则会显示，那些氢原子比氘原子取代了：在  $(M + 1)^+$  或  $(M + 2)^+$  处，而不是  $M^+$  处有峰值。

烯醇化通常意味着在 C 处失去一个质子，并且在 O 处得到一个。但在  $\text{D}_2\text{O}$  中，所有的“质子”事实上都是“氘离子”( $\text{D}^+$ , or  ${}^2\text{H}^+$ )，因此开始时生成的是带有“OD”基团的烯醇。这并不是问题，因为烯醇式返回酮式时 O 上的 D 就会失去。真正发挥作用的是，在返回酮式的过程中，C 攫取了氘离子而不是质子。



■ 注意，烯醇中的双键既可以是 E，也可以是 Z。在这里我们画作 Z，但实际上它可能是两者的混合物。但这与烯醇的反应无关，在本章中我们不要求考虑烯醇的几何结构；但在后面的章节中，有几个反应是需要您用考虑到这一问题的。

这一过程现在还可以重复：烯醇化时 D 和 H 都可以离去，但可以肯定的是，由于溶剂中远多于 H 的、大量而过剩的 D，会使得化合物中与羰基毗邻的两个 H 原子最终都被 D 取代。



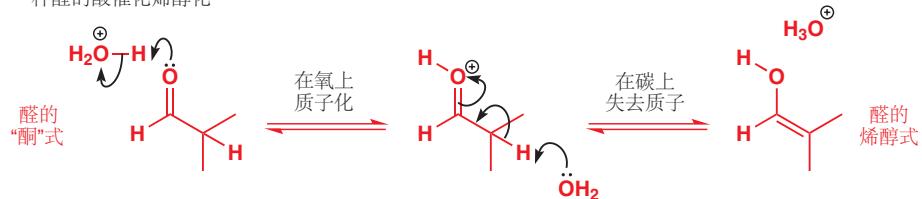
■ 还有一些会在质子 NMR 光谱中发生的事情。 $\text{CH}_3$  基的信号在原本的酮中表现为三峰，但它的两个 H 会被 D 取代，进而变成单峰。在碳谱中，还会发生对氘的耦合：您还记得  $\text{CDCl}_3$  峰的形状吗 (Chapter 18)。

我们可以从羰基邻位碳原子上 2H 信号的缓慢消失察觉这种交换现象。当然，分子中剩余的八个氢原子并不受烯醇化的影响。

## 平衡由酸或碱催化

事实上，在中性溶液中烯醇化是一个相当缓慢的过程。上文描述的在  $\text{D}_2\text{O}$  中的同位素交换过程，在室温下，每个周期可能需要持续数小时至数天。如果我想使其更加迅速地发生，可以使用酸或碱催化。在酸催化反应中，分子首先会在羰基氧上被质子化，第二步则是在 C 上失去质子。下面以一个醛为例展示了酸性下烯醇的生成，酸、碱催化的烯醇化反应在任何羰基化合物中都分别以相同的方式进行。

一种醛的酸催化烯醇化



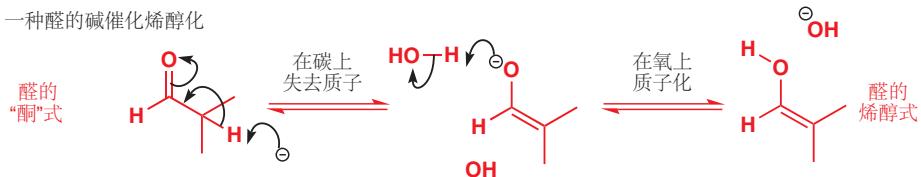
■ 在 Chapter 17 (p. 388) 中我们讨论了，机理中所画的质子直接“脱落”，其实代表着它被碱性的溶剂分子夺去。在本章和本书的其余部分，您会持续看到这种写法及其变种，它们代表的都是同一件事。

Interactive mechanism for base-catalysed enolization

这是比我们从前画过的更为详细的烯醇化机理，因为它显示了从碳上移去质子的物质（本例中为水分子）。虽然这个反应比在酸催化下更快，但平衡并不会因此而改变，我们也不能在其光谱上察觉到烯醇。

碱催化反应中，C–H 质子首先被碱（例如氢氧根离子）去除，然后在第二步中又有质子添加到氧原子上。

一种醛的碱催化烯醇化



这也是一个很好的机理，因为显示了必须有某物从碳上夺去质子，也显示了氧质子化时质子的来源（本例中为水分子——碱性溶液当然不能直接提供质子）。

注意到，这两个反应中的酸和碱都是只起催化作用的。在酸催化机理的结尾，又重新生成了质子（以  $\text{H}_3\text{O}^+$  的形式）；而在碱催化机理的结尾，也重新得到了氢氧根阴离子。

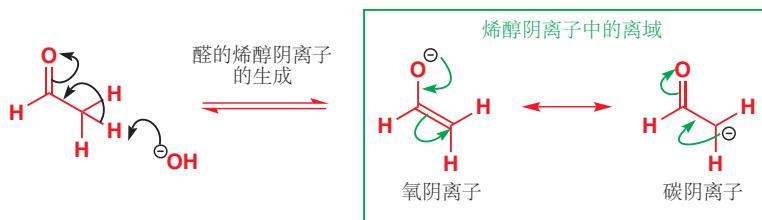
## 碱催化反应的中间体为烯醇阴离子

您还能从碱催化反应中洞悉到更多的见解。其中间体离子被称为 **烯醇阴离子 (enolate ion)**。它是

烯醇的共轭碱，即可以通过羰基化合物直接失去 C–H 质子形成，也可以通过烯醇失去 O–H 质子形成。



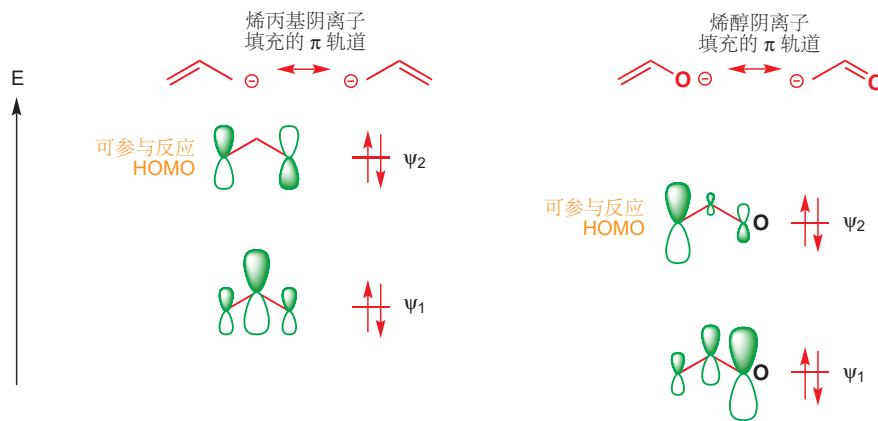
烯醇阴离子是与您在 Chapter 7 中所遇到的烯丙基阴离子有联系的三原子四电子体系。负电荷主要分布在氧，最具电负性的原子上。以最简单的 ( $\text{MeCHO}$  生成的) 烯醇阴离子为例，我们可以用弯曲箭头说明这一点。



烯醇阴离子是一个离域体系，负电荷在 C 和 O 上均有分布——我们使用共轭双箭头连接两种极限式，碳阴离子和氧阴离子，同一事物的两种表达。我们通常倾向于使用氧阴离子的形式，因为它更接近实际。

■ 认识到共轭和互变异构 (羰基化合物酮式与烯醇式的相互转化) 的区别是很重要的。互变异构是两个不同的结构之间存在的真实平衡，必须以平衡箭头表述。

我们可以用轨道说明同样的事情。



如果您不知道这些轨道是从哪里来的，请参看 Chapter 7.

左侧表示的是烯丙基阴离子的充满轨道，右侧表示的是与之对应的烯醇阴离子。烯丙基阳离子固然是对称的，然而当我们用氧原子取代其中一个碳原子后，会有两种改变发生。其一是氧更加负电性，因此两个轨道的能量都被降低了，轨道也发生了变形。其二是低能的原子轨道，即氧的原子轨道对低能分子轨道 ( $\psi_1$ ) 的贡献更大，与之相应，也对  $\psi_2$  的贡献更小。电荷来自两个充满轨道，因此分布于所有三个原子上，但却绝大部分地分布在两端。最重要的是，烯醇阴离子可参与反应的 HOMO ( $\psi_2$ ) 轨道，在末端的碳原子上具有更大的占比。

注：酸性烯醇化得到的物种是中性的烯醇 (enol)，碱性得到的是烯醇阴离子 (enolate anion)，但由于后文中常见直接用“enolate”表示烯醇阴离子的用法，故我会将这种情况译为“烯醇盐”。

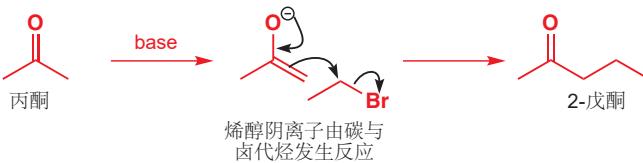
在烯醇阴离子中，氧原子最多的负电荷，而碳原子则分布有最多的 HOMO。因此我们可以期待，以电荷和静电吸引为主导因素的反应发生在氧上，而以轨道相互作用为主导因素的反应发生在邻位碳上。对羰基化合物 (酰氯) 的亲核进攻是以静电吸引为主导因素的，于是烯醇盐对酰氯的进攻发生在氧上，得到烯醇酯。

■ 换句话说，氧是一个硬的亲核位点，而碳是一个软的亲核位点。见 Chapter 15, p. 357.



而对卤代烃的亲核取代反应则发生在碳原子上。

■ 注意，在绘制由碳反应的机理时，并不需要先将负电荷定位在碳上。我们更建议您以更具代表性的氧阴离子结构为起始物，来绘制烯醇盐反应的机理。

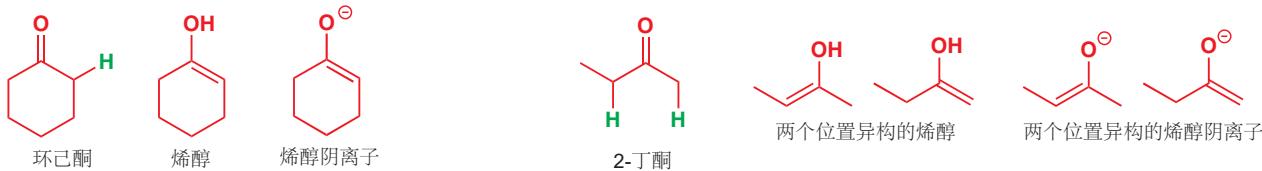


我们会在 Chapter 25 更细致地讨论这一反应。而本章的剩余部分，我们会转向烯醇化导致的一些更简单的结果，和一些烯醇盐与简单的杂原子亲电试剂的反应。

## 烯醇和烯醇盐的种类

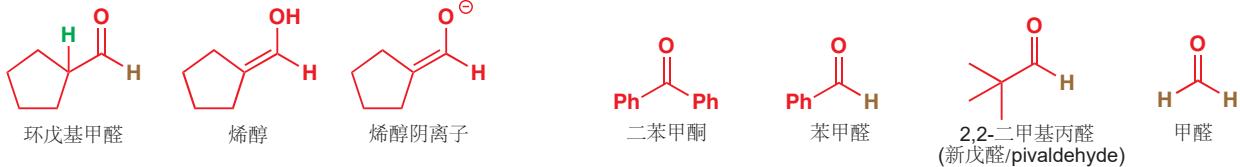
是时候总结和概括由羰基化合物生成的烯醇、烯醇盐的种类了。您已经看到过酮和醛的烯醇化。对于一个不对称的酮，可能生成两种不同的烯醇或烯醇盐。

### 可烯醇化的(Enolizable)酮



醛也可以烯醇化。但，当然，邻位没有氢原子的羧基化合物是不可能发生烯醇化的。

### 可烯醇化的醛

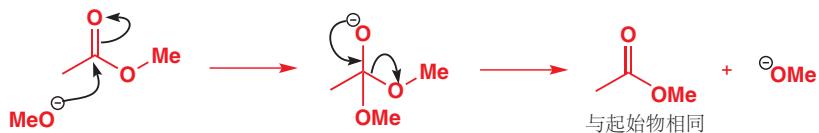


■ 注意，醛基上的质子(棕色所示)是不会发生烯醇化的。它的机理不能被画出。

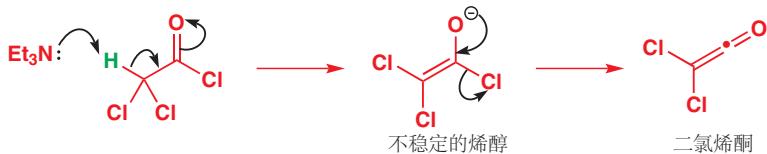
所有羧酸衍生物都具有生成烯醇的这一性质。对于酯则尤为重要，酯的烯醇和烯醇阴离子都可以很轻易制得。显然，酸碱催化时有必要避免水的出现，否则酯在这些条件下水解。一种解决办法是使用酯所对应的醇的烷氧基阴离子做碱（例如甲酯中用  $\text{MeO}^-$ ，乙酯中用  $\text{EtO}^-$ ），来生成烯醇阴离子。



然后，即使烷氧基阴离子做亲核试剂了，也会生成与起始物相同的酯，而对体系没有任何影响。



羰基化合物的烯醇化和被亲核进攻这两个过程中，都有羰基接受电子的一步。因此最亲电的化合物同样是最容易烯醇化的，这使得酰氯非常容易烯醇化。我们不能因为要避免被亲核进攻，而使用氯离子作为碱，因为氯离子并不是碱性的，我们必须找到一个非亲核性碱，例如叔胺。所得烯醇并不稳定，它会消去氯离子，并形成烯酮。这在使用二氯乙酰氯制备二氯烯酮的反应中效果尤为突出，因为要移去的质子酸性很强。

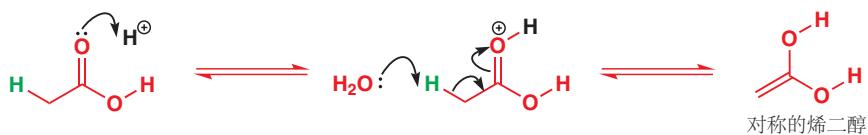


烯酮 (ketene, p. 403) 是有一个同时与一个 O 和一个 C 成两根双键的碳的化合物。这是一个 E1cB 消除，您在 Chapter 17 以及看到了这类内容。

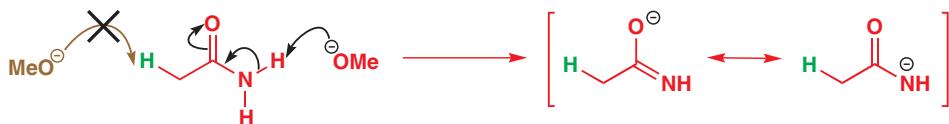
**羧酸**不能轻易地形成烯醇阴离子，因为碱首先会移去酸性的 OH 质子。这种性质也保护了羰基，使其不受绝大部分亲核试剂的进攻。



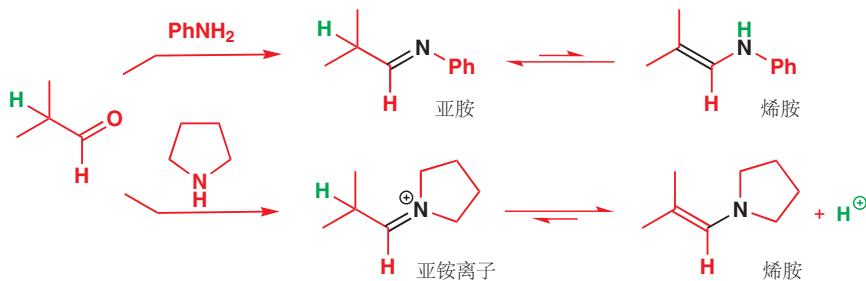
在酸性溶液中没有这一问题，并能够形成“烯二醇 (ene-diols)”。



**酰胺** (除了叔胺) 氨基上的质子，虽然比不上羧基质子，但仍有相当强的酸性。试图形成烯醇阴离子时，碱依然会先移去 N–H 质子而不是 C–H 质子。酰胺也是所有的羧酸衍生物中最不活泼 (受亲核进攻时)、最不易烯醇化的，它们对应的烯醇和烯醇盐很少被用于反应。



很多相似的反应甚至没有必要有羰基。亚胺 (Imines) 和烯胺 (enamines) 之间也是类似的互变异构平衡。



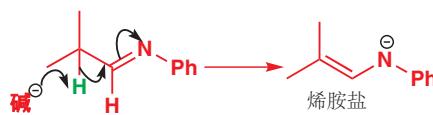
■ 您要确保您能写出醛转变为亚胺的机理：我们在 Chapter 12 中讨论过它们。

对于伯胺 (此处的  $\text{PhNH}_2$ )，可以形成较稳定的烯胺；但对于仲胺 (此处简单的环胺)，却不能形成烯胺本身，而只能形成比烯胺不稳定的烯胺盐。

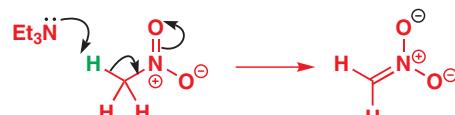
就像烯胺是烯醇的氮杂类似物一样，它同样能形成烯醇盐的类似物，**烯胺盐 (aza-enolates, 氮杂烯醇盐)**。并可由烯胺在强碱下去质子得到。另一种类似物，硝基烷烃也有类似的套路，但硝基烷烃酸性较强，可以在相当弱的碱性下互变为阴离子。

您会在 Chapters 25 和 26 中看到烯胺和烯胺盐所起的作用。硝基烷烃的去质子化在 Chapter 8 (p. 177) 已经讨论过。

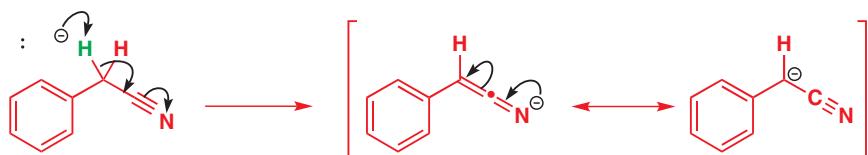
### 烯胺盐的形成



### 硝基甲烷阴离子的形成



腈也可以生成阴离子，但由于负电荷仅能离域到氮原子上，因此需要强碱生成。这个离子是类似烯酮、累计双烯和二氧化碳的直线型物种。



### ● 烯醇化的需求

任何有吸电子官能团的有机化合物，在一个至少含有一个氢的饱和碳原子上连有一个以上的  $\pi$  键，就可以在中性或酸性溶液中生成烯醇。其中的很多还可以在碱性溶液中生成烯醇盐 (除去羧酸，伯胺，仲胺)。

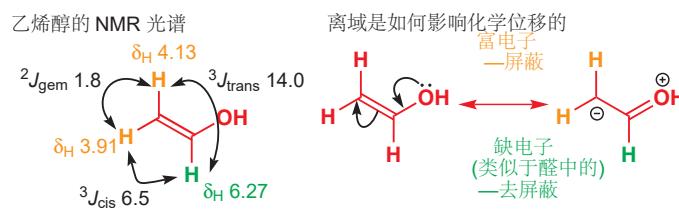
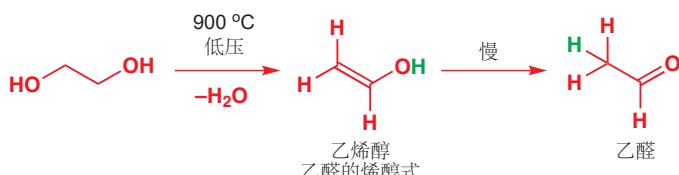
绝大部分化合物的烯醇式在溶液中都不大可能被检测到 ( $10^4$ – $10^6$  份的酮式中有一份的烯醇式)。而有些化合物则有相比之下很稳定的烯醇，这就是下一节的主题，过后我们会回到烯醇和烯醇盐的反应性上来。

## 稳定的烯醇

我们已经确认过，同一分子的烯醇式一般都不如酮式稳定。探索稳定的烯醇有两种方法，其一是在分子上增添一些能使烯醇式稳定的特征，即在热力学上稳定烯醇。其二则是寻找向酮式转化的速度较慢的烯醇——换句话说，就是在动力学上稳定。本节首先考察后者。

### 动力学稳定的烯醇

烯醇式的生成由酸或碱催化。因此这个反应的逆反应——由烯醇式转化到酮式的过程——也一定会被相同的酸或碱催化。如果您在严格的不含酸碱的条件下制备简单的烯醇，当然要使用除去互变异构的其他方法制备，那么它们就会有很长的寿命了。一个很有名的例子是最简单的烯醇，乙烯醇的合成：通过在低压下高温 ( $900^\circ\text{C}$ ) 加热 1,2-乙二醇 (甘醇，glycol——一种防冻剂) 即可获得。乙二醇失去质子，并形成乙醛的烯醇式。它的寿命足以让质子 NMR 光谱观测到，但也会缓慢地转变为乙醛。



光谱说明了双键上氧原子的电子效应。就像您期待的，OH基会不断地向双键放入电子，因此烯烃中紧挨着OH的质子（绿色）被去屏蔽，而另一个碳原子上的两个质子则被屏蔽。双键的耦合常数也如同预期：较大的反式耦合（14.0 Hz）和较小的顺式耦合（6.5 Hz）。极小的偕偶则是末端双键CH<sub>2</sub>基的典型特征。

碳原子很难被质子化是这类烯醇稳定的原因。右侧的例子中，两个苯环取代基包围了烯醇，并阻止了电子化试剂的靠近。环扭曲出双键的平面两侧，并在两个方向阻碍质子的进攻。

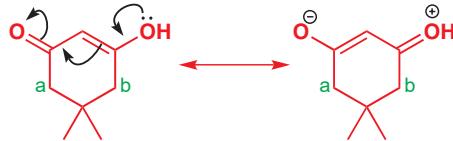
烯烃中的耦合常数在 p. 293 已经解释。

### 热力学稳定的烯醇：1,3-二羰基化合物

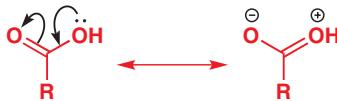
本章是由一个热力学上较稳定的烯醇开始的，即双甲酮的烯醇式，在溶液中占比33%（如右侧所示）。然而，这只是1,3-二羰基化合物（1,3-dicarbonyl compounds）中的一个例子而已（也称为β-二羰基β-dicarbonyls化合物）；这类化合物很多都可以形成大量的烯醇，有些甚至可以在极性溶剂中完全烯醇化。

我们现在需要考察为什么这些烯醇是如此的稳定。主要原因是两个羰基独特的（1,3）排列，使烯醇式中存在共轭——很像羧酸中的共轭。

双甲酮烯醇式中的离域

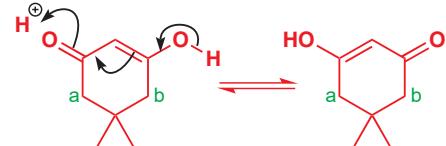


羧酸中的离域

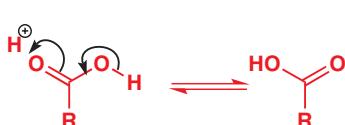


回头看看双甲酮的NMR光谱（p. 450），在烯醇式中，环内的两个CH<sub>2</sub>基（a和b）显然是不相同的，但在光谱中它们却表现为等价的——我们刚才提出的离域观点并不能解释这一现象。这只能意味着烯醇与另一与之完全相同的烯醇处在快速的平衡中。并非离域——由于有质子在移动——因此它也是一种互变异构现象。

双甲酮烯醇式中的互变异构



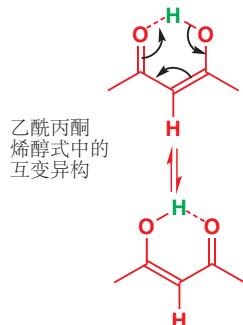
羧酸中的互变异构



我们在 Chapter 16, p. 374. 中谈论到了 NMR 光谱“平均信号”的问题。

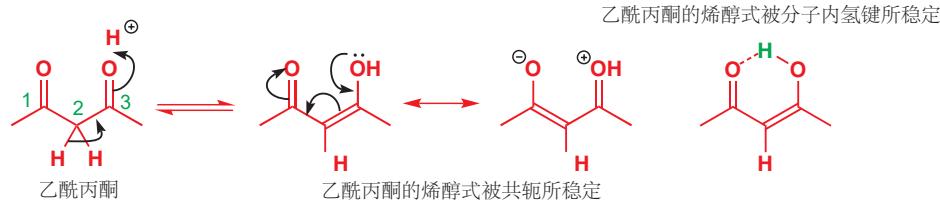
请再次仔细互变异构和离域(共轭)的区别。此处几个例子中两种烯醇的转化,由于质子在分子中的移动,因而是互变异构,用平衡箭头连接;而离域则是电子的移动(当然,不是真实发生的移动),两种结构是同一事物的不同描述方法,之间应用双向箭头链接。

这种氢键在双甲酮中是不存在的。



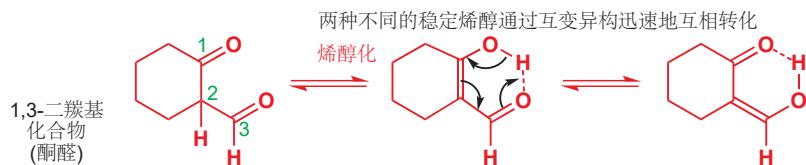
这与羧酸中的情况也是类似的。两种烯醇在  $\text{CDCl}_3$  溶液中迅速达到了平衡(互变异构平衡),以至于 NMR 光谱仪记录的是平均信号。相比之下,本例中烯醇式和酮式之间的平衡则会慢到可以被 NMR 光谱仪记录为分开的信号。

其他的 1,3-二羰基化合物 也大量以烯醇式存在。一些例子中会有额外的稳定化因素,例如分子内氢键。乙酰丙酮 (Acetylacetone, 2,4-丙二酮) 对称烯醇式的稳定化因素,不仅有共轭,还有十分有利的六元环分子内氢键。



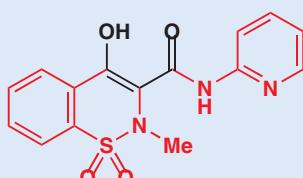
有氢键的烯醇结构看上去不对称,但事实上,就像在双甲酮中的一样,质子转移会导致两种等价的烯醇式结构迅速地转化,即通过互变异构现象。

1,3-二羰基化合物 不需要是对称的,如果它们不对称,那么两种不同的烯醇式会通过质子转移相互转化。下面的环酮醛,几乎完全以一对迅速平衡的烯醇存在。这三个物种的比例可以通过 NMR 测量得到:酮醛占 <1%, 第一种烯醇占 76%, 第二种占 24%。

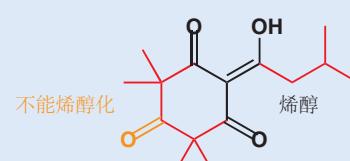


### 更多稳定的烯醇的例子

辉瑞公司开发的消炎药“费啶”(用于治疗关节炎,商品名为吡罗昔康)是一种基于 1,3-二羰基化合物的稳定烯醇。它也含有酰胺基和磺酰胺基,但您应该能找出烯醇的部分。



Piroxicam (Feldene®)  
治疗关节炎 每日一次



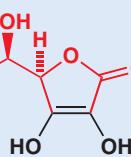
Leptospermone (Callisto®)  
瓶刷状植物美花红千层生产的除草剂

自然界中也存在稳定的烯醇。美花红千层 (*Callistemon citrinus*),一种瓶刷状植物 (bottle-brush plant) 可产生用于抑制竞争的除草剂成分纤精酮 (Leptospermone),目前在玉米保护领域有商品名“Callisto”。它是一种四酮,但几乎完全以互变着的烯醇式存在。注意橘色的羰基并不能形成烯醇:它没有  $\alpha$ -氢。维生素 C 有一个包含两个羰基的五元环,但它一般以一个共轭得十分好的烯二醇(ene-diol)存在。

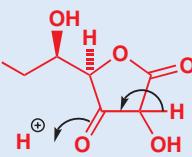
### 一种不稳定的酮式



### 维生素 C 的稳定烯二醇式



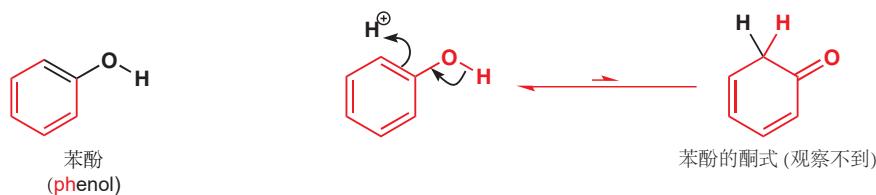
### 另一种不稳定的酮式



我们可以画出离域，并同时解释为什么维生素 C 被称为抗坏血酸(ascorbic acid)。去掉绿色质子后，得到能在 1,3-二羰基体系中离域的离子，因此绿色的质子是有酸性的。



稳定烯醇的极限是“苯-烯醇”(Ph-enol)。芳香醇，亦称酚，它们更倾向于选择芳香性的实质优势，而不是  $C=O$  比  $C=C$  双键略占的一点优势。它们完全以酚的形式存在。就像抗坏血酸，苯酚也颇具酸性 ( $pK_a$  10)——它过去常被称为石炭酸(carabolic acid)。

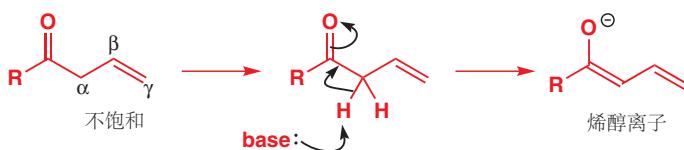


您会在 Chapter 21 看到，这种“酮式”结构会作为苯酚在苯环上的一些反应的中间体。

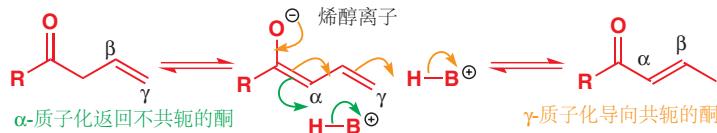
## 烯醇化的结果

### 不稳定的羰基化合物喜好共轭

保持  $\beta,\gamma$ -不饱和羰基化合物的存在是很困难的，因为在有痕量酸或碱的存在下，这种化合物就会通过转变为有共轭的中间体。即在酸性下的烯醇，或者在碱性下的烯醇盐。



然后，如果在  $\alpha$  位质子化，分子会转换回不共轭的酮，而在  $\gamma$  位的质子化则会得到其更稳定的、共轭的异构体。这些反应都处在平衡中，因此这一共轭的异构体则会最终占主导地位。

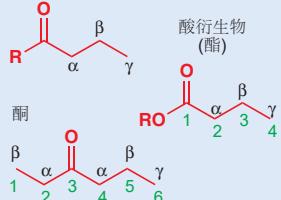


### 外消旋

任何在羰基邻位的立体中心(包含氢)都是不稳固的，因为羰基的烯醇化会摧毁它。尝试制备有光活性的  $\beta$ -酮酯是十分愚蠢的事情，因为唯一的立体中心在两个羰基之间。虽然酮酯是手性的，但烯醇却是平面型的，因而不能有手性，这样在烯醇化和逆烯醇化的平衡中就会最终导致有光活性的酮酯的外消旋。

希腊字母  $\alpha, \beta, \gamma$  等被用作标记与羰基(或其他官能团)相连的碳链上的位置，以邻位开始计算。

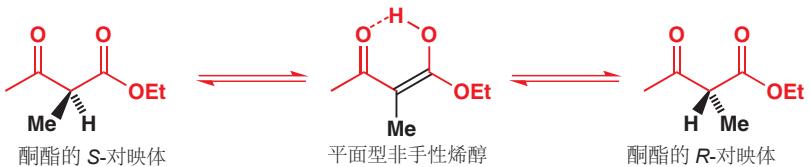
标记羰基化合物中的碳原子



烯醇化位点通常是  $\alpha$ ，在不对称的烷基酮中有两个。 $\alpha, \beta, \gamma$  系统独立于 IUPAC 系统命名规则，系统命名按照如图绿色的序号标记碳链中的原子。

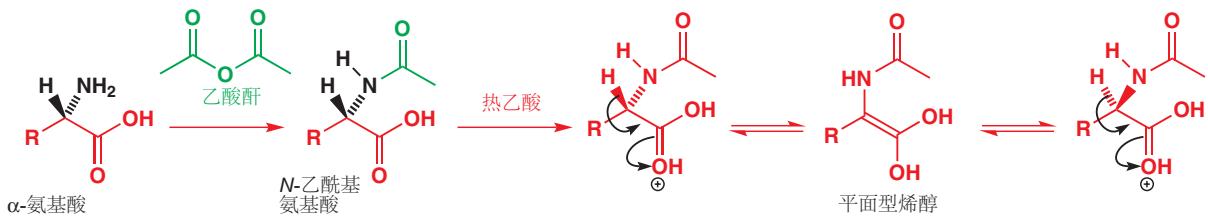
相同的术语规则也可被用于例如氨基酸和酮酯中。





在立体中心旁边有一个羰基的化合物是可以合成的，但需要非常小心。 $\alpha$  氨基酸，蛋白质的组成化合物，就是这样的化合物；但它们非常稳定，在酸或碱的水溶液中不会外消旋化。在碱中，它们以羧酸阴离子的形式存在，如上文所说，不发生烯醇化。酸性下的烯醇化则又会被  $-\text{NH}_3^+$  基的形成而阻止，它会抑制烯醇化中十分必要的质子化。

氨基酸可以与乙酸酐反应，得到它们的 *N*-乙酰基衍生物。这些 *N*-乙酰基酰胺在热乙酸下重结晶，则会发生外消旋化，这无疑是烯醇化导致的。乙酰化后，氨基不再具碱性，不会在酸中质子化，因此对羰基的质子化与由此进行的烯醇化，现在就是可行的了。



我们在 Chapter 14 中讨论了用旋光性拆分剂将对映体转化为非对映体的拆分方法。

将有活性的氨基酸外消旋化，这是个疯狂的主意，看似没有什么用处。然而，假设您正在从外消旋的氨基酸中拆分您想要的纯净 *(S)*-氨基酸，那么这一过程结束后一半的原料则会是您不想要，因此只能丢掉的 *(R)*-对映体。但如果此时您将它们外消旋化，并加入下一次的拆分中，那么您还可以得到占其中一半的 *(S)*-酸。如果您的产物很多，您可以这样一步步外消旋化直到满意。

### 发生在体内的外消旋化

一些化合物会在人体内发生外消旋化。细菌细胞壁的一部分是由人类无法消化的“非自然”*(R)*-氨基酸组成的。但我们可以用酶使其外消旋化。

下面是一种重要的止痛药物，布洛芬，包含基于芳香丙酸的结构。它可以以 Nurofen 为名在药店的柜台上买到。布洛芬仅有 *(S)*-对映体 是有效的止痛药，但该化合物则是以外消旋体的形式提供的。这是由于即使提供了光学纯的对映体，人体本身也会做余下的工作，通过烯醇化使其外消旋化。

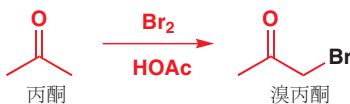


### 烯醇或烯醇盐做中间体的反应

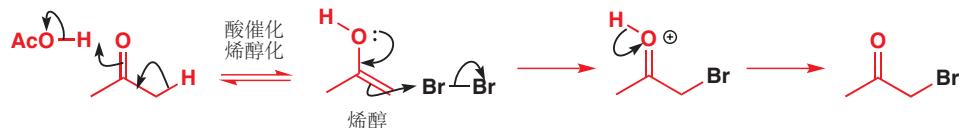
关于烯醇，我们已经看到了同位素交换，双键的移动和共轭，以及烯醇作为中间体的外消旋化过程。而现在，我们要来考察一些经历烯醇的中间体，并且有显著变化的羰基化合物的反应。

## 卤代(酸促)

羰基化合物可以在酸或碱性溶液中与卤素单质(例如溴,  $\text{Br}_2$ )反应, 在 $\alpha$ 位发生卤代。酸催化的反应更加简单, 我们将首先进行讨论。乙酸溶剂下, 酮通常可以干净利落地发生溴代。

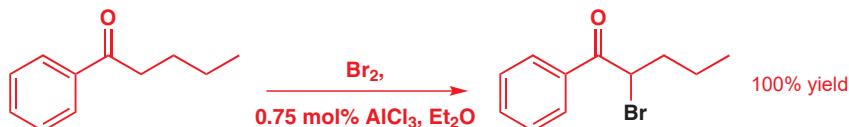


反应的第一步是酸催化的烯醇化, 然后亲电的溴分子进攻烯醇上亲核的碳。箭头可以表示出进攻位点特别地在其中一个碳原子上的原因。

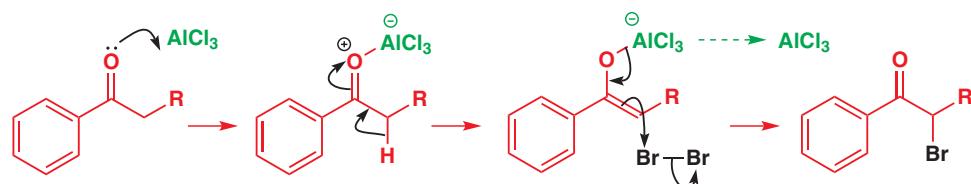


Interactive mechanism for acid-catalysed ketone bromination

注意, 酸催化剂在反应的最后一步重新生成。这个反应并不需要在酸性溶液, 甚至是质子酸中进行。Lewis 酸既可作为酮溴代的良好催化剂。下面是一个不对称酮在乙醚作溶剂,  $\text{AlCl}_3$  催化的条件下 100% 地转化为溴代酮的例子。

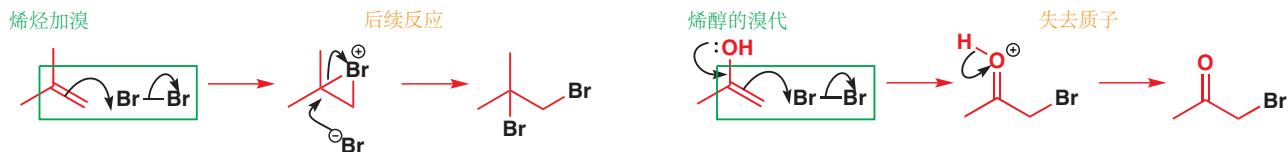


溴代不会发生在分子中的其他位置——不会发生在苯环上(您会在下一章学习的反应, 也许会在上述条件下发生), 因为烯醇比芳香环更加活泼; 也不会发生在脂肪侧链的其他原子上, 因为只有一个位点可以生成烯醇。



本反应的机理与烯烃加溴的机理(p. 427)异曲同工, 只是对溴的进攻被氧原子上的电子对协助了。烯醇的亲核性比普通的烯烃更强——HOMO 能量的升高是其与氧原子上孤对电子的相互作用所引起的, 这看起来与我们在 p. 453 讨论过的烯醇离子 HOMO 的情况没有上面不同。其产物不是溴𬭩离子(并参与后续反应), 而是失去质子(或 Lewis 酸)转化回酮。

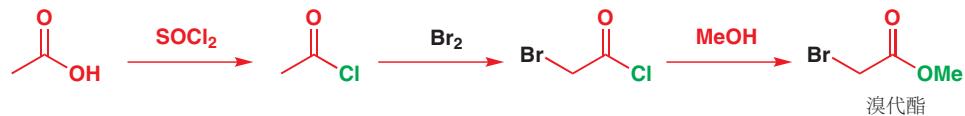
这是这个反应机理的一种不重要的变种写法。从前, 我们用氧的孤对电子协助烯醇对  $\text{Br}_2$  的进攻, 然后在另一个单独的步骤中失去酸催化剂。但左侧的机理意思是  $\text{AlCl}_3$  的离去和来自  $\text{Br}_2$  的进攻同步发生, 这当然是省略步骤的简写。但区分这一点是不必要的, 这两种机理在未来您都会遇到。



羧酸衍生物的溴代反应通常不使用羧酸本身发生, 而是先将其转化为酰氯或酰溴, 不经分离, 直接用其烯醇式制备 $\alpha$ -溴代酰卤。这一过程过去常常直接用红磷和溴单质一步完成, 但现在则通常

■ 在溴代酰氯与甲醇的反应中，进攻发生在羰基上。因为亲核试剂甲醇，是“硬的”亲核试剂（受电荷吸引控制）。如果我们想取代 $\alpha$ -溴，那么我们需要使用软的（轨道主导的）亲核试剂。三苯基膦( $\text{Ph}_3\text{P}$ )可以做这种情况的亲核试剂——产物为可用于Wittig反应的𬭸盐（在Chapters 11和27讨论）。软硬亲核试剂在亲核取代反应中的区别在Chapter 15中已被讨论。

倾向于使用两步；并且溴代酯的制备也不需要任何中间体的分离。我们可以整个过程总结如下。



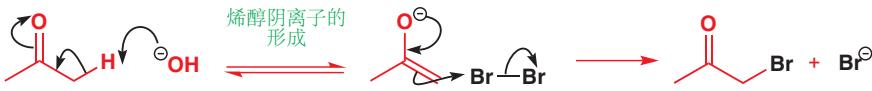
与 $\text{SOCl}_2$ 反应转化为酰氯的过程，和与 $\text{MeOH}$ 反应，将 $\alpha$ -溴代酰氯转化为溴代酯的过程，都是我们在Chapter 10中讨论过的很简单的羰基上的亲核取代反应。居中的过程，很容易烯醇化的酰氯的溴代反应，是一个很典型的烯醇溴代。



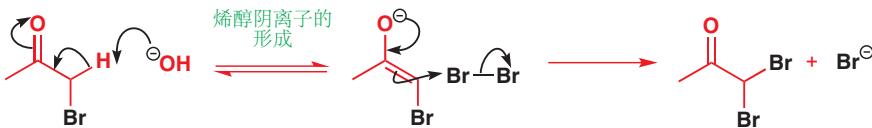
### 碱促卤代(卤仿反应)

碱性下的溴代反应与酸性下的不同，而且较复杂，因为反应通常不会随着仅一个溴原子的引入而终止。我们将以丙酮的溴代为例：第一步是碱催化下的烯醇化，得到烯醇阴离子；烯醇阴离子对溴的进攻与烯醇对溴的进攻相似，烯醇阴离子当然会比烯醇更加活泼（烯醇阴离子带有负电荷）。

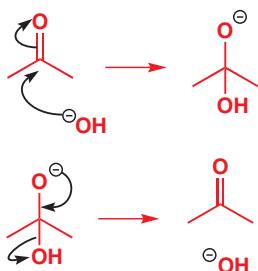
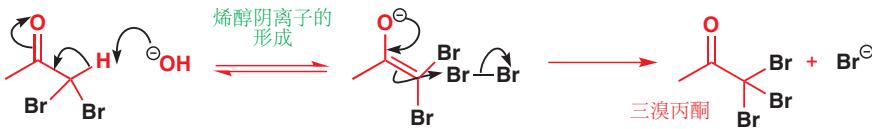
■ 注意，这个反应中的氢氧根离子不会再生——溴离子并不具有碱性，无法和水反应以再生氢氧根离子（Chapter 8）。我们因此需要加入完全等量的氢氧根。



问题在于，反应不会就此而终止。刚刚反应的第一步为去质子，而此时在羰基与溴原子之间的质子比原始的酮中的质子更加具有酸性，因为溴原子有吸电子作用。溴代酮比酮更容易形成烯醇盐。



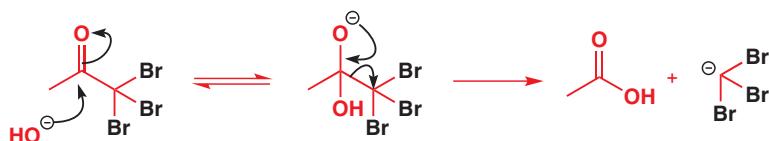
于是形成了二溴丙酮。现在我们还剩一个质子（在羰基与两个溴原子间）。这个质子的酸性又得到了增强，因此会更加快速地生成新的烯醇离子。因此无论溴单质的添加量如何，第一个观察到的产物都会是三溴丙酮。



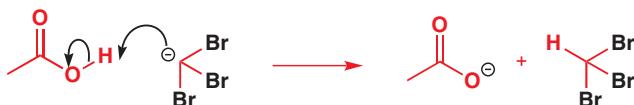
但这也还不是故事的结局。我们需要稍微回溯一点，来探寻它的原因。对于碱性下的烯醇化，您都可以问这样一个问题：“为什么氢氧根作为亲核试剂，不去进攻羰基呢？”答案是，它确实会进攻，左侧边栏是反应的过程。生成四面体中间体。

但接下来会发生什么？四面体中间体会通过逐出一个最容易离去的基团，而转换回羰基化合物。 $\text{Me}^-$ 不可能做这个离去基团，唯一可能的离去基团还是氢氧根离子（水的 $\text{pK}_a = 15.7$ ），因此氢氧根离去，和没进攻时一样。

这种情况持续到三溴代酮的生成。此时 $\text{CBr}_3^-$ 的碳阴离子被三个溴原子所稳定，可以作为离去基团离去。真正意义上的反应发生了：



然后所得的两个产物交换质子，进而得到反应的最终产物——羧酸离子和三溴甲烷 ( $\text{CHBr}_3$ )。



与碘也会发生类似的反应，我们可以用一般结构，含甲基的羰基化合物，总结整个过程。羰基化合物必须含甲基，这是因为碳阴离子离去基团的生成，需要有三个卤原子的参与。

这一反应通常被称作“碘仿”反应 (iodoform reaction)。碘仿是三碘甲烷的旧称，如同氯仿 (chloroform) 直至现在还一直被用于指代三氯甲烷。这是羰基上的亲核取代中，最后导致 C–C 单键断裂的罕见情形之一。



### ● 卤代反应的最佳条件是酸性

羰基化合物的卤代反应应当在酸性溶液中进行。试图在碱性溶液中进行，则会导致多取代和 C–C 键的断裂。

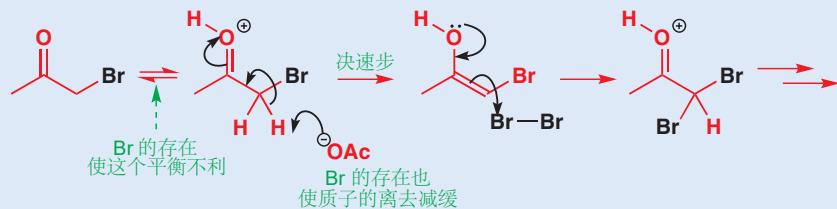
### 为什么酸促卤代反应能很好地进行？

碱促卤代反应会导致所有的氢原子被卤代，其原因已经很清楚了：每一次成功的卤代都会使剩余的质子更具酸性，进而更容易烯醇化。但为什么酸促卤代反应在引入一个卤原子后就停止了呢？更准确的说法是，如果仅加入一当量的卤单质，是可以在单卤代后停止的；如果体系中有更多的卤单质，则卤代反应还会继续。



然而，第二个卤原子在羰基的另一侧取代。很明显，第二次卤代比第一次卤代慢。酸促卤代的大多数中间体都是带正电的，因此卤素的存在会使它们不稳定。溴丙酮的碱性比丙酮弱（氧的电子云密度低），因此更少地生成可反应的质子化形态，这从第一步上就减缓了后续的亲电进攻。

#### 酸性溶液中相同位置上第二个溴的加入 (通常不发生的过程)



$\alpha$  位溴原子的存在还减缓了第二步，即烯醇化的决速步的速率：如果可以从另一个没有 Br 存在的  $\alpha$  位去质子，那么反应更倾向于走那一条路。过渡态表明了溴原子减缓这一步骤的原因，因为结构中邻近溴原子的部分被富集了正电荷。

译者注：

原书上仅在文字框中提了酸性的烯醇、碱性的烯醇阴离子生成时区域选择性的问题(烯醇倾向于多取代，烯醇阴离子倾向于少取代).但我认为有必要再总结一下。

烯醇阴离子(碱性)生成的决速步是去质子的步骤，质子酸性的强弱决定区域选择性。烷基给电子，烷基多的一侧质子酸性弱，因此烯醇阴离子在烷基少的一侧形成。

烯醇(酸性)生成的决速步不是去质子，而是在羰基氧上得电子的步骤，这使得影响烯醇阴离子生成的质子酸性因素并不影响烯醇的生成。反之，羰基吸电子而烷基给电子(稳定正电荷)，在二者之间的键更加稳定，因此双键(烯醇)更容易在这里形成。

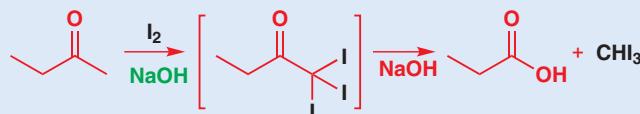
由上述观点来看，烯醇的区域选择性是热力学控制的，而烯醇阴离子是动力学的。如果酮过量，能建立有效的平衡，烯醇阴离子也会倾向于多取代(比如弱碱三乙胺下烯醇硅醚的形成是多取代选择性，而过量的强碱 LDA 下烯醇锂的形成是少取代选择性的)，见 p.599.



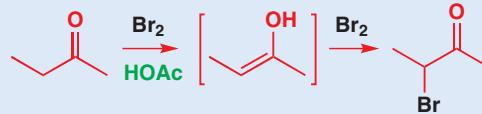
去质子步骤的过渡态

我们可以用一个证据证明这个听起来比较弱的解释：不对称二烷基酮的卤代反应在酸性和碱性下得到不一样的结果，碱促卤代倾向于发生在甲基，取代较少的一侧上；而与之对比，酸促的反应首先(或只)发生在多取代的一侧。这是由于烷基与溴原子取代的效果正好相反——烷基能稳定正电荷。因此烯醇的，有带正电的过渡态的反应，在多取代的位点发生得更快；而烯醇阴离子的，有带负电过渡态的反应，则在少取代的碳原子上发生得快。

### 碱促卤代

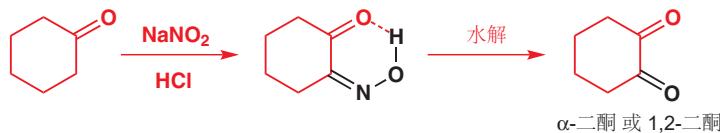


### 酸促卤代



## 烯醇的亚硝化

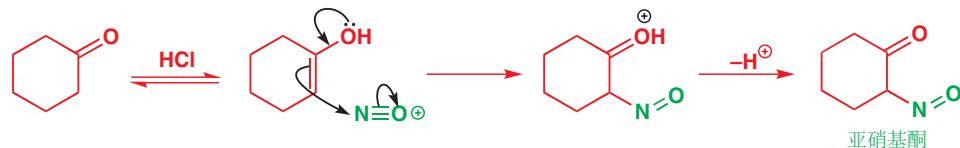
下面是一个氯做亲电试剂的反应，这既是一个有关烯醇反应性的例子，又能提醒我们，除去羰基外的其他官能团(如亚胺)也能发生互变异构。现在，假设您有一个羰基化合物，并想在原先的羰基的邻位引入一个另一个羰基。那么下面是您可能会选择的一种方法：



第一步包含弱酸亚硝酸 nitrous acid ( $\text{HNO}_2$ , 或  $\text{HONO}$ ) 在其钠盐与强酸  $\text{HCl}$  的存在下形成的过程。亚硝酸随后会质子化，并失去水，生成可反应的亲电试剂  $\text{NO}^+$ .

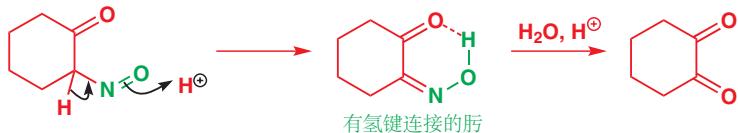


这个双原子阳离子，与一氧化碳等电子。它以氮做亲电位点，进攻酮的烯醇式，得到一个不稳定的亚硝基化合物 (nitroso compound).

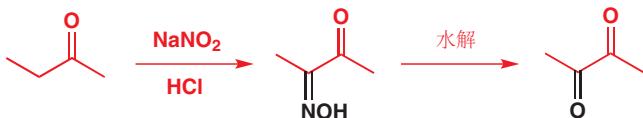


亚硝基化合物不稳定，可以通过质子由碳向氧的转移互变异构化。这一过程很与烯醇化很相似，仅是将 C=O 换做了 N=O，产物“烯醇”则换做稳定的肟（oxime）。肟上的 O—H 可以与邻位的酮羰基形成分子内氢键。肟的水解得到第二个酮。

亚硝基官能团， $\text{N}=\text{O}$ ，可能对您来说是陌生的；您在 Chapter 11 曾遇到过肟。亚胺（或肟）的水解在 Chapter 11 中也讨论过。



这个反应在酸性下进行，因此如果酮是不对称的，它就会以与酸促卤代反应相同的原因在多取代的一侧进行（见 p. 463 文字框）。

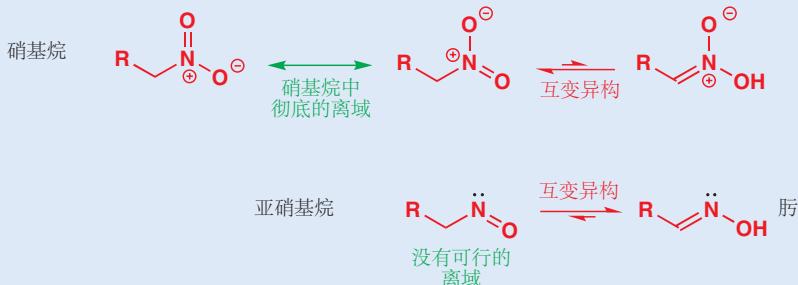


学习更多反应之前，我们希望您从烯醇、烯醇盐与  $\text{Br}_2$  和  $\text{NO}^+$  的反应中总结一些信息：

- 烯醇和烯醇盐通常在碳上与亲电试剂反应。

## 亚硝基

硝基（nitro）和亚硝基（nitroso）的区别在于氧化态和共轭。更稳定的硝基有一个没有孤对电子，三角型的氮原子； $\text{N}=\text{O}$  键是离域的。而亚硝基官能团则有一个有孤对电子在平面上的三角型氮原子； $\text{N}=\text{O}$  键不是离域的。它们都可以形成“烯醇”，但平衡偏向不同方向。



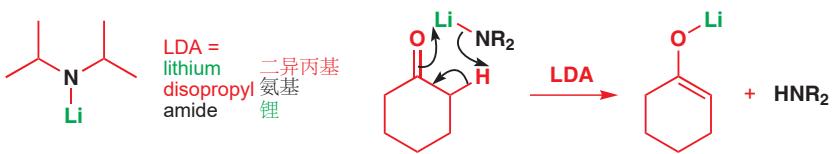
## 稳定烯醇等价物

### 烯醇锂

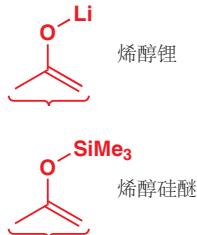
即使是像氢氧根，或者烷氧基阴离子这样比较强的碱，都只能使大部分羰基化合物烯醇化很少的程度。有代表性的羰基化合物中，羰基邻位（ $\alpha$ ）质子的  $\text{pK}_a$  大约在 20–25，而甲醇的  $\text{pK}_a$  为 16，因此理论上每  $10^4$  份羰基化合物会烯醇化 1 份。用更强的碱会改变这种情况，烯醇会定量地由羰基化合物生成，我们会在 Chapters 25 和 26 中利用这一重要的结果。这种碱通常是 LDA（二异丙基氨基锂），它按如下方式作用：

您已经在 Chapter 17 中遇到过 LDA 催化的消除反应（p. 398），但这种碱的其他各用途都比不上我们现在要告诉您的这个重要。目前为止，LDA 最大的用途就是制备烯醇锂。

 Interactive mechanism for lithium enolate formation with LDA



■ 不要用 BuLi 作为羧基化合物的去质子试剂。因为 BuLi 一贯会作为亲核试剂进攻羧基。

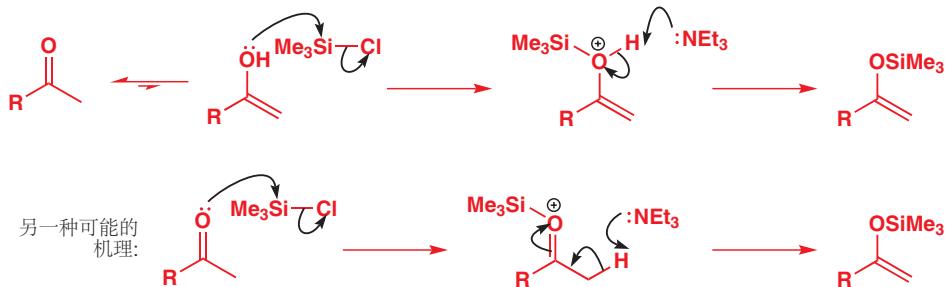


LDA 是叔胺，因此它不会作为亲核试剂进攻羧基，只会用作碱——二异丙基胺的  $pK_a$  大约为 35，其阴离子用作羧基邻位的去质子化绰绰有余。烯醇锂 (lithium enolate) 在低温 ( $-78^{\circ}\text{C}$ ) 下稳定，但用作反应也是足够的。烯醇锂是化学上最常用的稳定烯醇等价物。

### 烯醇硅醚

仅次于烯醇锂的稳定烯醇等价物是烯醇硅醚 (silyl enol ethers). 硅和锂相比亲电性较弱，而烯醇硅醚也更加稳定，反应性较差。它们通过烯醇盐与硅亲电试剂的反应制备。硅亲电试剂与烯醇盐的反应一贯首先发生在氧上，第一个原因是因为硅亲电试剂较硬 (见 pp. 357 和 467)，第二个原因是因为非常强的 Si—O 单键。最常见的硅亲电试剂是三甲基氯硅烷 ( $\text{Me}_3\text{SiCl}$ )，一种在工业上批量生产的中间体，常被用于制造 NMR 标准，四甲基硅烷 ( $\text{Me}_4\text{Si}$ )。

硅—氧 键很强，因此即使在没有强碱催化烯醇的形成时，也可以与羧基化合物在氧上反应：反应很可能是通过中性溶液中存在的较少量的烯醇分子进行的，然后需要弱碱 ( $\text{Et}_3\text{N}$ ) 从产物中移去质子。另一种看法是烯醇直接与羧基氧反应，然后碱用于将锌离子转化为烯醇硅醚。下方展示了这两种机理——它们都可能是正确的。这是由几乎任何可烯醇化的羧基化合物，制备稳定烯醇等价物的两种最佳方法之一。

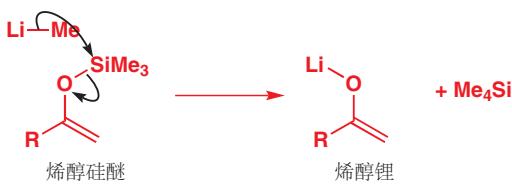


烯醇硅醚也可以由烯醇锂与三甲基氯硅烷的反应制备。



► 在 Chapter 25 中，您会了解执行这一看起来毫无意义的反应的原因 (为了制备多取代区域选择性的烯醇锂)。

偶尔，我们也需要进行这一反应的逆过程，由烯醇硅醚生成烯醇锂。我们可以用甲基锂完成这一过程，甲基锂会亲核进攻硅原子，并得到烯醇锂和四甲基硅烷。



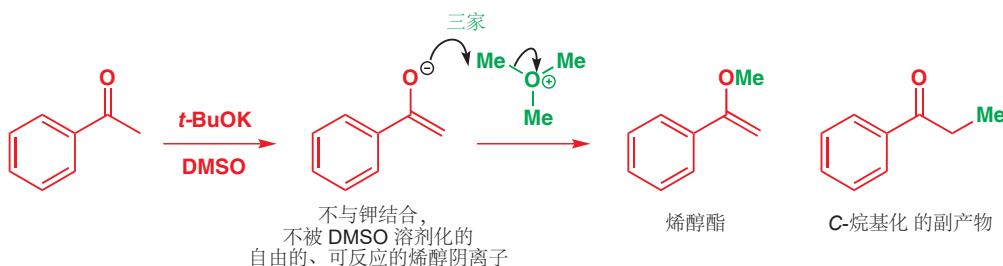
我们还会在本书中继续讨论烯醇硅醚和烯醇锂，但此时您只需要将其简单地看作足够稳定的，可以定量地由羰基化合物形成的，能进行烯醇的后续反应的烯醇盐生物即可。

## 烯醇和烯醇盐氧参与的反应：烯醇醚的制备

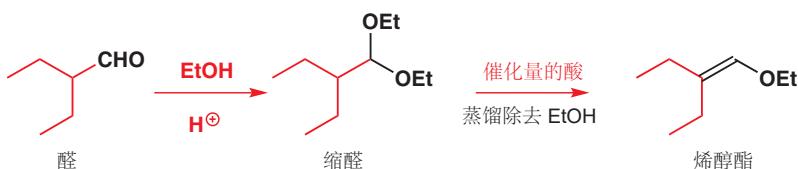
您刚刚已经看到了烯醇硅醚可以很容易地制得。如果烯醇离子的氧原子上带了其大部分的负电荷，它就应当也能够用于制备普通的，基于碳的醚。但通常烯醇和烯醇盐倾向于与烷基化试剂（例如烷基卤）在碳原子上反应（Chapter 25）；在氧原子上反应则需要异常的条件。如果烯醇离子处于有钾盐碱的非质子偶极溶剂（例如二甲亚砜，DMSO），即不能溶剂化氧阴离子的溶剂中，就可以与硫酸二甲酯或三甲基锌离子——最好是有带正电原子的，很强的甲基化试剂反应，得到烯醇醚。 $\text{Me}_3\text{O}^+$  出现于较稳定（但也很活泼）的化合物三甲基锌四氟合硼酸盐（trimethyloxonium tetrafluoroborate），或 Meerwein 盐（Meerwein's salt）， $\text{Me}_3\text{O}^+\text{BF}_4^-$  中。这一化合物和硫酸二甲酯， $\text{Me}_2\text{SO}_4$ ，都是有高度极化的 C–O 键的硬亲电试剂，因此可以与烯醇盐在较硬的 O 上，而不是较软的 C 上反应。



→ 软硬试剂的概念在 Chapter 15, p. 357 讨论过。



这一反应的产率大约为 60–70% 的烯醇酯，剩余的大体上是 C-烷基化 产物。制备烯醇酯更可靠的方法是在严格除水、酸催化的条件下分解缩醛。



■ 缩醛的生成已在 Chapter 11 中讨论过。第二步中如果有水存在，则体系会水解回最初的醛。

反应的开始（阳离子的生成）也出现于缩醛的水解中，但此情况下由于没有水的存在，替代水的进攻的是质子的离去。换句话说，如果没有合适的亲核试剂用作  $S_N1$  取代，那么 E1 消除就会发生。



烯醇醚相当稳定，尤其是酸性催化下（下一节将介绍的）；它并不能像烯醇硅醚一样用于反应。我们接下来将考察这两类烯醇醚的类烯醇反应。

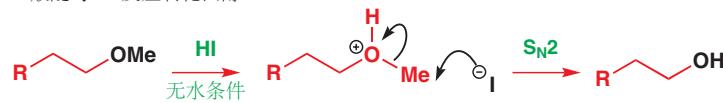
## 烯醇醚的反应

### 烯醇醚的水解

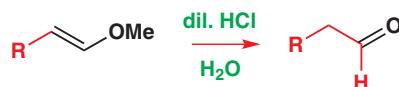
见 p. 351 中关于“一般”醚的不反应性的讨论。

烯醇有 OH 基，也属于一类醇。一般的醇在生成稳定醚后都很难再转化回醇，我们在 Chapter 15 中讨论过这一过程，它需要很强的试剂例如 HI 或  $\text{BBr}_3$ ，与 HI 的反应是对质子化的醚上甲基的  $\text{S}_{\text{N}}2$  攻击，因此需要对饱和碳原子反应性好的亲核试剂，例如碘或溴离子的参与。与之对比，烯醇硅醚相对不稳定，在酸性水溶液中——例如稀 HCl 或  $\text{H}_2\text{SO}_4$  中就轻易地转化回羰基化合物。

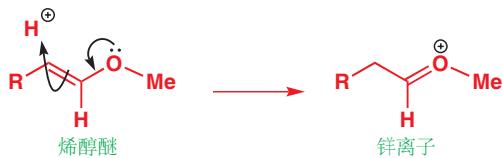
一般醚与 HI 反应转化回醇



烯醇醚与酸的水溶液反应水解



这种差异来源于何处？原因在于，烯醇醚可以通过氧原子上孤对电子的离域，使碳原子质子化，进而得到一个易反应的锌离子。



随后锌离子可以以与一般的醚相同的方式，在甲基上被进攻。

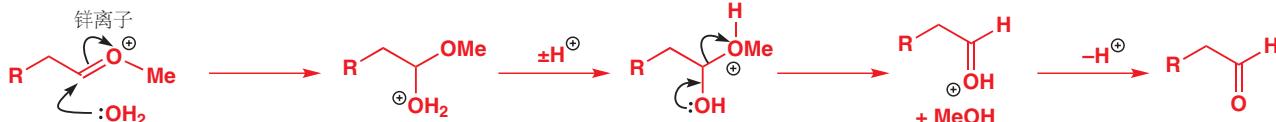


我们看不出这一过程比普通醚上的同一过程要快多少，因此必定有另一个更好的、更快的机理存在。这种机理是对  $\pi$  键的进攻，而不是对  $\sigma$  键的进攻。

■ 对  $\pi$  键的进攻比对  $\sigma$  键的进攻天生的速率优势，这是因为较弱的  $\pi$  电子更容易因 C 和 O 电负性的差异而极化。

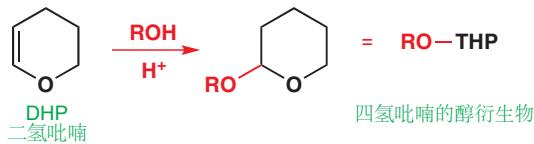


在酸的水溶液中，亲核试剂  $\text{X}^-$  就是水，这与缩醛的水解 (Chapter 11, p. 226) 是十分一致的，这两个反应机理都有作为中间体的锌离子。

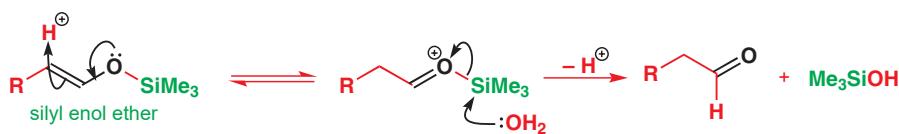


在酸性的醇溶液，没有水的存在下，也会发生另一个类似的反应。这也是缩醛水解的机理，只不过正好反过来，是生成缩醛的机理。下面是 THP (四氢吡喃，tetrahydropyran) 的醇衍生物生成的实用例子；您会在 Chapter 23 中看到 THP 的醇盐生物用作保护基。

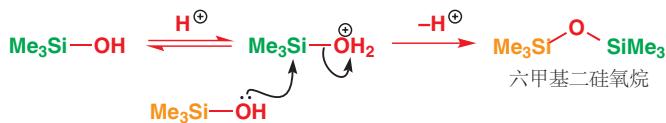
→ 这一反应的机理可以参考 p. 550 中 THP 保护基的内容，然而您应当是可以独立写出的。



烯醇硅醚的水解是通过一个略有不同的机理完成的，虽然第一步——氧上孤对电子协助的碳的质子化是相同的。我们之前已经看过，亲核试剂对硅的进攻是十分容易的，尤其是以氧或卤素作为亲核原子的亲核试剂。因此下一步中最快的过程是水直接进攻硅的反应。

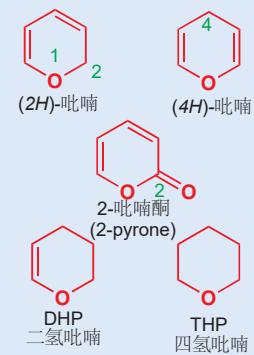


醛立即生成。而另一个产物则会与另一个同样的分子结合，给出二硅基醚 (disilyl ether, 也称二硅氧烷 disiloxane)，这一后续过程也说明了硅容易被亲核进攻的本质。



### 吡喃

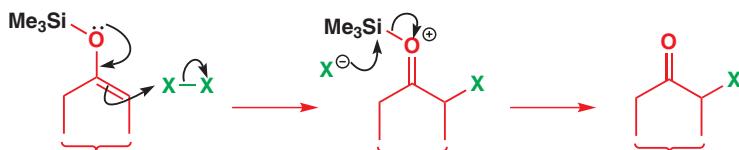
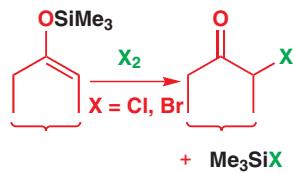
吡喃 (Pyran) 是含氧的六元杂环，包含两个双键。它并不是芳香性的。类似的有一个双键的化合物称为二氢吡喃 (dihydropyran)，饱和的环体系则成为四氢吡喃 (tetrahydropyran)。



### 烯醇醚与卤素和硫的亲电试剂的反应

作为醚，任何种类的烯醇醚都比其他醚活泼。而作为烯烃，由于有带孤对电子的氧原子，它们的反应性也比普通烯烃强。它们也与亲电试剂例如溴、氯单质在  $\alpha$  碳原子上反应，这是烯醇衍生物的行为方式，而并不类似于普通烯烃。

亲电进攻发生在  $\alpha$  碳上，在同一步中卤素离子被释放，然后卤素离子会进攻硅原子，并得到产物分子和会在后处理中被水解的  $\text{Me}_3\text{SiX}$ 。

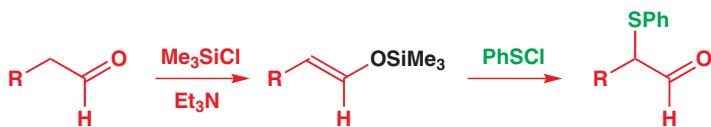


这一程序避免了我们先前描述的醛酮卤代的一大困难。即它可以用于制备在羰基化合物较少的一侧卤代的卤代酮。

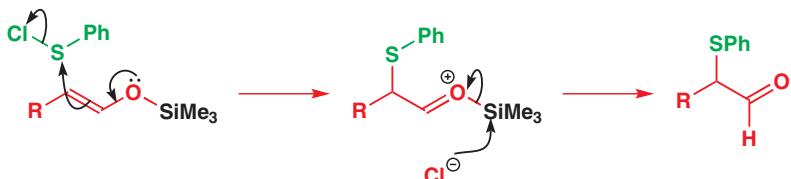


→ LDA 移去羰基较小空阻的质子，这一性质 p. 600 还有更多讨论。

用类似的方法，换成另一个较好的软亲电试剂  $\text{PhSCl}$ ，则还可以在羰基邻位硫基化 (sulfenylation)。



机理十分相似：亲电的硫原子进攻 烯醇硅醚的  $\alpha$  碳原子，失去的氯离子移去中间体中的  $\text{Me}_3\text{Si}$  基。



## 小结

现在您已经看到了烯醇和烯醇盐如何与基于氢 (氘)、碳、卤素、硅、硫和氮的亲电试剂反应。以通常的亲电模式，与烷基卤或另一羰基化合物反应，形成新的 碳–碳 键的过程还有待考察，这是 Chapters 25–26 中要讨论的主题。接下来我们将着眼于芳香化合物与亲电试剂的反应，您会感受到它与烯醇行为方式的相似性。

## 延伸阅读

S. Warren, *Chemistry of the Carbonyl Group*, Wiley, Chichester, 1974; of *Practical Organic Chemistry*, Longman, 5th edn, 1989, 在 pp. 722–725 有关于羧酸卤代的描述，在 pp. 782–783 有亚胺和烯胺生成的描述，在 pp. 627–631 有烯醇亚硝化的描述。

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 芳香亲电取代

## 联系

### 基础

- 分子结构 ch4
- 共轭 ch7
- 机理和催化剂 ch12
- 对烯烃的亲电加成 ch19
- 烯醇和烯醇盐 ch20

### 目标

- 苯酚，芳香烯醇
- 苯和烯烃的对比：芳香化合物的特点是什么？
- 苯上的亲电进攻
- 对苯环的活化和钝化
- 取代的位置
- 详细描述芳香结构：竞争与合作
- 一些芳香取代反应的问题与解决的方法

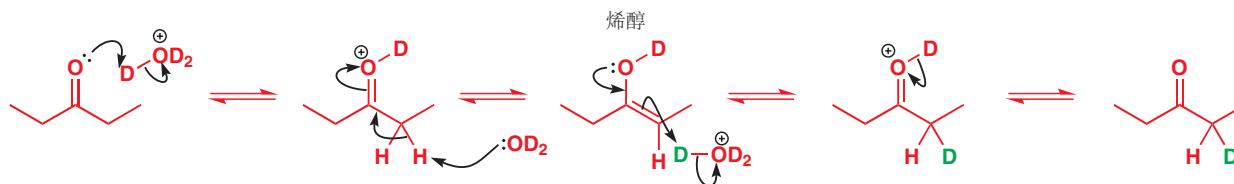
### 展望

- 芳香亲核取代反应 ch22
- 氧化和还原 ch23
- 区域选择性和邻位锂化 ch24
- 逆合成分析 ch28
- 芳杂环 ch29 & ch30
- 重排 ch36
- 过渡金属催化的芳香化合物的偶联 ch40

## 引入：烯醇和酚

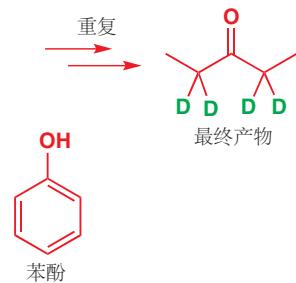
在上一章中，您看到很多酮都有一个有亲核性的“他我(alter ego)”，称为一个烯醇互变体。烯醇互变体的生成由酸或碱催化。并且，由于酮和烯醇处于平衡，在  $D_2O$  存在下的酮的烯醇化会导致其  $\alpha$  位的质子被氘原子所取代。以下是 3-戊酮在酸性  $D_2O$  中的变化：

■ 如果您还没有阅读 Chapter 20，请至少先翻到 p. 451 了解烯醇互变的原理。

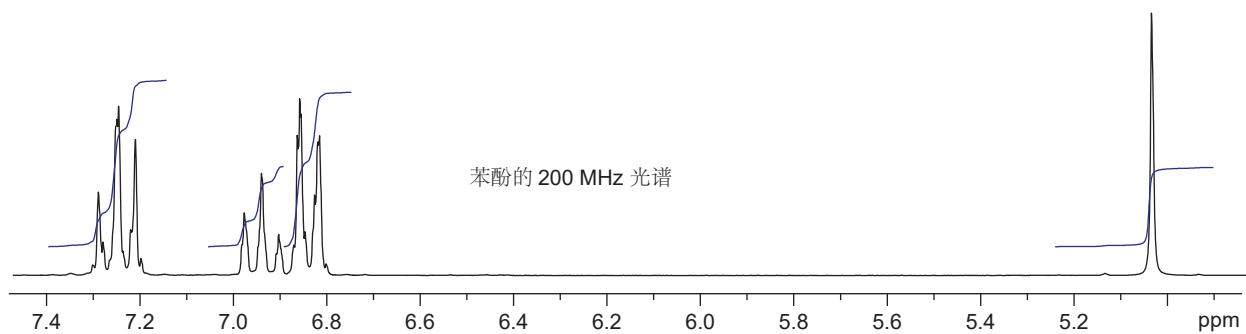


由于烯醇化和氘代的过程可以重复，最后全部的  $\alpha$ -质子都会被氘原子取代。

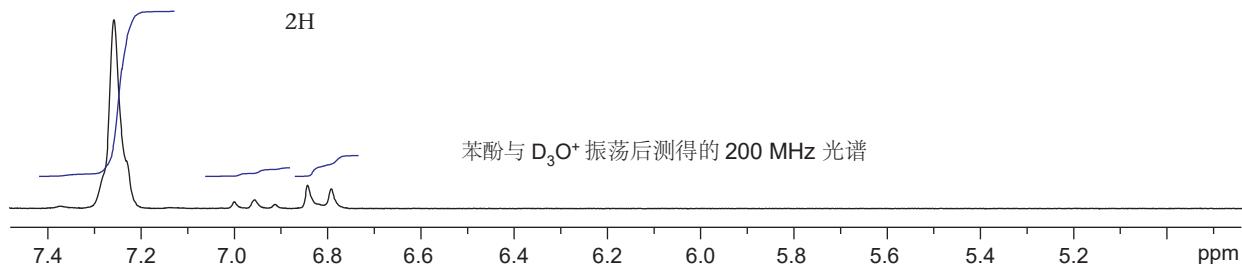
酮氘代的过程证实了烯醇式的存在，而 酮/烯醇平衡 往往会偏向酮式的一侧。在本章中我们将要讨论与上一章类似的一类反应，但其中的化合物却是完全以其烯醇式存在的。这种稳定的烯醇就是苯酚(phenol)，它稳定存在的原因是苯环的芳香性所导致的。



苯酚的质子 NMR 光谱如下所示。在阅读本页阐释的其他内容前，请确保您能分配光谱。

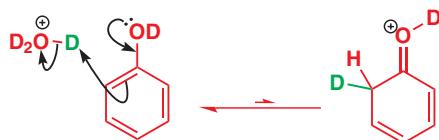


下一幅图为用酸性  $D_2O$  振荡苯酚后所得的 NMR。大多数峰几乎都消失了，因为 H 原子被 D 原子所取代。只有一个信号仍保持相同的尺寸，由于它失去了原有的与相邻质子的偶合，因此也被简化了。

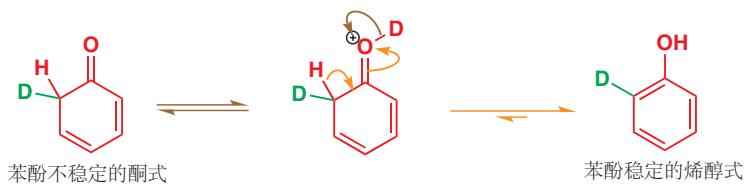


剩下的信号是芳环 3 和 5 号位质子的信号，因此产物应如边栏所示。我们可以用前一页酮的反应的相同机理解释这一现象。苯酚与其他烯醇以相同方式被氘代，唯一的区别是得到的酮式产物会回到非常稳定的、芳香的烯醇式。第一步（不算 OH 初期被 OD 取代）是  $D_3O^+$  对烯醇的加成。

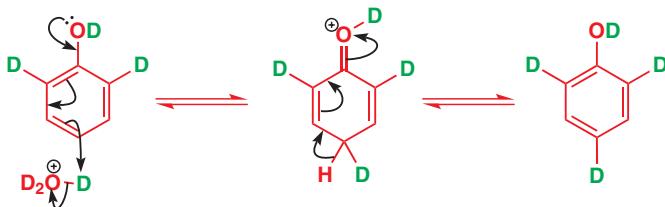
这个平衡已在 p. 456 讨论。



现在，这个阳离子可以从氧上失去 D 以留下一个酮（棕色箭头），也可以从碳上失去一个质子得到苯酚（橘色箭头）。或者，它也可以从碳上失去 D，但这会回到起始原料，这也是为什么上方图表中用的是平衡箭头。



光谱告诉我们，三个质子被 D 取代——在 2, 4, 和 6 号位的三个。OH 另一侧的邻位，C-6 上的质子如何被取代是不难被看出的。但 4 号位的 D 是如何得到的呢？苯酚的烯醇是共轭的，我们可以像下图这样，将弯曲箭头再往前推一步。

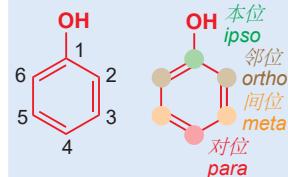


在  $D_3O^+$  中处理苯酚得到的最终产物，是在 2, 4, 和 6 位 (即邻位 *ortho* 和对位 *para*) 的质子被氘原子取代的产物。 $D_3O^+$  做亲电试剂，整个过程被称为亲电取代 (*electrophilic substitution*)。这不仅是苯酚的特征反应，而且也适用于其他芳香化合物，这就是本章的主题。

- 芳香化合物与亲电试剂，往往通过芳香亲电取代反应。

### 芳环上的取代基

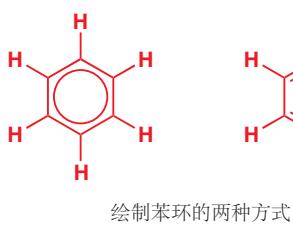
提醒，苯环上相对于某一取代基的其他位点有自己的名称 (见 pp. 36 and 416)：



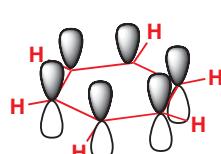
*Ortho*, *meta*, 和 *para* 有时缩写作 *o*, *m*, 和 *p*。

## 苯及其与亲电试剂的反应

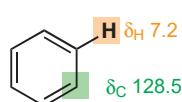
我们将从最一般的芳香化合物——苯开始。苯是一个对称的平面六边形，有六个三角型 ( $sp^2$ ) 碳原子，每一个碳都带有一个位于环平面上的氢原子。所有的键长均为  $1.39 \text{ \AA}$  (对比  $C-C$   $1.47 \text{ \AA}$  和  $C=C$   $1.33 \text{ \AA}$ )。每个  $^{13}\text{C}$  位移都相同 ( $\delta_{\text{C}}$  128.5)。



绘制苯环的两种方式



$\pi$  体系



NMR 数据

苯特殊的稳定性 (芳香性) 来源于由六个碳的 p 原子轨道重叠构成的，带有六个  $\pi$  电子的三个分子轨道。这些轨道的简并为分子提供了额外的稳定性 (理论上比有三根共轭的双键的分子稳定  $140 \text{ kJ mol}^{-1}$ )，六个等价氢在 NMR 光谱中的位移 ( $\delta_{\text{H}}$  7.2) 也是有位于离域  $\pi$  体系中的环的证据。

► Chapter 7 中讨论了苯的分子轨道。

### 如何绘制苯环

苯是对称的，在结构中画一个圆圈，最能说明这一特点。然而，这种表示方法不允许我们绘制弯曲箭头的机理，因此我们通常会使用三根双键交替的 Kekulé 式 (Kekulé form)。但这并不代表我们认为双键是定域的！您可以随意选择两种 Kekulé 结构——任何机理在两种结构上都同样可以画的很好。

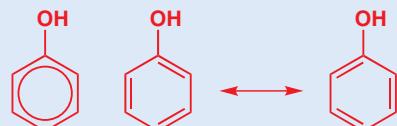
圆圈结构式可以很好地表示离域的  $\pi$  电子。



这两种 Kekulé 结构都是用于绘制机理的最好表达。它们也是等价的。



三种可以接受的苯酚画法。  
Kekulé 画法是等价的。



萘 (Naphthalene)。中间的结构是最好的表达；第一种结构不能准确地表示电子数；最后一种结构不能清楚地表达中间的短键。

在有取代基的芳香分子，例如苯酚中，环上的 C-C 键长不再完全相等。然而，基于绘制的目的，使用哪种表达也都是正确的。而对于另一些芳香化合物，例如萘，由于键长的交替分布，就需要合理地选择 Kekulé 结构式了。只有第一种 Kekulé 式表达了中心键是整个分子中最强、最短的，而 C1-C2 键又比 C2-C3 键短。如果在环中画圆圈表示六个  $\pi$  电子，那两个圆圈就应表示 12 个，不过萘只有 10 个，这使圆圈表达式不再令人满意。

### 对苯和环己烯的亲电进攻

简单的烯烃，包括环己烷，都可以与溴、过氧酸 peroxy-acids/peracid (Chapter 19) 等亲电试剂反应。溴给出反式加成的产物，环己烷给出顺式加成的环氧化物。但在相同条件下，苯却不能与这些试剂反应。



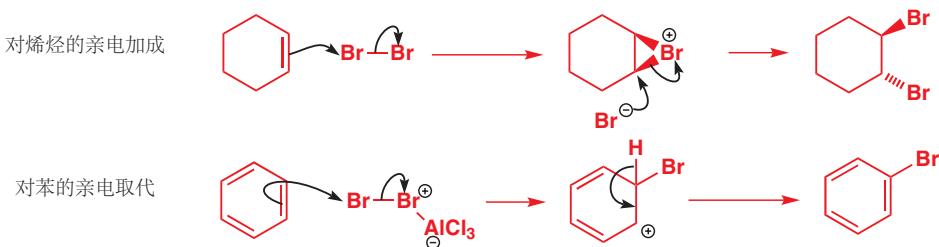
► p. 180 介绍了 Lewis 酸。

如果加入 Lewis 酸催化剂，例如  $\text{AlCl}_3$ ，苯则勉强可以与溴反应。产物包含溴原子，但其过程既不是顺式加成，也不是反式加成。



溴原子取代了其中一个氢原子，因此这是一个取代反应。溴 ( $\text{Br}_2$ ) 是亲电试剂，苯是芳香化合物，因此这个反应是本章在讨论的，**芳香亲电取代 (electrophilic aromatic substitution)**。

我们可以将环己烯与苯的溴化反应进行对比。



两个反应的中间体都是阳离子，但环己烯的反应随后是阴离子的加入，而苯的反应随后则是质子的离去，以恢复芳香体系 (regenerate/restore aromaticity)。另外要注意到，烯烃直接与中性的溴反应，而苯的反应，则需要阳离子  $\text{AlCl}_3$  络合物。溴本身就是很活泼的亲电试剂，它是一种需要特殊预防措施的危险化合物。就算如此，它仍然不能直接和苯反应。这说明了苯与任何试剂反应的困难性。

#### ● 苯十分不活泼

- 它只与非常活泼 (通常是阳离子的) 亲电试剂反应。
- 它给出取代产物，而非加成产物。

### 芳香亲电取代的中间图是一个离域的阳离子

我们将在本章中反反复复地提到芳香亲电取代的机理。其机理最一般的形式包含两个阶段：亲电试剂进攻得到中间体阳离子，和阳离子中质子的离去以恢复芳香性。

芳香亲电取代的一般机理



阳离子中间体，当然与起始原料、产物相比，都是不稳定的。但它归根结底被离域所稳定。下方共振式展示了正电荷在两个邻位和一个对位离域的情况，也可以用带有半键的离域结构式表示，这三个碳原子，每个带三分之一个单位的正电荷 (+).



画出棕色的 H 是为了强调，这个离域的阳离子是非芳香性的。

很重要的一点是，虽然这个阳离子是离域的，但它并不具有芳香性：环包含一个四面体型 ( $sp^3$  杂化的) 碳原子，因此并没有环状排列的 p 轨道。这个碳原子就是取代位点的碳原子，在上图中，我们通过画出其上的氢原子来强调它是四面体型原子——这个氢原子会伴随芳香性的恢复而离去；我们建议您在绘制芳香亲电取代的机理时，也这样做。由于这一步 (阳离子的生成) 包含芳香性的丧失，因此它理所当然是芳香亲电取代的决速步。

### 我们怎么知道阳离子中间体的存在？

在强酸中，亲电试剂是质子，并且这种阳离子事实上可以被观察到。我们需要选用一个既没有亲核性，也没有碱性的反荷离子  $X^-$ ，例如  $SbF_6^-$ 。在这个八面体型阴离子中，中心锑原子被氟原子环绕，负电荷分布于七个原子上。质子化的过程在  $-120^\circ\text{C}$  的  $FSO_3H$  和  $SbF_5$  混酸中进行。在 Chapter 15 中，我们用相似的方法证明了  $S_N1$  机理中阳离子中间体的存在。



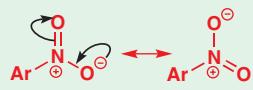
这些条件允许我们记录阳离子的  $^1\text{H}$  和  $^{13}\text{C}$  NMR 光谱。位移表明，正电荷分布在环上，并在邻位和对位分布最密 (i.e. 电子云密度最低)。用  $^1\text{H}$  和  $^{13}\text{C}$  NMR 位移的数值 (分别是  $\delta_H$  和苯的  $\delta_C$ )，可以计算出电荷分布的多少，这与我们用共振式预测的高度吻合。

	位置	$\delta_H$	$\delta_C$
0.26+      0.26+	1	5.6	52.2
0.09+      0.09+	2,6	9.7	186.6
0.30+      0.30+	3,5	8.6	136.9
	4	9.3	178.1
苯 (用作对比)		7.33	129.7

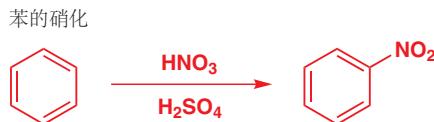
### 苯的硝化

刚才介绍的是芳香亲电取代的一般规则，现在我们需要着眼于细节，探究一些苯的真实反应。每个情形中，为了使苯做亲核试剂参与反应，都需要很强的阳离子亲电试剂。

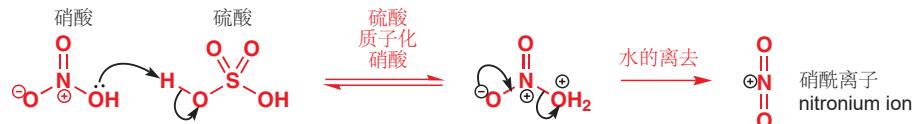
■ Chapter 2 讨论过硝基的离域结构。



我们将以硝化反应，硝基( $\text{nitro, } \text{NO}_2$ )的引入开始。硝化反应需要很强的试剂，最典型的是浓硝酸和浓硫酸的混酸。



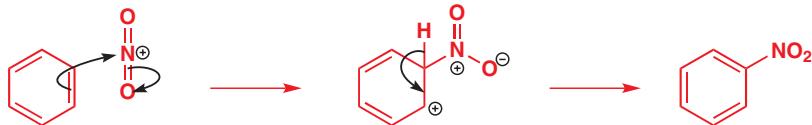
硫酸做强酸，用于质子化硝酸，离去水后产生强亲电试剂  $\text{NO}_2^+$ 。



硝酰离子( $\text{NO}_2^+$ )是直线型的——与  $\text{CO}_2$  等电子，中心氮原子为  $\text{sp}$  杂化。苯进攻这个氮原子，然后为避免五价氮(five-valent nitrogen)的产生，断裂其中一根  $\text{N}=\text{O}$  键。

Interactive mechanism for nitration of benzene

■ 提醒您：画出取代位点的  $\text{H}$ ，这能帮助您完成芳香亲电取代的机理。



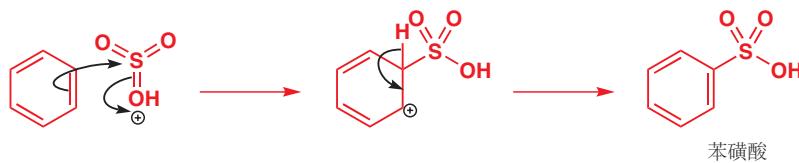
● 硝化反应指芳香化合物( $\text{ArH}$ )向硝基芳香化合物( $\text{ArNO}_2$ )的转化，试剂为由  $\text{HNO}_3 + \text{H}_2\text{SO}_4$  产生的  $\text{NO}_2^+$ 。

## 苯的磺化

苯与硫酸给出苯磺酸(benzenesulfonic acid)的反应进行得很慢。一分子的硫酸被另一分子的硫酸质子化，然后离去水。这一步与上文硝化反应的第一步是相似的。



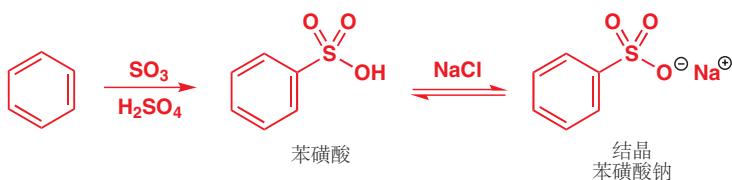
生成的阳离子非常活泼，与溴化、硝化反应以相同的机理进攻苯环——对  $\pi$  体系缓慢的加成，和随后发生的，伴随芳香性恢复的快速的质子离去。



Interactive mechanism for sulfonation of benzene

产物包含磺酸基(sulfonic acid group)—— $\text{SO}_3\text{OH}$ 。磺酸是强酸，大约与硫酸本身相同。它们比  $\text{HCl}$  酸性强，可以通过加入过量的  $\text{NaCl}$  以其钠盐的形式从混合溶液中结晶分离出来。能与  $\text{NaCl}$

反应的化合物并没有多少！

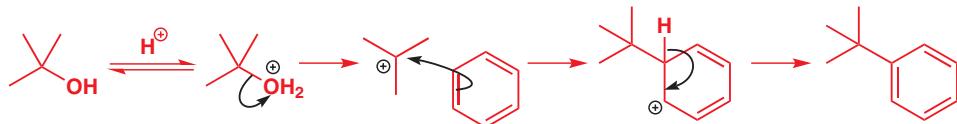


► 在 Chapter 15 中，您遇到过以极好的离去基团出现过的对甲苯磺酰基，也是与之相关的磺酸根离子。

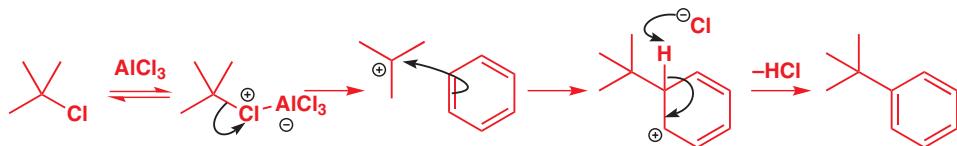
- 磺化反应是  $\text{H}_2\text{SO}_4$  或  $\text{SO}_3$  在  $\text{H}_2\text{SO}_4$  中将芳香化合物 ( $\text{ArH}$ ) 转化为芳香磺酸 ( $\text{ArSO}_3\text{OH}$ )。其中亲电试剂为  $\text{SO}_3$  或  $\text{SO}_3^{\text{H}+}$ 。

### 苯环可以通过 Friedel–Crafts 反应添加烷基或酰基取代基

到目前为止，我们所添加的都是杂原子——溴、氮，或硫。但如果想在此不情愿的芳香亲核试剂上，添加碳取代基，那么就需要高活性的碳亲核试剂，即碳阳离子。在 Chapter 15 中曾提到，任何亲核试剂，无论有多弱，都会与碳阳离子发生  $\text{S}_{\text{N}}1$  反应：苯环也毫不例外。由叔丁醇在酸性下生成的叔丁基阳离子，就是经典的  $\text{S}_{\text{N}}1$  亲电试剂。

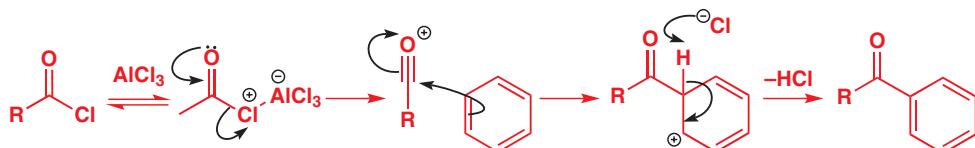


这种反应的一种更为普遍的变体被称作 Friedel–Crafts 烷基化反应 (傅-克烷基化反应, Friedel–Crafts alkylation)，方法是用叔烷基氯与 Lewis 酸  $\text{AlCl}_3$  处理苯。与苯溴代的反应不同， $\text{AlCl}_3$  先从  $t\text{-BuCl}$  上移去氯，并释放  $t\text{-Bu}$  阳离子，以进行烷基化反应。



我们通常不会去追究移去中间体质子的，是哪一种碱。上个例子中，这种碱是氯离子，生成副产品  $\text{HCl}$ ，您也能发现，多么弱的碱都可以胜任这份工作。水、氯离子，或者其他强酸的共轭碱，都是可以的，您不需要考虑确切的试剂。

比起烷基化更加重要的，是 Friedel–Crafts 酰基化反应 (傅-克酰基化反应, Friedel–Crafts acylation)，试剂为酰氯和  $\text{AlCl}_3$ 。三氯化铝于酰氯的反应类似于其与氯代烷的反应——移去酰氯的质子，并留下一个阳离子。此时，阳离子是直线型的酰基离子 (acylium ion)，并且相邻氧上的孤对电子还对碳阳离子起稳定作用。当酰基离子被苯环进攻时，得到的是芳香酮：苯环于是被酰基化了。



法国化学家 Charles Friedel (1832–1899) 和美国的采矿工程师 James Crafts (1839–1917)，都曾在 Wurtz 的实验室学习，后来它们一起在巴黎工作，并在那里，于 1877 年发现了这两个反应。

Interactive mechanism for Friedel–Crafts alkylation

Interactive mechanism for Friedel–Crafts acylation

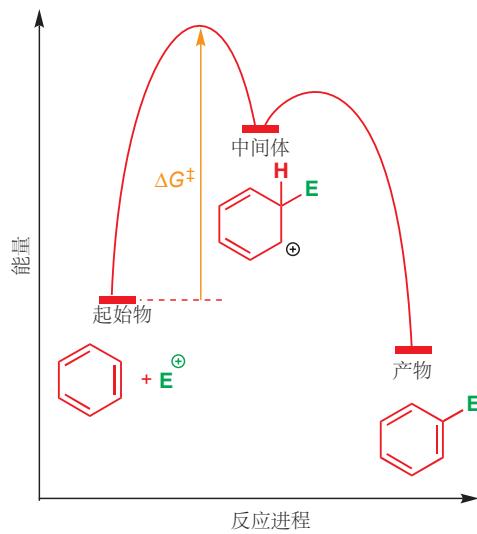
► We'll come back (on p. 492) to why this is and what can be done about it.

酰基化比烷基化更加好用，这是因为它对酰氯的结构特征没有特殊要求——R 可以是任何基团。而在烷基化中，最基本的要求是烷基阳离子可以形成，否则后续的反应都不能很好地进行。另外，酰基化反应会在一次取代后便停止，而烷基化反应通常给出混合的产物，这是我们接下来要探索的内容。

### ● Friedel-Crafts 反应

Friedel-Crafts 烷基化：叔丁基氯与 Lewis 酸（通常是  $\text{AlCl}_3$ ）参与反应，给出叔丁基苯。更可靠的 Friedel-Crafts 酰基化反应：酰氯与 Lewis 酸（通常是  $\text{AlCl}_3$ ）参与反应，给出芳基酮。

### 总结苯上的亲电取代



■ 这一结论是建立在 **Hammond 假说 (哈蒙德假说, Hammond postulate)** 的基础上的，该假说认为，能量上相近（能够直接在彼此间转化）的两个结构，在结构上也是相近的。更多讨论见 Chapter 39。

### ● 苯环亲电取代的主要反应

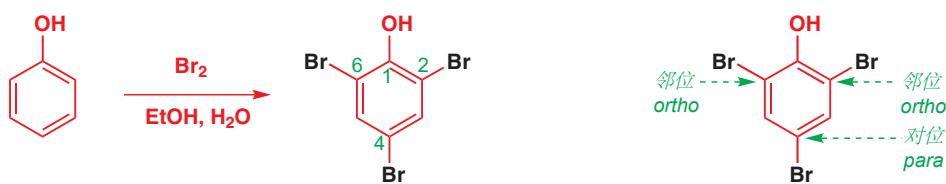
反应	试剂	亲电试剂	产物
溴代	$\text{Br}_2$ 和 Lewis 酸 e.g. $\text{AlCl}_3$ , $\text{FeBr}_3$ , Fe 粉		
硝化	$\text{HNO}_3 + \text{H}_2\text{SO}_4$		
磺化	浓 $\text{H}_2\text{SO}_4$ 或 $\text{H}_2\text{SO}_4 + \text{SO}_3$ (发烟硫酸)		
Friedel-Crafts 烷基化	$\text{RX} + \text{Lewis 酸}$ 通常是 $\text{AlCl}_3$		
Friedel-Crafts 酰基化	$\text{RCOCl} + \text{Lewis 酸}$ 通常是 $\text{AlCl}_3$		

## 苯酚上的亲电取代

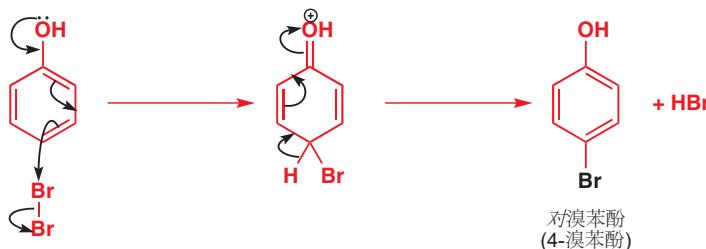
本章是以酚和烯醇的对比开篇的，而现在我们将重回到酚亲电取代的讨论，并且会更加具体。您会发现它的反应比苯本身的反应更容易理解，因为酚就像是烯醇，而酚进行的同样的反应（溴代，硝化，磺化，以及 Friedel-Crafts 反应）也都更容易发生。并且，有一个新的问题油然而生了：酚环上的各个位点不再等价——那么取代该发生在哪呢？

### 苯酚与溴迅速反应

苯只会在 Lewis 酸催化作用下才能和溴反应，但酚与之截然不同：不需要 Lewis 酸的催化，反应也能很迅速地发生，产物为在三个特定的位点溴代的三溴苯酚。将溴滴入苯酚的乙醇溶液中就可以开始这个反应。起初，溴的黄色消失，当颜色稳定时加入水，白色沉淀 2,4,6-三溴苯酚就随时生成了。



产物表明，溴代发生于对位和两个邻位。这与苯形成了多么鲜明的对比呀！苯酚在室温下，不需要催化剂，反应三次；而苯则需要 Lewis 酸的催化，才能勉强使反应进行一次。这种区别的原因在于苯酚的烯醇性质。氧非键轨道上孤电子对的参与，使苯上原本低能的成键轨道成为更高能的 HOMO。我们将用机理展示这一理论，由对位的溴代开始：

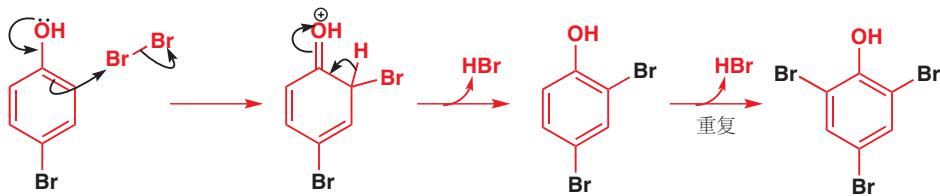


为什么在一些描述中，我们既然用了数字表示位点，例如 2,4-二溴苯酚，但还是要用邻位和对位这样的用语呢。命名化合物时，用数字是最好的选择；但在叙述取代基间的相对位置时，对位、邻位这些用语就很有用了。如果我们想说两个邻位溴代的苯酚，在这个分子中它们可能是位置 2 和 6，但如果 OH 基不在 C1，它们又会有其他编号，这时用邻位就能叙述更加普遍的规律。您应在叙述时选择适合自己观点的描述方式。

■ 这一机理会让您想起 Chapter 20 中烯醇的溴代。

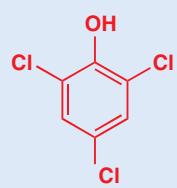
注意，箭头发端于 OH 基上的孤对电子，这对电子穿过环，在对位出现，并进攻溴分子。这个过程中，苯环起了导体 (conductor) 的作用，使得 OH 上的电子可以流向溴分子。

反应再次进行，这时电子对出现的位点变为了两个等价的对位中的一个：



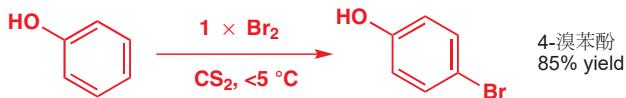
OH 基的孤对电子再次穿过苯环，并出现于邻位。第三次的溴代发生于剩下的邻位——您可以画出机理用作练习——得到最终产物 2,4,6-三溴苯酚。

与氯发生的类似反应用做生产一种广为人知的防腐剂 TCP (2,4,6-三氯苯酚)。TCP 独有的味道也是很多其他酚类的特征气味。

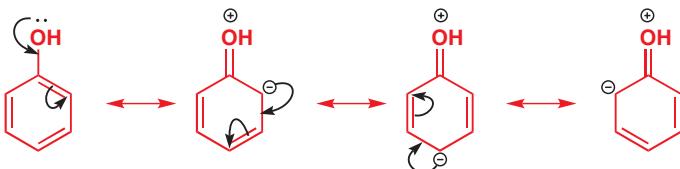


2,4,6-三氯苯酚 (TCP)

如果您仅想在苯酚上加入一个溴原子，那么您必须在低温 ( $<5^{\circ}\text{C}$ ) 下进行反应，并只加入一当量的溴。最好的溶剂是相当危险的挥发性二硫化碳 ( $\text{CS}_2$ )， $\text{CO}_2$  的硫代物。在这些条件下，可以以很好的产率生成主产物对溴苯酚（这也是为什么我们刚刚画三溴代机理时由对位出发）。次要产物为邻溴苯酚。

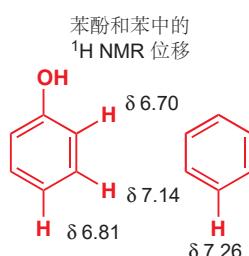


我们称 OH 基对亲电试剂有 **邻对位定位 (ortho, para-directing)** 作用，此之谓定位效应 (directing effect, 或 orientation)。取代不发生与任何一个间位。我们可以通过观察弯曲箭头，或者观察分子轨道来理解这一现象。在 Chapter 20 (p. 453) 中我们考察了一个烯醇阴离子的  $\pi$  体系，它的电子云密度主要集中于末端原子（氧和碳）。在酚中，富电子的原子是邻位和对位的原子（当然还要氧本身）。我们可以用弯曲箭头表示这一特征。



弯曲箭头的表述可以反映 HOMO 的电子分布。这是因为，HOMO 轨道系数的分布是交替的 (alternate)，就像是烯丙基阴离子在两端，而不是中间有较大的系数 (Chapter 7)。

### NMR 对电子分布的验证



苯酚的  $^1\text{H}$  NMR 位移反映了  $\pi$  体系的电子分布。某一核周围的电子云密度越大，它受屏蔽就越多，进而位移也就越小（见 Chapter 13）。酚中所有环质子的化学位移都比在苯中的 (7.26 ppm) 小，这意味着总体上酚环的电子云密度大于苯。邻位和对位间的区别很小：它们都是电子云密度最大的地方，因此也是亲电进攻的位点。间位的化学位移与原本的苯环相比，区别都不显著——这是电子云密度最低的地方。

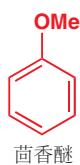
#### ● 苯酚上的亲电进攻

苯环上的 OH 基是邻对位定位基、活化基。

如果您将箭头始于 OH 基上的孤对电子，您会得到正确的产物。

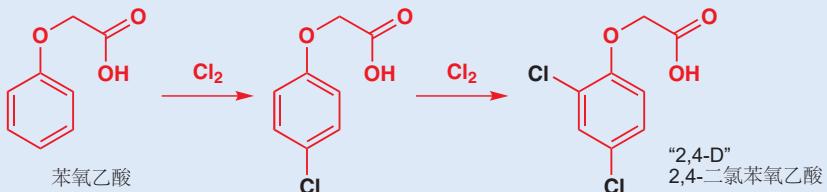
### 氧取代基活化苯环

想使苯酚溴代，我们只需要将溴与苯酚混合就可以了一——但如果我们换做苯，那么什么也不会发生。因此我们说，相比于苯，苯酚中的 OH 基活化 (activate) 了面对亲电进攻的环。OH 基既是活化 (activating) 基，又是邻对位定位基，其他可以给出电子的基团同样有这两点性质。茴香醚（苯甲醚）是苯酚的“烯醇醚”。它与亲电试剂的反应比苯快。

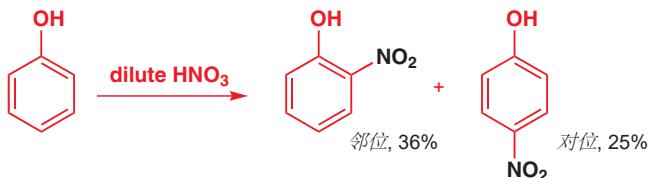


2,4-D

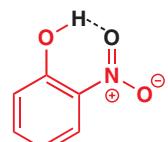
另一种氧取代化合物，苯氧乙酸的多氯代可以得到一种有用的产物。用两当量的氯来氯代可得到 2,4-二氯苯氧乙酸，也就是除草剂 2,4-D。氧取代基再一次火化了环，并将氯代位点定位在邻、对位。



苯酚的硝化也进行的非常快，但在通常的硝化条件( $\text{conc. HNO}_3$ ,  $\text{conc. H}_2\text{SO}_4$ )下会出现问题，因为浓硝酸会氧化苯酚。解决方案是使用稀硝酸。虽然此时  $\text{NO}_2^+$  的浓度小，但对于活化的苯环仍然是足够的。



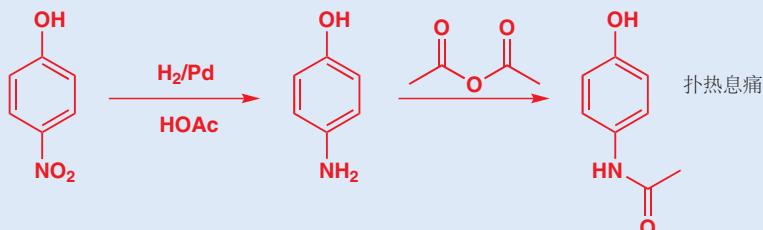
产物是邻-、对-硝基苯酚的混合物，其中，邻位化合物可以通过水蒸气蒸馏 (steam distillation) 蒸出以分离。强的分子内氢键降低了 OH 形成分子间氢键的可行性，因此邻位化合物有较低的沸点。



强的分子内 H 键

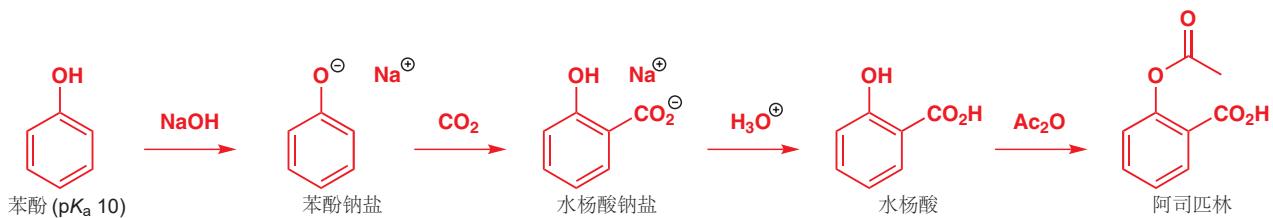
#### 由酚生成扑热息痛

剩下的对-硝基苯酚可用于批量生产止痛药扑热息痛 paracetamol (也被称作对乙酰氨基酚 acetaminophen)。

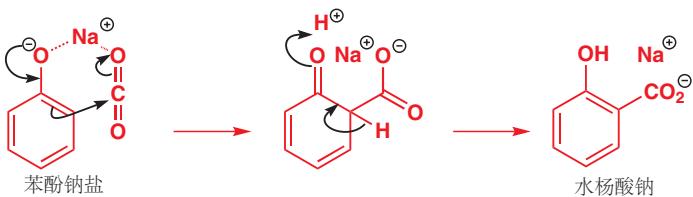


苯氧基离子 (phenoxide ion) 面对亲电进攻甚至有比酚更强的反应性。它甚至于二氧化碳这样弱的亲电试剂发生反应。这一反应被称作 **Kolbe–Schmitt 过程** (**Kolbe–Schmitt process**)，工业上被用于制备水杨酸 salicylic acid (2-羟基苯甲酸)，合成阿司匹林的前体。

■ 水杨酸 (Salicylic acid)  
即 2-羟基苯甲酸，首次分  
离于柳树 (柳属, *genus Salic-*  
*x*)，进而得名。

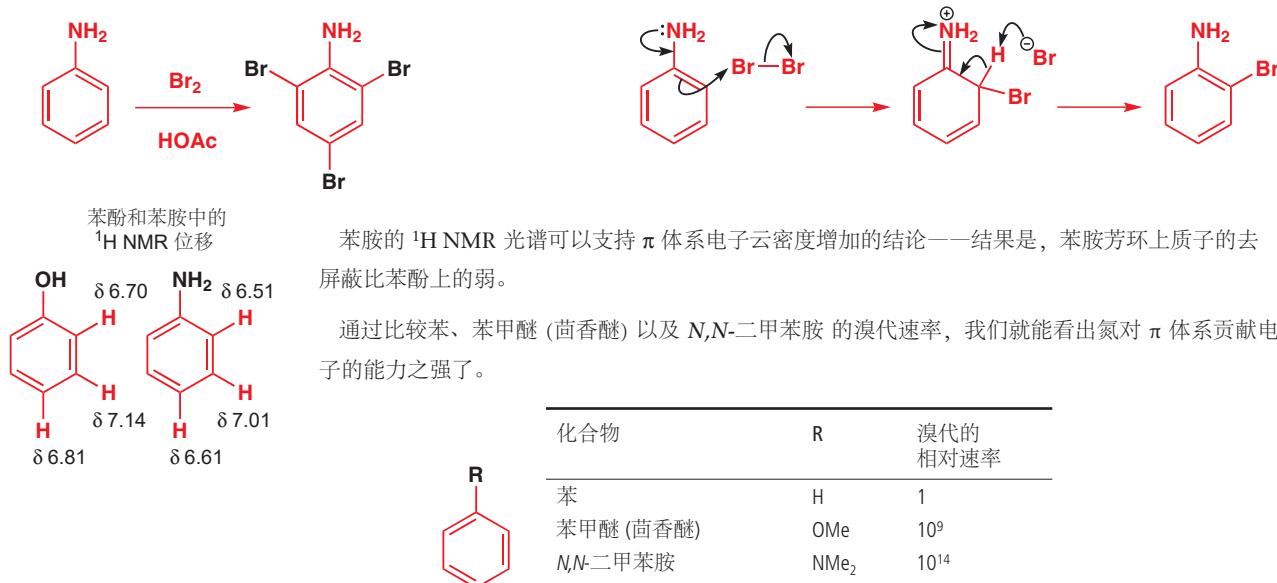


$\text{O}^-$  取代基是邻对位定位基，但与  $\text{CO}_2$  的亲电取代则主要是邻位产物。这是因为钠离子同时与酚氧原子、 $\text{CO}_2$  存在配位作用，进而将亲电试剂送至邻位。



## 氮上孤对电子的活化作用

苯胺 (Aniline) 对于亲电试剂的反应性比苯酚、苯酚醚甚至苯氧基离子都要强。这是因为氮的电负性比氧小，进而，相比于氧，其孤对电子的能量更高，因此也更容易与  $\pi$  体系相互作用。苯胺与溴的反应非常剧烈，迅速地给出 2,4,6-三溴苯胺。这个反应的机理与苯酚溴代的机理类似，因此我们仅展示邻位取代的机理用于提醒，您应当熟悉这种套路。

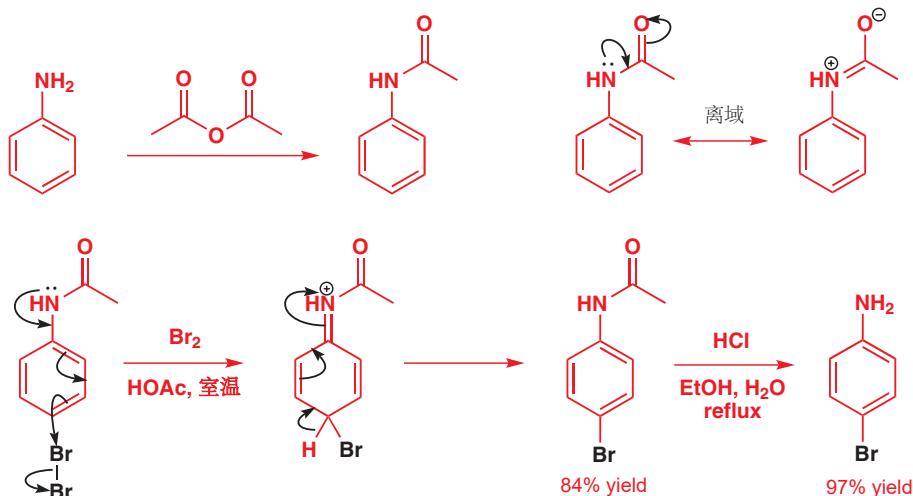


## 使芳香胺反应性降低

芳香胺的高反应性也会成为一个问题。假设我们只希望在环上加入一个溴原子。对于苯酚是可行的 (p. 480)，只要我们缓慢地将溴加入苯酚的二硫化碳溶液中，并将温度保持在 5 °C 以下，即可使对溴苯酚作为主要产物。但如此操作苯胺是行不通的，其主要产物仍然是三取代的。



那么我们如何防止过度取代的发生呢？我们的思路必然是减弱氮上的孤电子与  $\pi$  体系的相互作用。幸运的是，这一点很容易办到。在 Chapter 8 (p. 175) 中，我们曾看到酰胺上的氮原子由于能于羰基共轭，因此比普通氮原子碱性弱得多。此处也应用相同的战略——乙酰化氨基，得到一个酰胺。氮原子上的孤电子照例与羰基共轭，但在苯环上的离域就比苯胺中的弱了。酰胺氮仍然有孤电子，可以起到氮应有的作用，只是相对来说，向环贡献的电子较少，亲电芳香取代被控制住了。反应在邻位和对位进行（主要在对位），只进行一次。



由苯胺酰化生成的酰胺有时也被称作酰苯胺(anilides)。如果它们是乙酰衍生物，则被称为乙酰苯胺(acetanilides)。

反应结束后，酰胺可以通过水解（此处使用酸的水溶液）回到胺。

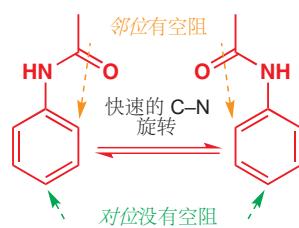
- 苯胺迅速地与亲电试剂反应，得到多取代产物。它们的酰胺衍生物以更加可控的方式，得到对位取代产物。

### 邻位和对位的选择性

酚和苯胺由于电子因素(electronic reasons)都在邻位和/或对位反应。这是决定苯环上亲电取代点最重要的因素。当我们面对邻位和对位内部的抉择时，就应当也将空阻因素纳入考虑。您会注意到，我们只见过一个邻位选择性的反应——由苯酚生成水杨酸的反应（事实上似乎还有苯酚的硝化）——但却见过诸多对位选择性的反应，例如我们才讨论的酰苯胺的溴代。

如果反应仅仅按统计学规律发生，那么我们应当期待邻位的产物是对位的两倍，因为邻位本身有两个。然而，在邻位取代意味着新的取代基与旧的一个待得很近，即空阻很大。对于大的取代基，例如酰胺基，空阻会变得很显著，因此我们更高得到占比很大的对位产物，也不值得奇怪。

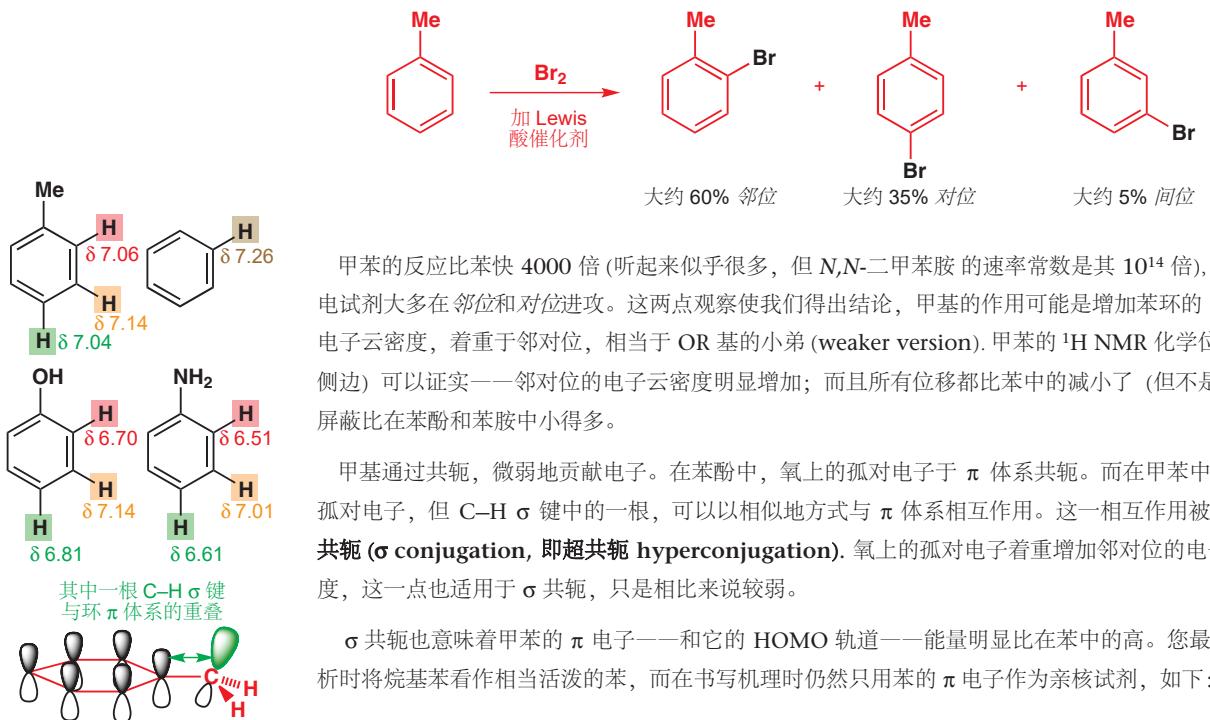
另有一种降低邻位取代的因素，即负电性取代基的吸电子诱导(inductive)效应。如您所见，氧、氮，虽然它们是负电性的，但却通过它们的孤电子贡献  $\pi$  电子云密度，以活化苯环。但在同时，C=O 或 C=N  $\sigma$  键也会极化偏向 O 或 N 原子——换句话说，它们向  $\pi$  体系贡献电子云密度的同时，也在从  $\sigma$  骨架吸收电子云密度。这是吸电子诱导效应——对与 O 或 N 原子离得最近的原子影响最大，影响随距离增长而减弱；受影响深的地方，即邻位，比对位进攻的可能性小。



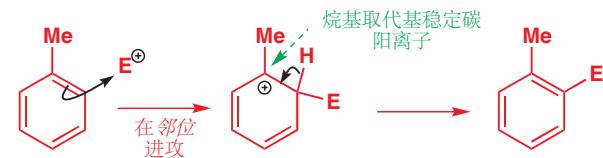
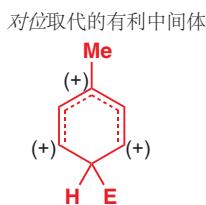
→ 诱导效应的介绍在 p. 135.

## 烷基苯也在邻位和对位反应

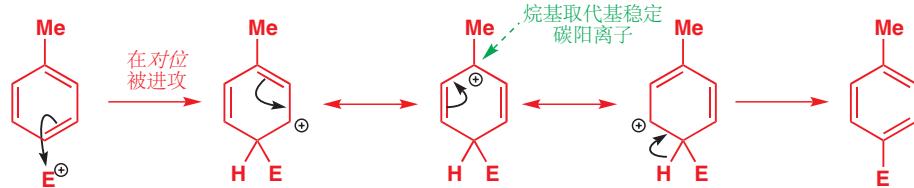
这是甲苯 (toluene) 遇上溴时发生的变化:



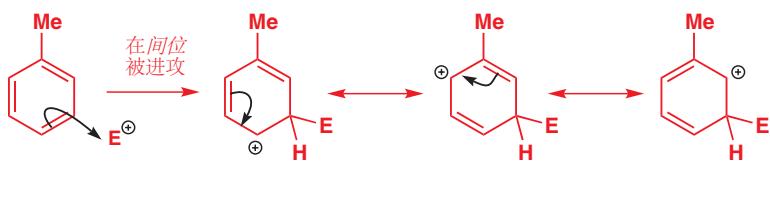
对于：取代越多的碳阳离子稳定 (Chapter 15, p. 335)  
取代越多的烯烃稳定 (Chapter 17, p. 394)。这些观点您已经很熟悉了。我们在这里讨论也是这个。



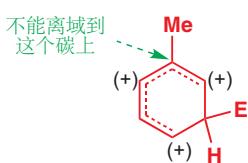
亲电试剂进攻烷基苯后，正电荷落在带有烷基的碳上。这个碳是叔碳，因此所生成的碳阳离子更稳定。甲苯在邻位被进攻满足上述描述，上面已经给出演示，而甲苯在对位被进攻也是满足上述描述的；因为这两种情况下，正电荷都会离域在同样的三个碳原子上。



如果，换一种情况，亲电试剂在间位进攻，那么正电荷则会结束于在另三个原子间的离域上，而其中没有一个是叔碳，因此并不能获得附加的烷基的稳定化效果，这种情况并不比苯本身好到哪里去。反之，在邻对位进攻的反应却比苯的反应快  $10^3$  倍。尽管如此，和苯酚不同的是，甲苯仍然会给出痕量的间位取代产物。

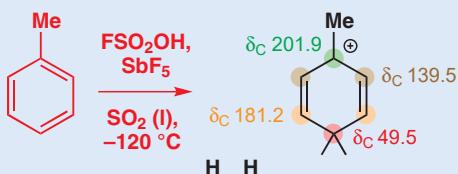


间位取代的不利中间体



### 用超强酸(superacid)质子化甲苯

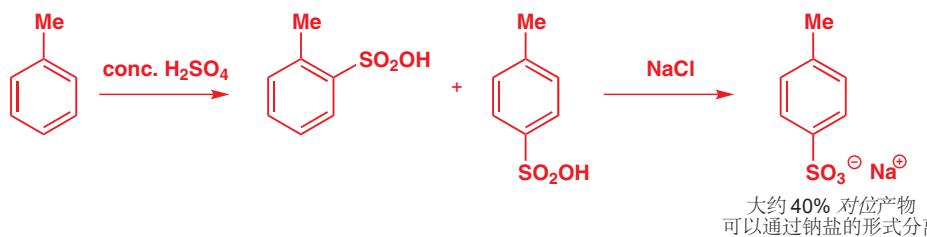
在 p. 475 我们描述了如何用超强酸在 NMR 管中观察苯被质子化的亲电取代反应的阳离子中间体。用甲苯做类似的实验，则会发现取代发生在对位。



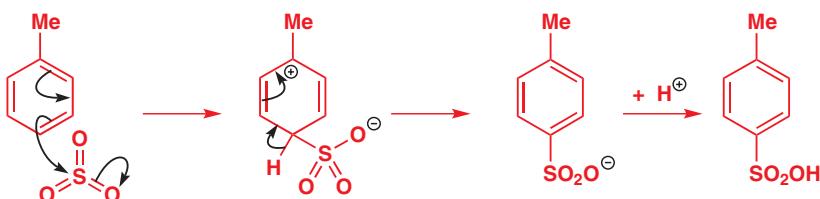
邻位碳(与 Me 基处于邻位)的位移( $\delta$  139.5)仅比苯( $\delta$  129.7)高 10 ppm, 而本位和间位碳都有很大的位移, 这使我们联想到阳离子。电荷主要离域在这些原子上, 并集中于本位。

### 甲苯的磺化

用浓硫酸直接磺化甲苯, 会得到邻位和间位取代的混合磺酸, 其中大约占 40% 的对甲苯磺酸可以以其钠盐的形式分离。

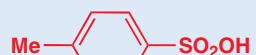


在此情况下, 我们将用  $\text{SO}_3$  作为亲电试剂, 来画出本位碳带正电荷的中间体, 并展示甲基提供的稳定化效果。



### 对甲苯磺酸

产物对甲苯磺酸作为方便使用的固体酸, 常用于做酸催化反应中的强酸。它十分重要。比起粘稠的、有腐蚀性的硫酸, 和浆状的磷酸来说非常容易处理。它在缩醛的形成 (Chapter 11) 以及醇通过 E1 机理的消除 (Chapter 17) 上很有价值。简称为 tosic acid,  $\text{TsOH}$ , 或 PTSA, 其硫酰氯衍生物是我们曾见过的对甲苯磺酰氯 (tosyl chloride),  $\text{TsCl}$  (Chapter 15)。



对甲苯磺酸  
 $p$ -toluenesulfonic acid  
= tosic acid =  $\text{TsOH}$  = PTSA

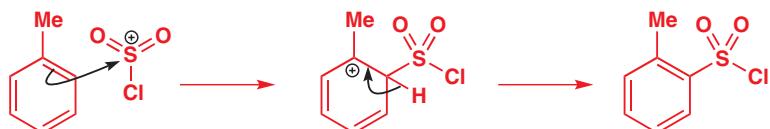
对甲苯磺酰基 (tosylate, OTs) 是欲在醇上进行  $\text{S}_{\text{N}}2$  反应 (Chapter 15, p. 349) 所需的重要的离去基团, 用于生成对甲苯磺酰基的对甲苯磺酰氯 (tosyl chloride,  $\text{TsCl}$ ) 可以通过对甲苯磺酸与  $\text{PCl}_5$  反应的常规方法 (p. 215) 制备, 也可以直接通过氯磺酸 (chlorosulfonic acid)  $\text{ClSO}_2\text{OH}$  直接磺化甲苯制备。这个反应更倾向于对位磺化, 对位产物可通过蒸馏分离。



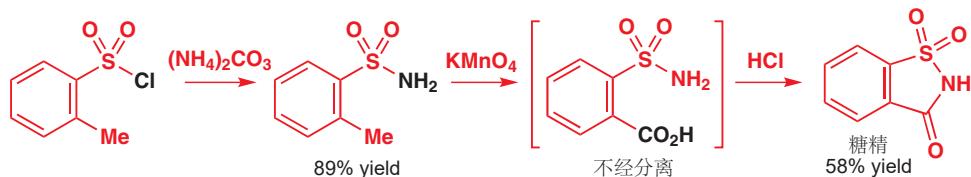
这一过程不需要其他酸的加入，因为氯磺酸本身就是很强的酸，可以质子化它本身并给出亲核试剂。这也解释了为什么 OH 是离去基团，而 Cl 并不是；即为什么结果是氯磺酰化 (chlorosulfonylation) 而不是磺酰化 (sulfonation)。



在绘制机理时，我们又可以将正电荷生成在本位叔原子上。这个反应不需要加入 NaCl 处理，因为主要产物（邻甲苯磺酰氯）是通过蒸馏分离的。



氯磺酰化过程的主要产物是邻位取代的酰氯，这也是一件幸运的事，因为它可以用于糖精 (saccharin)，首个无热量甜味剂的合成。磺酰胺的形成于普通酰胺是一样的，但高锰酸钾氧化甲基的过程可能对于您是新鲜的。这是一个相当剧烈的反应，但它却是一个将甲苯衍生物转变为苯甲酸衍生物非常实用的方法。



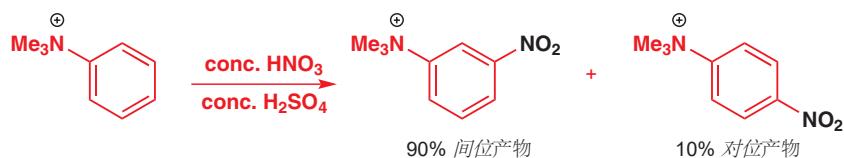
- 烷基苯与亲电试剂的反应比苯快，并给出邻对位取代产物的混合。

## 吸电子取代基给出间位取代产物

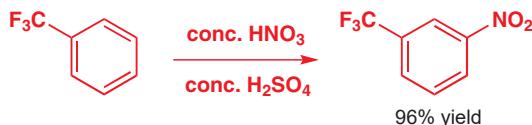
到目前为止，所有我们考虑过的苯环取代基都具有贡献环电子云密度的能力：尽管是氧、氮这样负电性原子都有可以与环  $\pi$  体系共轭的孤对电子；甲基的  $\sigma$  共轭也有类似，但更微弱的作用。这类取代基的出现会导致两个结果：环比苯环更加活泼，取代发生于邻位和对位。

那么当我们把环电子拉向环外时，会发生什么呢？例如三甲铵基取代基：氮是负电性原子，但由于苯胺不同的是，这个负电性并不会与孤对电子的给电子作用抵消——因为氮是四面体型的，不再有任何可以给出的孤电子。苯基三甲基铵离子的硝化产率集中于间位。并且它进行的也很慢——硝化

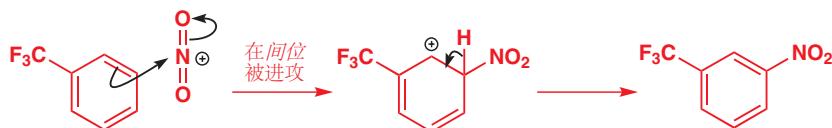
的速率比苯慢  $10^7$  倍。



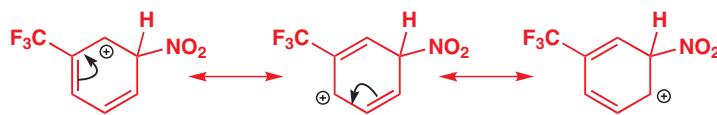
同样的事情发生于  $\text{CF}_3$  基取代时。三个非常负电性的氟原子使 C–F 键强烈极化，进而使 Ar–C 键也发生极化。三氟甲基苯的硝化几乎定量地给出间位硝基化合物。



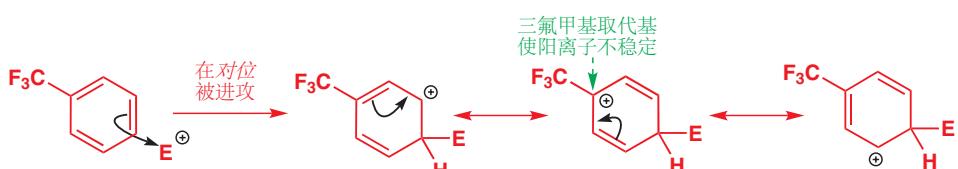
画出这一反应的机理，您就会知道这个反应切换为间位选择性的原因。



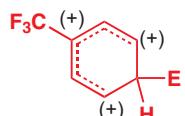
中间体阳离子再一次离域于三个原子之间，但更重要的是，其中没有一个原子与  $\text{CF}_3$  基相连。



而在另一方面，亲电试剂如果进攻邻位或者对位（假定的对  $\text{CF}_3$  对位的进攻机理如下所示）。那么在中间体中，与  $\text{CF}_3$  相连的碳原子就得带有正电荷，这对于吸电子基是不稳定的，因此会使这一中间体高能。



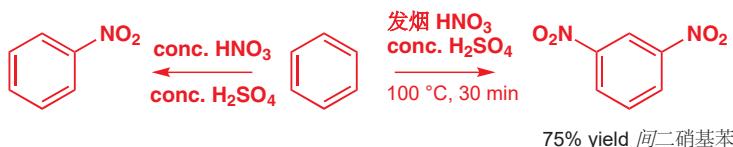
对位取代的不利中间体



换种方式思考：缺电子环会相当不愿意和亲电试剂反应（因此这里的速率缓慢），但如果它必须这样做（亲电试剂非常活泼时），那么它会选择糟糕的结果中最不糟糕的一个，基团将正电荷原理吸电子基——这意味着间位取代。

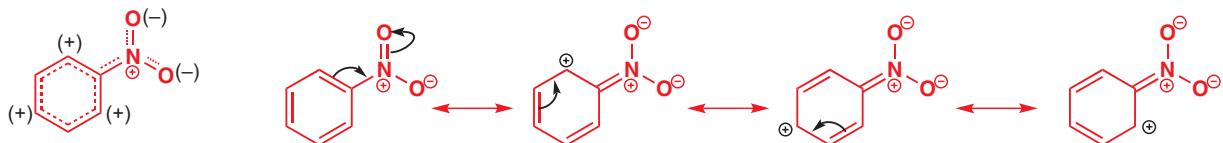
### 通过共轭吸电子的取代基

芳香硝化反应是一个十分方便地在环上加入硝基取代基的反应，它能干净地停留在单取代物，这也是这个反应重要的原因。双取代的硝基苯是可能的，但需要非常强硬的条件——用发烟硝酸 (fuming nitric acid) 替代普通的浓硝酸——并且将混合物置于  $100^\circ\text{C}$  左右回流。



第二个硝基的引入发生在第一个的间位：显然，硝基是钝化(deactivating)基和间位定位(meta-directing)基。

硝基与苯环的  $\pi$  体系共轭，并且它强烈地吸电子——尤其在邻位和对位吸电子。我们可以用弯曲箭头表示：

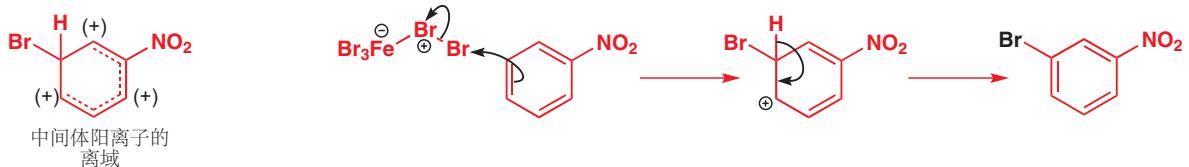


硝基吸取环  $\pi$  体系的电子云密度，因此使环面对亲电试剂的活性降低。由于邻位和对位被吸电子的效果最显著，因此间位成为最不缺电子的位点。于是硝基是间位定位基。在苯环的硝化中，第二次添加硝基困难许多，如果我们坚持这样做，那么第二个硝基在第一个的间位加入。

另一个反应与之类似：硝基苯的溴代反应高产率地得到间溴硝基苯。这个不利的反应需要铁粉和溴结合提供的必要的 Lewis 酸催化剂 ( $\text{FeBr}_3$ )，还需要在高温下进行，由于硝基苯的沸点超过  $200^\circ\text{C}$ ，这个反应的高温也容易提供。



在绘制机理时，最好将中间体画出来，并强调正电荷无法离域到承载硝基的碳原子上。



硝基只是由于共轭吸电子作用，面对亲电试剂，起钝化作用、间位定位作用的取代基中的一个。另外还有羰基(醛、酮、酯，等)，腈和磺酸酯。带有这类取代基的苯的  $^1\text{H}$  NMR 位移验证了：它们原则上从邻位和对位移去质子。

$^1\text{H}$ NMR 化学位移	硝基苯	苯甲醛	苯甲酸甲酯	苯磺酸甲酯	苯甲腈
nitrobenzene					
$\delta$ 7.26					

需要注意的点：

- 每个化合物都包含 Ph-X=Y 的单元，其中 Y 是一个负电性元素，通常是氧。
- 每个化合物中，所有的质子都有比苯大的化学位移，因为碳上电子云密度小。
- 间位质子有最小的化学位移，因此它们是相对来说电子云密度最大的位点。

硝基是这些基团中最吸电子的，而其他的一些化合物几乎与苯本身势均力敌（指在间位的）。例如，硝化苯甲酸甲酯是很容易的，然后间硝基的酯可以非常容易地水解得到间硝基苯甲酸。

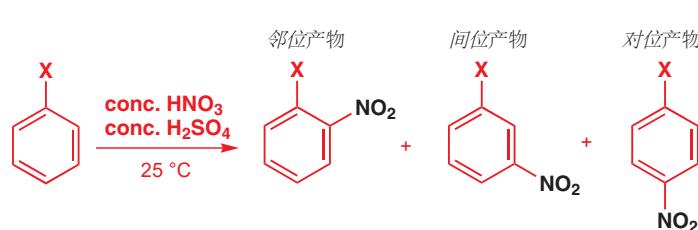


- 吸电子基团使芳环更加不情愿进行亲电取代，但如果它们这样做了，则会在间位反应。

我们还剩一类有点古怪，进而没有讨论的取代基。它们是邻对位定位基，但也是钝化基。它们就是卤素。

## 卤素既有吸电子又有给电子的特征

到目前为止，我们都在避开谈论苯的卤素衍生物的反应。在我们解释这些反应前，请先观察右测关于各个卤素取代的苯环，与苯环相比硝化速率的表格，并对产物情况给出预言。



化合物	生成的产物 (%)			硝化速率(与苯的相对值)
	邻位	间位	对位	
PhF	13	0.6	86	0.18
PhCl	35	0.9	64	0.064
PhBr	43	0.9	56	0.060
PhI	45	1.3	54	0.12

我们将会在下一页及以后探讨这个表格，而现在我们该做的第一件事就是记住，所有的卤苯（halobenzenes）都比苯本身反应得慢。显然，这些负电性的卤原子对环的吸电子作用可以作为原因。而第二件事需要记住的事可能会让您有点惊讶，不像我们从前讨论的那些钝化基，卤素是邻对位定位的——只会生成很少的间硝基产物。

对于这一现象，唯一说得通的解释是，卤素存在两种相反的效应：通过共轭的给电子效应和通过诱导的吸电子效应。卤素有三对孤电子，其中的一个可能会像苯酚、苯胺中的一样与环共轭。然而这种共轭远比不上苯酚和苯胺中的好。当 Cl, Br, 或 I 作为取代基使时，问题出在其大小上：碳的 2p 轨道与这些卤素更大的 p 轨道（氯为 3p，溴为 4p，碘为 5p）重叠得差。大小的不匹配很明白地解释了苯胺与氯苯活性的对比：氯和氮的电负性相差无几，氯苯胺比氯苯活性强，这是因为碳与氮

的 2p 轨道重叠得更好。氟的 2p 轨道有匹配的尺寸，并能与碳的 2p 轨道很好地重叠，但现在又有另一个问题：由于氟电负性之高，氟的轨道远比碳的低能。

因此，四个卤素在向环贡献电子时不及 OH 或 NH<sub>2</sub> 基；但卤苯不光是比苯酚、苯胺活性低，它甚至比苯本身也活性低。现在，当我们看苯胺和苯酚时，我们不会考虑诱导的吸电子效应，这是因为虽然氧和氮是负电性原子，但 N 和 O 孤对电子的共轭给电子作用显然重要得多。但在卤苯中，共轭给电子作用很弱，因此诱导吸电子会接替决定反应性的职务。

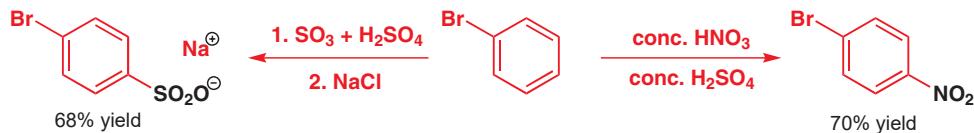
知道了这些，您会期望氟苯如何反应？通过诱导，大多数电子云密度首先从邻位被移去，然后是间位，最后是对位。氟上的孤对电子的任何共轭都会在邻位和对位增加  $\pi$  体系的电子云密度。这两种效应都有利于对位（邻位仅有第二种有利），而这正是取代发生的位置。但这个环比苯环更活泼还是更不活泼？这个问题很难下定论，有时会氟苯在对位会比苯活泼（例如在质子化、酰基化时——后面见到），有时氟苯也显著地比其他卤苯活泼。对位定位的结论有证据作为支撑，例如氟苯在有铁做催化剂时与溴反应（确实需要催化剂，因为它的活性仍比不上苯酚），在 -20 °C 只给出对溴衍生物。

我们现在可以解释上一页表格中结论中的两项：

- 邻位产物的百分率虽氟苯到碘苯增加。由于卤素大小的增加，我们可能期望邻位因为空阻效应的增加而比重降低，但事实正好相反。这是由于吸电子诱导效应主要作用于邻位，进而减弱它们的反应性，这一点随着氟到氯电负性的降低而缓解。
- 反应速率“U-形”排列：氟苯硝化最快，碘苯紧随其后，氯苯和溴苯的硝化速率在它们的一半左右。氯苯和溴苯都有相当大的电负性，然而却没有很好的孤对电子重叠：氟中，至少在重叠上是好的；在碘中，至少有较小的电负性。

我们在 p. 483 介绍了诱导效应影响在邻位和对位之间选择。

在实际应用中，通常有可能通过卤苯的亲电取代反应得到高产率的对位产物。溴苯的硝化和磺化都会得到足够的产物，使合成值得采用。虽然混合的产物难以用于合成，但亲电芳香取代的产物通常能找到可大规模进行的主产物分离方法，理想情况下是结晶。68% 产率的对溴苯磺酸钠可以通过在水中重结晶，70% 产率的对溴硝基苯可以通过在 EtOH 中重结晶，使它们与它们的邻位异构体分离。



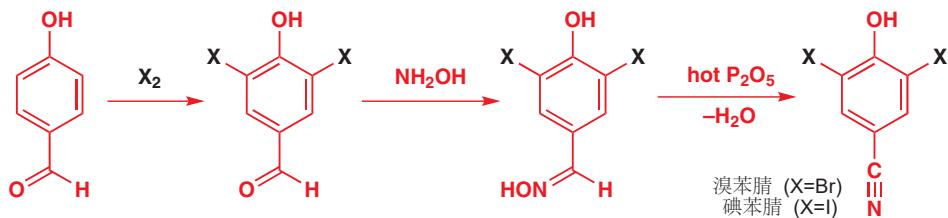
### ● 定位和活化效应的总结

现在我们可以总结，在这两种效应上，我们目前完成的阶段。

电子效应	离子	活化	定位
共轭给电子	$-\text{NR}_2, -\text{OR}$	很活化	仅邻对位
诱导给电子	烷基	活化	大部分邻对位, 有一些间位
共轭给电子并诱导吸电子	F, Cl, Br, I	钝化	绝大部分的对位和少量邻位
诱导吸电子	$-\text{CF}_3, -\text{NR}_2^+$	钝化	仅间位
共轭吸电子	$-\text{NO}_2, -\text{CN}, -\text{COR}, -\text{SO}_3\text{R}$	很钝化	仅间位

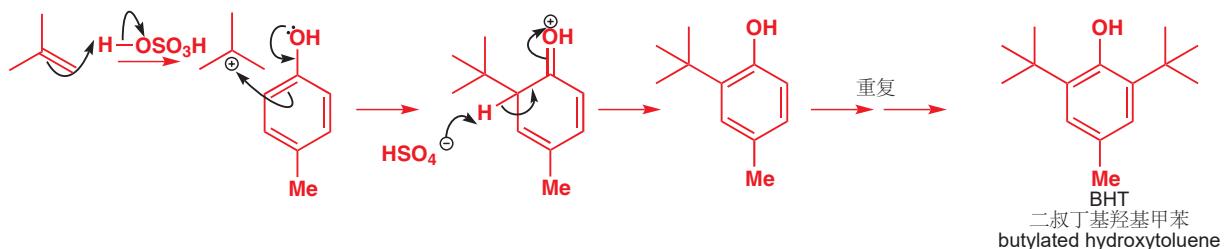
## 两个或多个取代基可能合作或竞争

两个或多个取代基的定位效应可能一同工作，或彼此对抗。溴苯腈（为俗称，Bromoxynil）和碘苯腈都是接触性除草剂（contact herbicides），尤其用于春季谷物中，控制杂草对其他除草剂的抵抗力，这两种化合物都是通过对羟基苯甲醛两次卤代获得的。醛基定位在间位，而 OH 基定位在邻位：两种效应合作，控制卤代发生于两个相同的位置上。



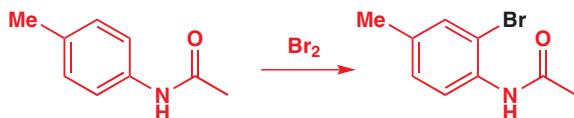
与  $\text{NH}_2\text{OH}$  的反应是醛和羟胺生成肟的反应，在 Chapter 11 中处理过。 $\text{P}_2\text{O}_5$  是一个脱水剂——使肟脱水成腈。

其他情况下，如果取代基定位的位点不同，它们则会发生竞争。抗氧化剂 BHT (p. 58) 是由 4-甲基苯酚（通常称为对甲酚, *p*-cresol）通过 Friedel–Crafts 烷基化生产的。通常，甲基和 OH 基都是邻对位定位基，很明显，两个取代基的对位显然都被阻挡了，然而它们的邻位又都是不同的。由于  $-\text{OH}$  基比甲基的定位能力更强，因此它在竞争中胜出了，亲电试剂（叔丁基阳离子）进攻羟基的邻位。

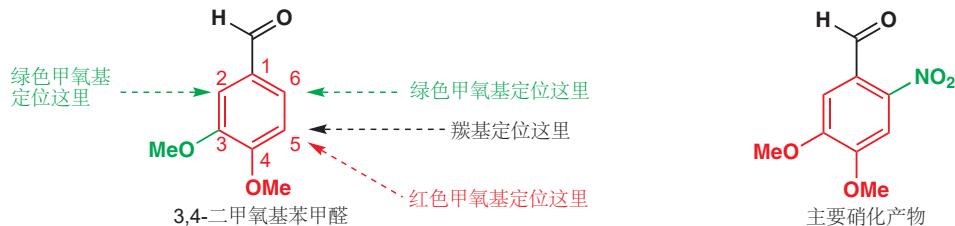


这个情形中，叔丁基阳离子是通过烯烃和质子酸生成的；也可以用叔丁醇和质子酸，叔丁基氯和  $\text{AlCl}_3$  这两种试剂替代。

即使是酰胺  $-\text{NHCOMe}$  这样“打了折扣”的活化基团，也能提供额外的一对电子，这就胜过了钝化基，或者弱活化的烷基。下面的酰胺的溴代发生在  $-\text{NHCOMe}$  基的邻位，尽管那也是甲基的间位。



当我们考察任何有竞争问题的化合物时，明智的做法是先考虑电子效应，再考虑空阻效应。对于电子效应，通常来说，任何活化效应都比钝化效应更为重要。例如，下面的醛有三个取代基——两个邻对位定位的甲氧基，和一个间位定位的醛基。



■ 如果您在一个酒吧里，有人要与您打架，虽然此时角落里一个温文的小子不愿看到打架，但这是无济于事的。好斗的 $-NR_2$ 和 $-OR$ 基都不会太多地受到在分子的角落中的温文的 $-Br$ 或 $-CHO$ 的影响。

尽管事实上，这个醛基从 2 和 6 位吸电子，但 C6 仍是硝化发生的位点。活化基甲氧基支配这一化合物的选择性，因此选择产生于 C2, C5, 和 C6. 然后再考虑空阻因素：反应发生在 C2 或 C5 都会导致三个取代基相连，因此取代发生于位置 6.

## 问题与机会

在本章中您已经看到了大量的、形形色色的芳香亲电取代反应，它们都是可靠并被广泛应用着的——例如溴代和硝化。但仍有下列问题：

- Friedel–Crafts 酰基化反应仅在中间体阳离子稳定时才工作，那么我们如何在芳环上加入正烷基链呢？
- 目前还没有在芳环上引入氧原子的好方法，那么我们如何构建 Ar–O 键？
- 给电子基通常定位在邻对位，那么我们如何在氨基的间位引入一个基团呢？

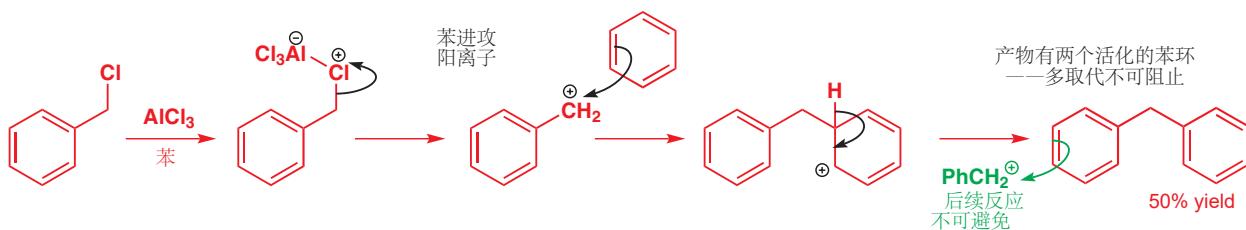
我们将在本章的最后一节对这些问题予以考虑。

## 细看 Friedel–Crafts 化学

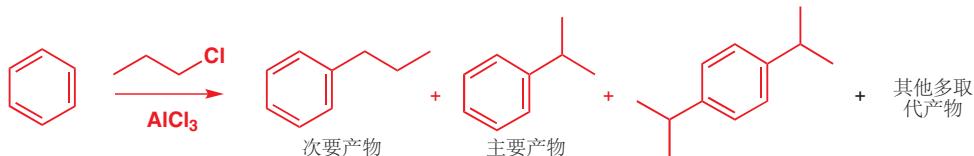
像硝化、磺化这样的反应都在引入强有力的钝化基团。这些反应通常干净地在单取代后就停止了，除非还有一个非常强的活化基存在，但即使那样控制在单取代也是可能的。弱的吸电子基团，例如卤素可以只添加一个，如果起始芳环上有强的活化基，例如 OH 和 NH<sub>2</sub> 则多取代更为常见。

### 回避使用 Friedel–Crafts 烷基化的两个原因

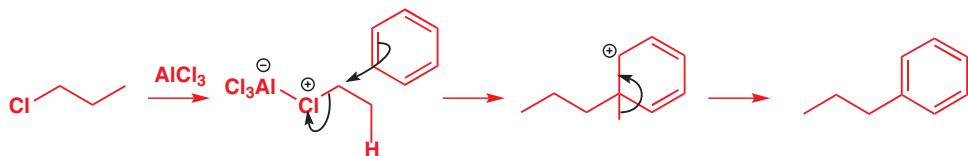
当芳环上加入了给电子取代基，多取代往往就会构成威胁。多取代成为真正问题的主要反应，是 Friedel–Crafts 烷基化反应。下面是一个例子：由苯和苄氯制备二苯甲烷的反应是一个很实用的反应，但其产物有两个比苯本身更活泼的苯环，这将与苯竞争与苄氯的反应。我们能做到的最好产率是 50%，这需要苯大大过量，以确保它能竞争过更为活泼，更为富电子的产物。



多取代只是 Friedel–Crafts 烷基化反应的潜在隐患之一。另一个重要的注意点是：Friedel–Crafts 烷基化反应仅适用于稳定阳离子。下面是当我们试图用正丙基氯完成 Friedel–Crafts 反应时，真正发生的变化。



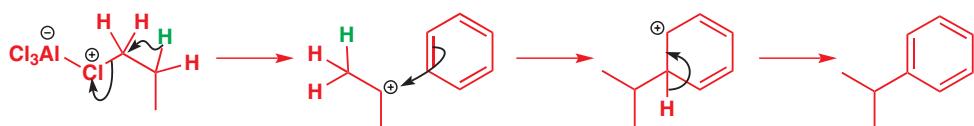
记得 Chapter 15 提过，伯卤代烃不能容易地生成碳阳离子，因此正丙基氯的 Friedel–Crafts 反应需要通过 S<sub>N</sub>2 机理进行。



那么这个反应的主要产物是怎么形成的呢？三个碳并不以正丙基的方式排列，而是以异丙基的方式排列：这是因为发生了重排。下面是机理：

我们在 Chapter 36 更深入地讨论重排反应。

导致异丙基苯生成的重排 (绿色 H 的迁移)

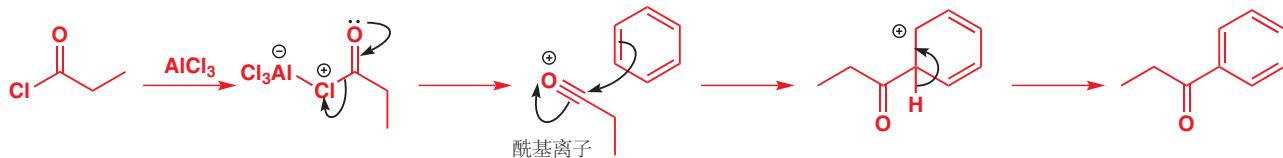


绿色的氢通过迁移 (migrates) 使仲阳离子 (而非伯阳离子) 得以生成，异丙基苯便是其结果。这为我们留下了问题：我们如何在苯环上添加伯烷基呢？

### 解决方案: 使用 Friedel–Crafts 酰基化替代

对于前面的两个问题，我们可以用 Friedel–Crafts 酰基化替代烷基化，并一石二鸟地解决。首先，酰基化的产物是一个酮：向芳环引入的是一个钝化基、吸电子基，而且羰基能与环共轭。因此产物比起始原料更加不活泼。反应会干净地停留在一次酰化。下面是苯与丙酰氯的反应。

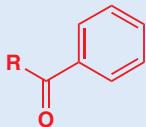
我们在 p. 477 介绍了 Friedel–Crafts 酰基化。



如果我们本就想要酮，那到此便十分圆满地完成了。而如果我们想要烷基化产物，那么简单的还原原则也能完成任务——这个化合物 (俗称苯丙酮, propiophenone) 可以用不计其数的还原反应中的

Interactive mechanism for Friedel–Crafts acylation

您可能也会遇到苯乙酮 (acetophenone), 二苯甲酮 (benzophenone) 这样的俗称。



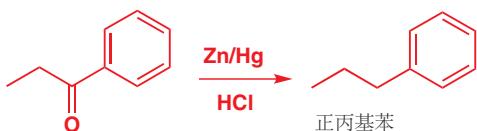
R = Me: 苯乙酮  
R = Ph: 二苯甲酮

▶ 更多能很好地找羰基麻烦的还原反应在 Chapter 23 中会讨论。

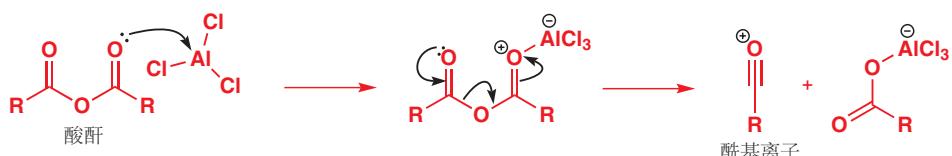
■ 注意  $\text{AlCl}_3$  需要多少量:  
Friedel–Crafts 烷基化使用烷基氯, Lewis 酸需要催化量。然而在酰基化中, Lewis 酸可以与任何氧原子配位, 包括产物中的羰基。因此, 酰基化反应需要更多的 Lewis 酸添加——比每个羰基配一个略多一些。

■ 确保您了解这些反应如何工作。

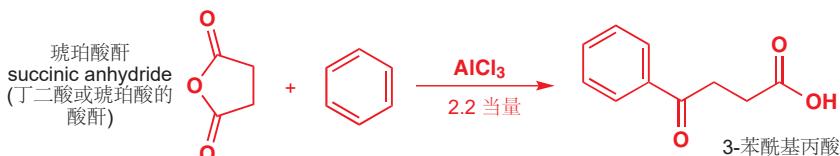
任意一种并还原为丙基苯, 例如使用盐酸中的锌汞齐 (zinc amalgam).



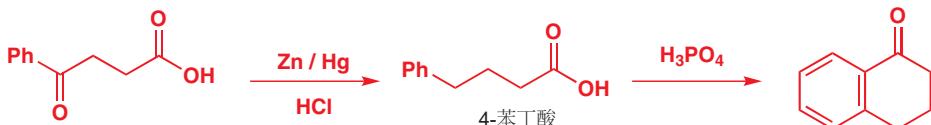
类似这样的 Friedel–Crafts 酰基化产物的还原通常给出正烷基苯, 这正是让 Friedel–Crafts 烷基化反应遇到麻烦的那一类化合物。当用酸酐替代酰氯时, Friedel–Crafts 酰基化也能很好地进行。酰基离子以相同的方式生成:



如果用环状的酸酐, 产物会是一个酮酸 (keto-acid).



这个酮的还原可以得到一种简单的羧酸, 然后我们可以更进一步, 再进行一次酰基化——分子内的反应, 甚至在仅有强酸 (磷酸) 加入时也能发生: 强酸用于将 OH 转换为好的离去基团 (水), 水离去后再次生成酰基离子中间体。



### ● 酰基化相比烷基化的优点

Friedel–Crafts 烷基化中出现的两个问题在酰基化中并不存在。

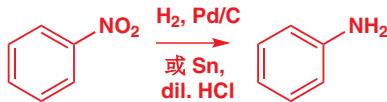
- 产物中的酰基吸取  $\pi$  系统电子, 使多取代难以发生。确实, 如果起始物环非常钝化, 那么 Friedel–Crafts 酰基化可能根本无法发生——硝基苯对 Friedel–Crafts 酰基化是惰性的, 它通常被用作这些反应的溶剂。
- 重排也不再是个问题, 因为亲电试剂, 酰基阳离子, 已经相对稳定了。
- 产物中的酰基可以通过还原得到伯烷基, 通过 Friedel–Crafts 烷基化干净地得到伯烷基是不可能的。

## 对硝基化学的利用

硝基出乎意料的实用性体现在如下几个方面:

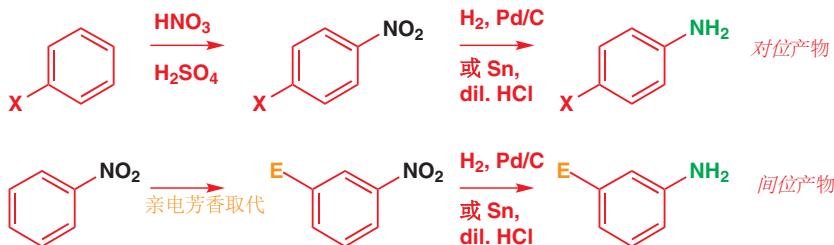
- 通过硝化反应 (p. 476), 硝基的引入非常容易。
- 与其它基于 N 或 O 的官能团不同, 它是间位定位基 (p. 488).
- 可以通过还原转化为氨基。
- 通过重氮 (diazonium) 化学, 可以转化为其他取代基。

您已经见过了前两个方面，但后两个对您来说是新鲜的。一个芳香硝基可以通过不计其数的试剂还原为氨基，其中最常见的是锡+稀 HCl，或者搭载在碳上的钯催化剂 (写作 Pd/C) 的催化氢化。

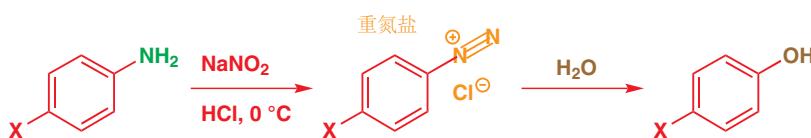


▶ 这些选择性还原剂在 Chapter 23 会被具体讨论。

这个简单的反应非常重要，因为它将间位定位的硝基转化为了一个邻对位定位的氨基 (在 p. 483 我们还提到了苯胺的反应性可以被控制，这使得苯胺的生成更为重要). 硝化-还原的过程，是向芳香分子引入一个有用的  $\text{NH}_2^+$  的等价方式，除此之外，在还原前进行其他取代，则可以让我们值得难以直接生成的 *间位* 取代氨基化合物。



氨基的进一步还原，还开放了用其他原子完全取代氨基的可能性，这一过程通过重氮基的中间体完成。用亚硝酸处理胺可以将其转化为不稳定的重氮盐 (diazonium salt)，重氮苯生成和反应的机理我们将在下一章讨论 (反应的机理包含对芳环的亲核取代)。但并不意外的是，重氮盐很容易失去氮气，即用其他亲核试剂取代  $\text{N}_2$ ，这一过程为由硝基苯衍生物生成其他苯衍生物化合物提供了更多可能。



▶ 重氮盐的讨论在 p. 520。  
Chapter 40 介绍了与芳环成键的方法中过渡金属的应用，而 Chapter 24 则重拾了当需要控制立体化学 (i.e. 邻位, 间位, 或对位选择性) 时所需要用的可行方法。

## 小结

### ● 芳香亲电取代产物

产物	反应	试剂	页码
	溴代	$\text{Br}_2$ 和 Lewis 酸, e.g. $\text{AlCl}_3$ , $\text{FeBr}_3$ , $\text{Fe}$ 粉	474
	硝化	$\text{HNO}_3 + \text{H}_2\text{SO}_4$	476
	硝基化合物的 还原	由 $\text{ArNO}_2$ ; $\text{Sn}, \text{HCl}$ 或 $\text{H}_2, \text{Pd/C}$	495

(接上页) 芳香亲电取代产物

产物	反应	试剂	页码
	重氮盐的取代	由 $\text{ArNH}_2$ ; 1. $\text{NaNO}_2$ , $\text{HCl}$ ; 2. $\text{X}^-$	见 Chapter 22, p. 520
<b>X = OH, CN, Br, I...</b>			
	磺化	浓 $\text{H}_2\text{SO}_4$ 或 $\text{H}_2\text{SO}_4 + \text{SO}_3$ (发烟硫酸)	476
	氯磺化	$\text{ClSO}_3\text{H}$	486
	Friedel-Crafts 烷基化	$\text{RX} + \text{Lewis 酸}$ , 通常是 $\text{AlCl}_3$	477
	Friedel-Crafts 酰基化	$\text{RCOCl} + \text{Lewis 酸}$ , 通常是 $\text{AlCl}_3$	477
	Friedel-Crafts 酰基化后还原	由 $\text{ArCOR}$ : $\text{Zn/Hg, HCl}$	493

### ● 芳香化合物底物

底物	样例	活化/钝化	定位效应	页码
苯, PhH		-	-	474
苯酚, PhOH		活化	邻位, 对位	479
苯甲醚, PhOMe		活化	邻位, 对位	480
苯胺, PhNH <sub>2</sub>		活化	邻位, 对位	482
ArNHCO <sub>R</sub> (酰苯胺)		活化	邻位, 对位	483
烷基苯, PhR		活化	邻位, 对位	484

(接上页) 芳香化合物底物

底物	样例	活化/钝化	定位效应	页码
硝基苯, $\text{PhNO}_2$		钝化	间位	488*
酰基苯, $\text{PhCOR}$ (苯甲酮, 二苯甲酮)		钝化	间位	489
苯腈, $\text{PhCN}$		钝化	间位	488
卤苯, $\text{PhX}$		钝化	邻位, 对位	489

\* 对于将硝基取代基还原为其他基团的方法, 重氮化 (diazotization) 和取代, 请见 pp. 520 和 567, Chapters 22 和 24.

## 延伸阅读

任何大部头的有机化学教科书都有这一主体的内容, 其中最好的一个是: F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry A, Structure and Mechanisms*, 5th edn, Springer, 2007, chapter 9 and B, *Reactions and Synthesis*, chapter 11. B. S. Furniss,

A. J. Hannaford, P. W. G. Smith, and A. T. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, Longman, 5th edn, 1989, sections 6.1–6.4 and 6.10–6.13 给出了很多本章涉及过的反应的实例。

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 22

## 共轭加成和芳香亲核取代

### 联系

#### 基础

- C=O 和 ch10 饱和 C 上的亲核取代 ch15
- 对烯烃的亲电加成 ch19
- 芳环上的亲电取代 ch21

#### 目标

- 共轭加成: 与吸电子基团共轭使烯烃亲电，并可接受亲核进攻
- 共轭取代: 亲电烯烃带有的离去基团可促进在 C=C 上相比于在 C=O 上的取代反应
- 芳香亲核取代: 一些缺电子芳环，可允许亲核试剂而不是通常的亲电试剂取代
- 特殊的离去基团和亲核试剂，允许芳香亲核取代在富电子环上发生

#### 展望

- 区域选择性 ch24
- 烯醇盐的共轭加成 ch26
- 芳杂环化合物的反应 ch29 & ch30
- 这也是本书第二个章节系列的最后一章，我们完成了对于重要而基本的有机反应类型的概述。下两章将由选择性方面着手对前文进行回顾。后续将会更细致地考察烯醇盐化学，以及制取分子的方法。

### 与羰基共轭的烯烃

在本章的开始，让我们先来回顾一下我们向您介绍的第一个反应：对羰基的亲核加成。有两个例子，都给出如您所料的产物。这里同样有产物的 IR 光谱的细节，以此来验证：第一，羰基在反应中失去；第二，烯烃仍然在原处。

如果您需要回顾 IR 光谱法，请返回 Chapter 3。任何 C=O 的峰都会在 1700 cm<sup>-1</sup> 左右。产物中没有这样的峰，替代的是 O-H 在 3600 cm<sup>-1</sup> 处的峰。而 2250 cm<sup>-1</sup> 处的为 C≡N；C=C 在 1650 cm<sup>-1</sup> 处。

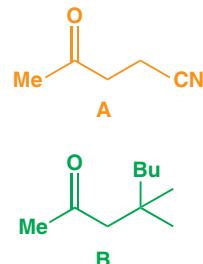
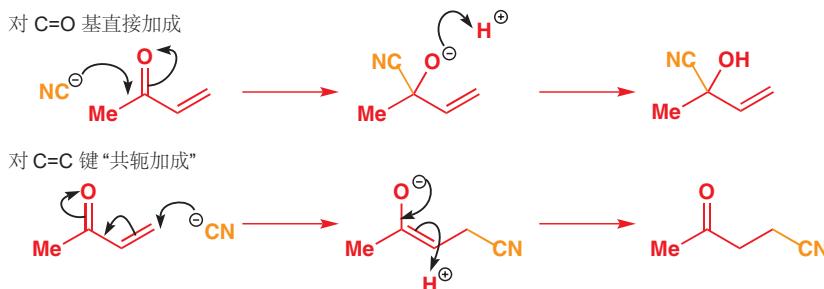


现在，让我们对条件进行调整：重复一个反应时，改在高温下；而在第二个反应中，则加入少许铜盐。此时产物就有所不同了：



产物 A 和 B 都保留了羰基 (IR 峰出现于  $1710\text{--}1715\text{ cm}^{-1}$ )，但它们却失去了  $\text{C}=\text{C}$ 。但对于 A，毫无疑问的是，它至少是一个加成产物，因为它保留了  $\text{C}\equiv\text{N}$ ，在  $2250\text{ cm}^{-1}$  处有峰。

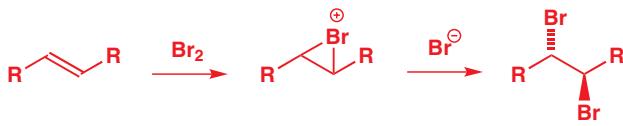
那么，A 和 B 的共性已经在此揭示出来了：它们都是加成的产物，但加成不是对于羰基，而是对于  $\text{C}=\text{C}$  键。如下是两种氰离子反应的机理：第一种是对  $\text{C}=\text{O}$  的直接加成，而第二种则对  $\text{C}=\text{C}$  键加成。



Interactive mechanism for conjugate addition of cyanide

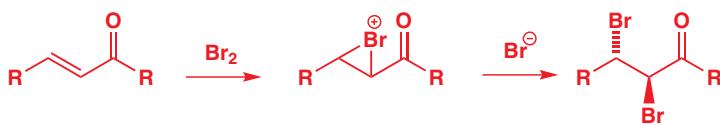
亲核试剂加入  $\text{C}=\text{C}$  双键的这种反应，被称作**共轭加成 (conjugate addition)**，而本章将要讨论的就是可以完成这种反应的烯烃（或芳烃）。我们也会解释，反应条件上如此小的改变（温度，或  $\text{CuCl}$  的存在）是如何神奇地改变反应结果的。

而首先，我们需要讨论共轭加成的情况。如您在 Chapter 19 中已经得出的结论，**烯烃是亲核性的**。几乎无论取代基如何，与它们反应的都是亲电试剂，例如溴，以生成烯烃的  $\pi$  键被两个  $\sigma$  键替代的加合物。



这类反应的讨论位于 Chapter 19.

即使是烯烃与一个吸电子基团共轭，像我们上一页所示的烯烃，虽然不容易，但它与溴的加成都仍然会发生。永远不要忘记：烯烃是亲核的。



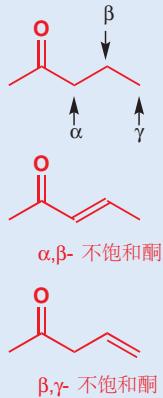
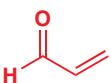
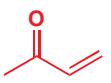
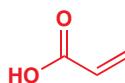
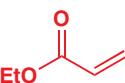
但如您所见，这种烯烃也可以与亲核试剂反应（例如氰离子，格氏试剂，后文中还有更多），现在我们需要考虑原因。

## 共轭烯烃可做亲电试剂

共轭加成仅在  $\text{C}=\text{C}$  双键与  $\text{C}=\text{O}$  基紧邻时才可发生。它们不会发生在不共轭的  $\text{C}=\text{C}$  键上 (p. 501 的文字框会说明这一点)。

双键与一个  $\text{C}=\text{O}$  基相邻的化合物被称作  $\alpha,\beta$ -不饱和羰基化合物 ( $\alpha,\beta$ -unsaturated carbonyl compounds)。很多  $\alpha,\beta$ -不饱和羰基化合物 有它们的俗称，下一页列出了一些。有一些由  $\alpha,\beta$ -不饱和羰基化合物 细分的小类别也有自己的名称，例如“烯基酮 (enone)”，由“ene”（烯，指双键）+ “one”（酮）。(注：烯基酮的命名中会出现“烯酮”二字，但切勿将烯基酮与双键、羰基共用一个碳原子的烯酮 ketene 混淆。)

$\alpha$  和  $\beta$  指示双键到  $C=O$  基团的距离:  $\alpha$  碳上挨着  $C=O$  的碳原子 (不是羰基碳本身),  $\beta$  碳为沿着链的下一个, 以此类推。

 $\alpha,\beta$ -不饱和醛  
(烯基醛 enal) $\alpha,\beta$ -不饱和酮  
(烯基酮 enone) $\alpha,\beta$ -不饱和酸 $\alpha,\beta$ -不饱和酯丙烯醛  
(俗称 = acrolein)3-丁烯-2-酮  
(俗称 = methyl vinyl ketone 甲基烯丙基酮)丙烯酸  
(俗称 = acrylic acid)丙烯酸乙酯  
(俗称 = ethyl acrylate)

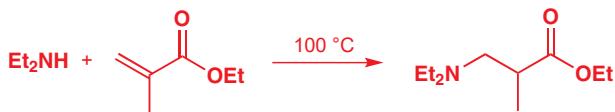
大多数种类的亲核试剂都可以通过共轭加成与  $\alpha,\beta$ -不饱和羰基化合物 反应, 下面举出了三个例子。注意, 这其中有很多并不与简单的羰基反应: 我们不就会做解释。共轭加成也被称作 Michael 加成 (迈克尔加成, Michael addition), 如下所示的可反应的  $\alpha,\beta$ -不饱和羰基化合物 通常被称作 Michael 受体 (Michael acceptors)。

亲核试剂:

氰离子



胺



醇



硫醇



溴离子



氯离子



苯

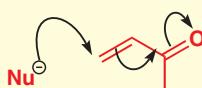
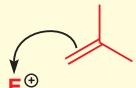


$\alpha,\beta$ -不饱和羰基化合物 反应性差异的原因是共轭, 这是我们在 Chapter 7 中讨论过的一个现象。那时我们向您介绍的观点, 是两个  $\pi$  体系若放在一起 (例如两根  $C=C$  键, 或一根  $C=C$  键和一根  $C=O$  键) 会得到一个使稳定的相互作用。它同时也修饰了反应性, 因为共轭  $\pi$  键不再作为独立的官能团, 而是作为单一的共轭体系作用。

## ● 共轭使烯烃更加亲电

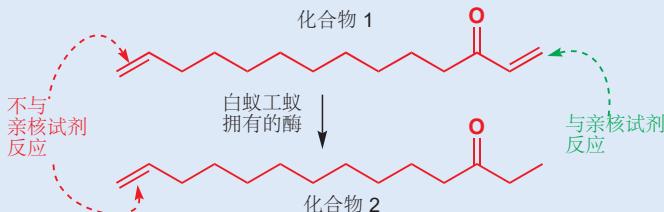
- $C=C$  双键是亲核的

- 带有羰基的  $C=C$  双键可以是亲电的



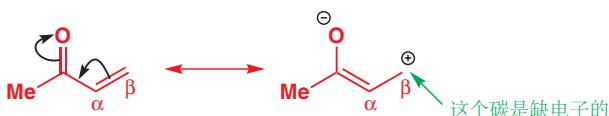
### 白蚁的自卫和烯酮的反应性

长鼻白蚁属 油梨长鼻白蚁种 (*Schedorhinotermes lamanianus*) 的白蚁兵蚁，通过带有下面所示的烯基酮(化合物 1)的分泌物保卫它们的巢穴，这种化合物能非常有效地参与与硫醇 (RSH) 的共轭加成。很多重要的生物化学物质都带有 SH 基(在 p. 508 中举了一个例子)，因此这种烯基酮有很高的毒性。相同物种的工蚁——筑巢者——需要避免在交叉火力中被抓住，因此它们装备了一种酶，可以将化合物 1 还原为化合物 2。这个化合物仍具一个双键，但因为它不与羰基共轭，因此并不能与亲核试剂反应。因此工蚁安然无恙。



### 与羰基共轭的烯烃存在极化

为了显示与羰基共轭的烯烃与非共轭烯烃的不同，我们用弯曲箭头表示了  $\pi$  电子在四个原子间的离域情况。这两个表达都是极限式，真实结构位于它们之间，氮极化结构表明了为什么共轭的 C=C 键具有亲电性，也表明了  $\beta$  碳会被亲核试剂进攻的原因。



### 极化可以被光谱法观察到

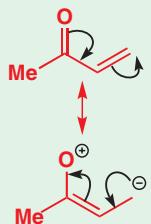
IR 光谱法为我们提供了与 C=O 共轭的 C=C 键发生极化的证据。一个不共轭的酮的 C=O 在  $1715\text{ cm}^{-1}$  处吸收，一个不共轭烯烃的 C=C 大约在  $1650\text{ cm}^{-1}$  处吸收(通常很弱)。而将这两个基团组成共轭的  $\alpha,\beta$ -不饱和羰基化合物则分别观察到了在  $1675$  和  $1615\text{ cm}^{-1}$  处的两个峰，并且都相当强。两个峰频率的降低和两个  $\pi$  键的同时减弱是一致的(注意有一定贡献的极化结构中 C=O 和 C=C 双键原来的位置只有一根单键)。而 C=C 吸收强度的增加与和 C=O 共轭带来的极化是一致的：共轭的 C=C 键的偶极矩显著地比不共轭的大。

C=C 键的共轭同样可以被  $^{13}\text{C}$  NMR 光谱验证，其中离羰基最远的  $\text{sp}^2$  碳的信号相对未共轭烯烃要显著地下降到大约  $140\text{ ppm}$ ，而另一个双键碳原子则仍保持在大约  $120\text{ ppm}$ 。

### 分子轨道控制共轭加成

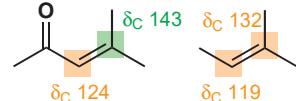
我们已经从光谱上证明了共轭的 C=C 键发生极化，并且我们也可以用弯曲箭头表示这一点，但真正的成键步骤需要包含亲核试剂 HOMO 中的电子向不饱和羰基化合物 LUMO 流入的过程。下面是一个很有效的(即使在  $0^\circ\text{C}$  下也能发生)共轭加成的例子，为甲氧基阴离子作亲核试剂对丙烯醛的加成。

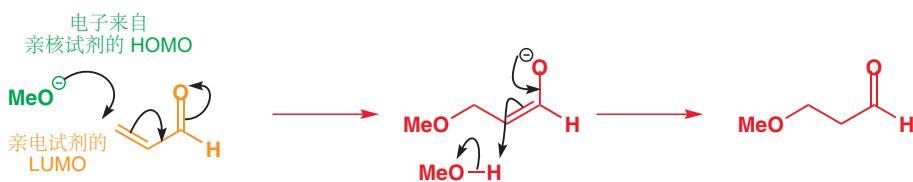
■ 您可能会问您自己，为什么我们不能像下面这样移动电子，以表示共轭结构呢。



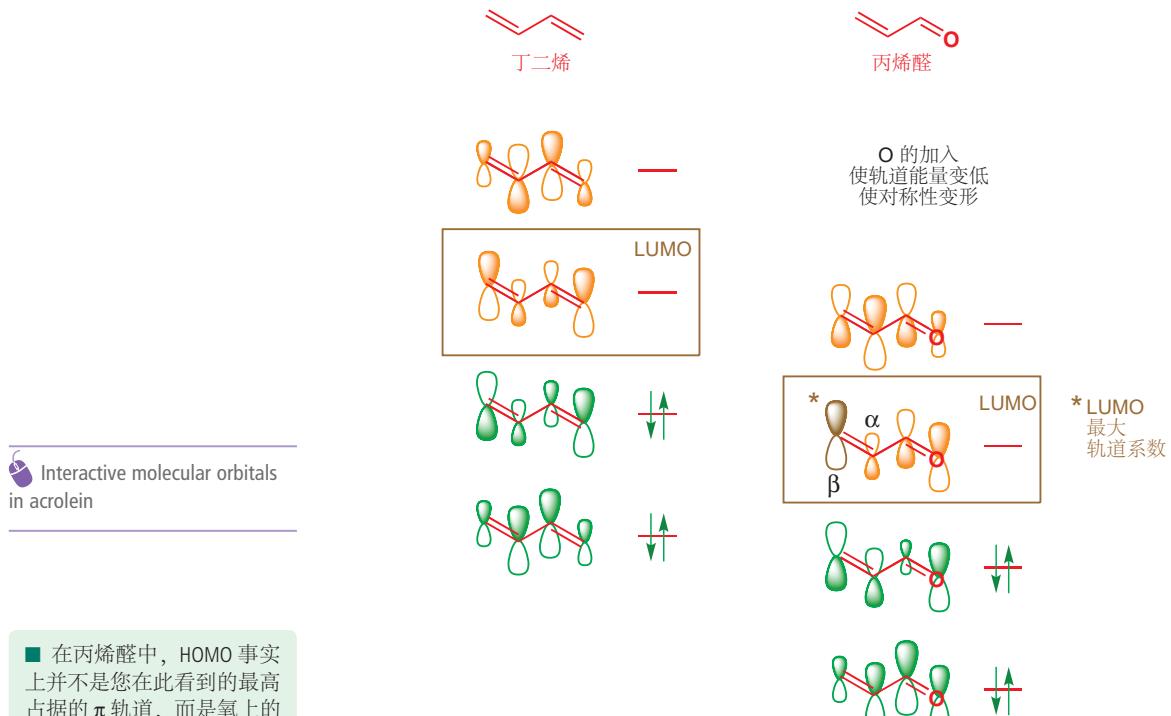
请从电负性上思考：O 的电负性远远大于 C，因此它很容易接受电子，而在上图中我们则夺走了它的电子，使之剩下六个电子。这个结构因此不能表示共轭体系中的电子分布。

$^{13}\text{C}$  NMR 化学位移：  
共轭烯烃                    非共轭烯烃





但 LUMO 是什么样子的？它无疑会比简单羰基的  $\pi^*$  LUMO 更复杂。目前为止（指在 Chapter 7 中）您分析过的最接近的物质是丁二烯（C=C 与 C=C 共轭），我们可以将其与  $\alpha,\beta$ -不饱和醛 丙烯醛（C=C 与 C=O 共轭）做对比。丁二烯和丙烯醛  $\pi$  体系中的轨道如下所示。它们是不同的，因为丙烯醛的轨道被氧原子扰乱了（键变形，Chapter 4）。您目前不需要关系轨道的大小是如何确切地得出的，只需要关心当亲核试剂进攻时，接受电子的 LUMO 的形状。



■ 在丙烯醛中，HOMO 事实上并不是您在此看到的最高占据的  $\pi$  轨道，而是氧上的孤电子。然而，这不重要，因为我们在考虑丙烯醛作亲电试剂的情况，我们感兴趣的只是它的 LUMO。

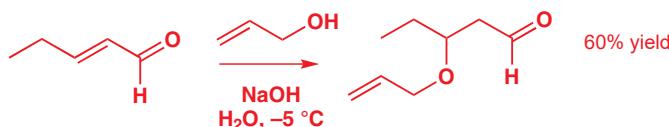
在 LUMO 中，最大轨道系数位于  $\alpha,\beta$ -不饱和体系的  $\beta$  碳上，图中标了星号。因此，亲核试剂的进攻发生于那里。刚刚的反应中，(亲核试剂的) HOMO 是甲氧基阴离子的孤对电子，因此关键的轨道相互作用会产生新的共价键。



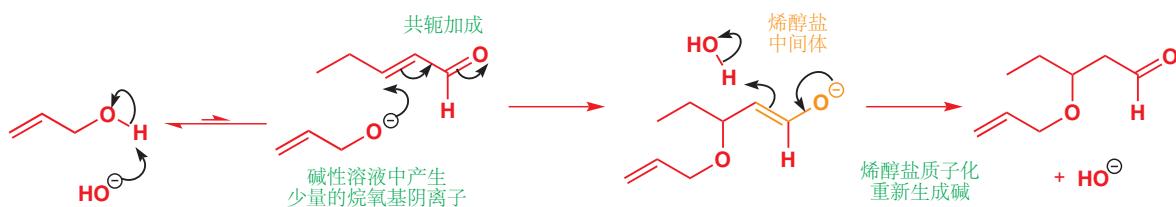
第二个最大的轨道系数位于 C=O 碳原子上，因此有些亲核试剂同样进攻羰基碳，也不会令您感到奇怪——记住本章开始的例子，氰离子进攻双键还说羰基取决于反应条件。在考察亲核进攻发生未知的问题前，我们将先看一些醇或胺做亲核试剂发生共轭加成的例子。

## 共轭加成有烯醇盐或烯醇的中间体

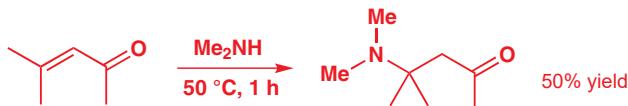
加成步骤的产物当然不是反应的最终产物——它事实上是一个烯醇盐。我们希望您能认出 Chapter 20 中所讲的这种物种，它当时由碱处理羰基化合物生成。共轭加成是另一种生成烯醇盐的方式，并且和其他的烯醇盐一样，质子化即可使之转化会羰基化合物。质子必须来自某个地方，因此共轭加成通常在质子溶剂（例如醇或水）中进行。下面是一个醇做亲核试剂的例子：



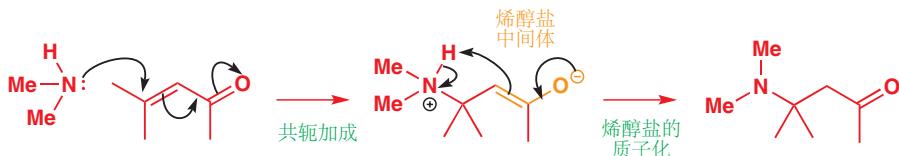
在碱性溶液中，少量的烷氧基阴离子会产生（醇的  $pK_a$  稍比水高），并会通过共轭加成进攻  $C=C$  双键。产物是一个烯醇盐，会被质子化以给出最终产物醛，同时也重新生成了氢氧根离子：此类反应仅需催化量的碱。



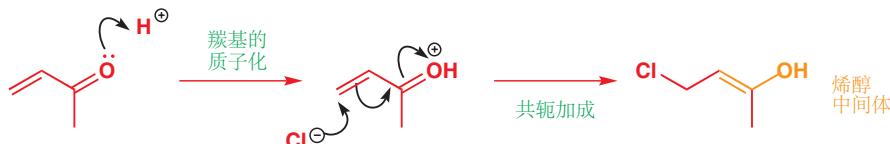
胺是对于共轭加成良好的亲核试剂。下面的反应在封闭系统中使用二甲胺的水溶液，以阻止二甲胺的挥发（二甲胺即使在室温下也是气体）。



胺是中性亲核试剂，而胺本身可以提供质子给烯醇盐。



如果您调查了 p. 500 中给出的共轭加成的初步概括，您会发现其中一部分在酸性条件下进行。例如用  $HCl$  处理下面的  $\alpha,\beta$ -不饱和酮，会给出氯代酮。第一步一定是羰基上的质子化，烯基酮带上正电荷后会更加亲电。氯离子进攻它的  $\beta$  碳并给出烯醇。



烯醇和烯醇盐的介绍位于 Chapter 20.

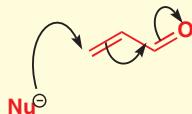
→ 互变异构的定义在 p. 451.



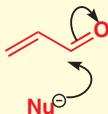
对羰基共轭加成还是直接加成？

我们已经向您展示了不少共轭加成的例子，有各种各样的亲核试剂和  $\alpha,\beta$ -不饱和羰基化合物，但我们还没有处理一个重要的问题。那就是，亲核试剂与羰基，什么时候发生共轭加成（也被称作1,4-加成），什么时候又发生直接加成（1,2-加成）？答案包含如下三个因素，我们会在下文中逐一将它们进行讨论。

- 对  $C=C$  共轭加成  
(也被称作 1,4-加成)



- 直接对  $C=O$  加成  
(也被称作 1,2-加成)

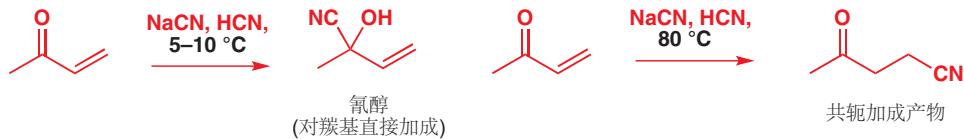


亲核试剂进攻的方式受决定于：

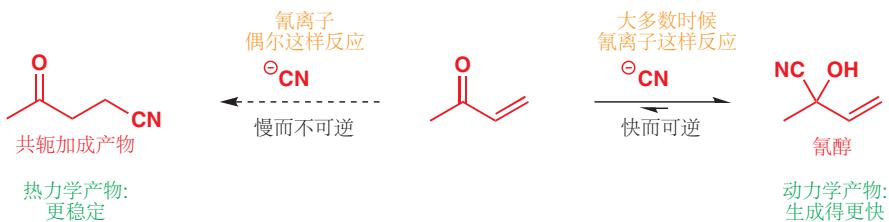
- 反应的条件
  - $\alpha, \beta$ -不饱和羰基化合物 的性质
  - 亲核试剂的种类

### 反应条件

本章最初的一个共轭加成反应就基于反应条件。用氰离子和酸性催化剂处理烯基酮时，低温下进行发生对  $C=O$  的直接加成，并给出氰醇，而如果加热反应混合物，则导致共轭加成。这是怎么回事？



我们会先考虑低温反应。如您在 Chapter 6 中了解的，氰离子在这样的条件下与酮反应形成氰醇是相当普通的。即使氰醇形成的平衡再偏向于产物的一侧，仍然会有少量的起始烯基酮剩余。大多数时候，会同时发生烯基酮反应形成更多的氰醇，以及氰醇分解回烯基酮和氰离子的两个过程——这是动态平衡的特征。不过起始烯基酮也会时不时地——以远远更慢的速度——与氰离子发生共轭加成。



而共轭加成的情况就不同了：它是一个基本上不可逆的反应，因此一旦有烯基酮转化为了共轭加成产物，那么它的命运就已经注定了：它不能重新变回烯基酮了。那么混合物中共轭加成产物会非常缓慢地积累。为了保持 烯基酮-氰醇 的平衡，任何因参与共轭加成而消耗掉的烯基酮，都会通过直接加成的逆反应予以补充。因此，即使在室温下，如我们所料，氰醇也会一点一点地转化为共轭加成产物，但这需要很长时间。而在高温下，速率得以提升，在 80 °C 下这个过程并不会持续太久，仅几个小时，氰醇就全部转化为共轭加成产物了。

这两个产物的对比是这样的：氰醇比共轭加成产物生成得快，被称作动力学控制（或动力学产物），而共轭加成产物则更加稳定，被称作热力学控制（或热力学产物）。一般来说，动力学控制的过程在较低温、较短的反应时间下进行，以确保只发生速率最快的反应；而热力学控制的过程在较高温、较长的反应时间下进行，以确保即使是慢的反应也有机会发生，而产物最终会都转变为最稳定的那个化合物。

▶ 动力学和热力学控制的介绍位于 Chapter 12.

### ● 动力学和热力学控制

- 生成得更快的产物被称作动力学产物。
- 更稳定的产物被称作热力学产物。

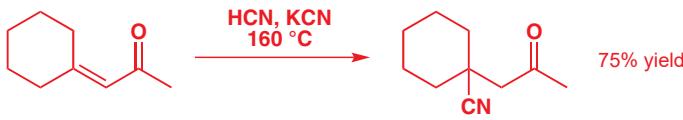
相似地，

- 产生动力学产物的条件被称作动力学控制。
- 产生热力学产物的条件被称作热力学控制。

为什么直接加成快于共轭加成？虽然在 C=O β 位的碳原子带有一些正电荷，但羰基碳原子带得则更多，因此对带电荷的亲核试剂的静电吸引会促使其直接进攻羰基，而不是经历共轭加成。

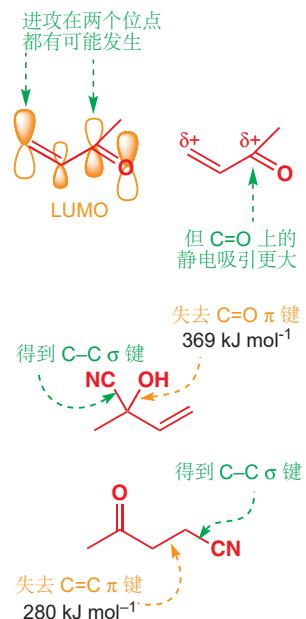
那么为什么共轭加成产物更加稳定呢？在共轭加成产物中，我们得到了一根 C–C σ 键，失去了 一根 C=C π 键，但保留了 C=O π 键。而在直接加成中，我们也得到了一根 C–C 键，但我们失去了 C=O π 键，而保留了 C=C π 键。C=O π 键比 C=C π 键更强，因此共轭加成产物更稳定。

在实际中，如果想要使共轭加成发生，您需要给反应大量的能量，或许也要大量的时间令其能找到最稳定的产物。下面是一个例子：注意温度！

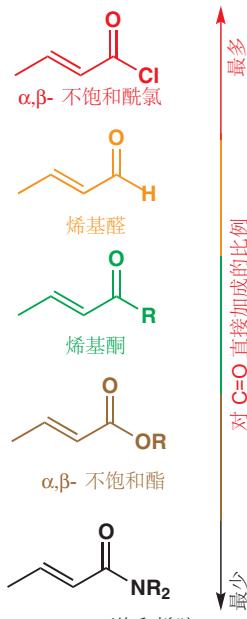
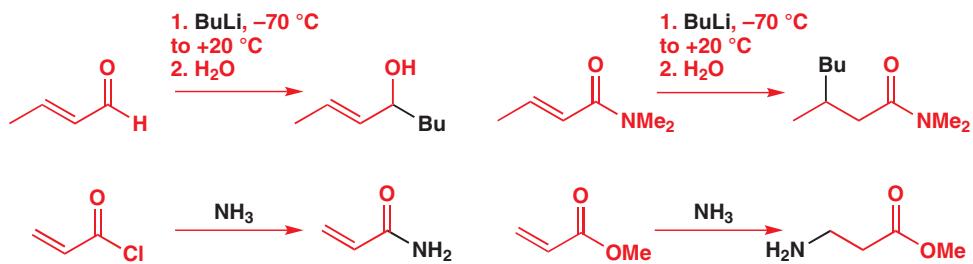


### 结构因素

到目前为止，我们主要向您展示的是 α,β-不饱和醛 和 α,β-不饱和酮 的共轭加成。而您不会感到意外的是，不饱和酸、酯、腈——事实上所有的羧酸衍生物——都可以参与共轭加成反应。下图中的右侧展示了了一个酰胺和一个酯的例子。这里反应的选择性取决于不饱和化合物的结构：对比丁基锂加入 α,β-不饱和醛 和 α,β-不饱和烯胺 的方式可知。两种加成都是不可逆的，但 BuLi 倾向于进攻醛上更活泼的羰基，而与较不活泼的酰胺发生共轭加成。相似地，氨与酰氯反应给出直接进攻衍生



的酰胺产物，却与酯经历共轭加成给出一个胺。

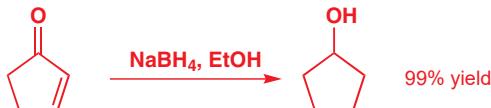


在这两个例子中，亲核进攻的位点仅仅取决于活性：羰基越活泼，越容易得到对  $\text{C}=\text{O}$  的直接加成。最活泼的羰基，如您在 Chapter 10 遇到的，是那些不与 O 或 N 共轭的（就像酯和酰胺），尤其活泼的是酰氯和酸酐。通常来说，对羰基直接加成的比例遵循侧边栏的反应性顺序。

硼氢化钠是一个您在将简单醛酮还原为醇时见过的亲核试剂，但它也会参与共轭加成。选择哪种方式取决于  $\text{C}=\text{O}$  基的反应性。 $\text{NaBH}_4$  通常与  $\alpha,\beta$ -不饱和醛通过对羰基的直接加成，给出醇。



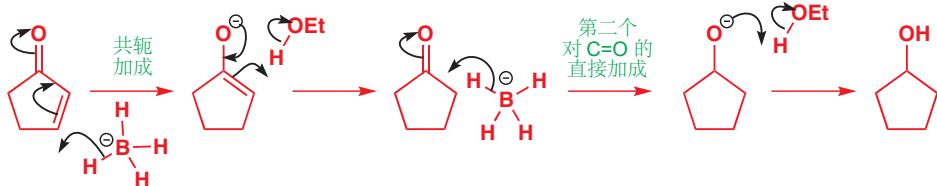
与酮的反应也很常见，结果如下。



四氢合硼酸根不仅会还原羰基，也会还原双键。事实上，是双键先通过共轭加成被还原，然后才是羰基的还原。

### Luche 还原

使  $\text{NaBH}_4$  仅进攻  $\text{C}=\text{O}$  是可能的，需要向反应混合物中加入  $\text{CeCl}_3$ ，这种改进被称作 Luche 还原 (Luche reduction)，以纪念它的发现者。



对于酯和其他较不活泼的羰基化合物，共轭加成是唯一发生的反应，因为  $\text{NaBH}_4$  不能还原酯或酰胺。



### 亲核试剂的性质：硬或软

用作共轭加成最好的亲核试剂是硫醇，醇的硫类似物。在下面的例子中，亲核试剂是苯硫酚（将苯酚中的 O 用 S 替换）。非凡地，不需要酸或碱的催化（就像醇的反应条件那样），在相当温和的反应条件下，它与  $\alpha,\beta$ -不饱和酮发生共轭加成。

件下产物以 94% 产率获得。



那么为什么硫醇如此特别呢？之前我们考察过，亲核试剂与亲电试剂之间的相互作用是由两种相关的相互作用控制的——静电吸引（正负电荷之间）和轨道重叠（亲核试剂的 HOMO 与亲电试剂的 LUMO）。成功的反应通常是二者结合的结果，但有时反应性也可被其中一个支配。这个支配因素是静电还是轨道控制，取决于参与反应的亲核试剂和亲电试剂。亲核试剂包含小、负电性的原子（例如 O 或 Cl）时，我们称其为“硬的”，倾向于主要在静电控制下反应，而包含较大的原子的“软的”亲核试剂（包括硫醇中的硫，以及 P, I, 和 Se 等）的反应则主要受轨道重叠的控制。

下面的表格将一些亲核试剂划归到了这两个分类中（有一些居中）——不要试图背诵它！宁可那样，不如考察表中每项的性质，让自己相信它们处于正确的位置上。其中有很多亲核试剂，您并没有见过它们参与反应，而在此阶段最重要的几个，已被**粗体**标出。



■ 我们在Chapter 15, p. 357, 中介绍了描述亲核试剂的术语**软**和**硬**。

### 软硬亲核试剂

硬的亲核试剂	分界	软的亲核试剂
$\text{F}^-$ , $\text{OH}^-$ , $\text{RO}^-$ , $\text{SO}_4^{2-}$ , $\text{Cl}^-$	$\text{N}_3^-$ , $\text{CN}^-$	$\text{I}^-$ , $\text{RS}^-$ , $\text{RSe}^-$ , $\text{S}^{2-}$
$\text{H}_2\text{O}$ , $\text{ROH}$ , $\text{ROR}'$ , $\text{RCOR}'$	$\text{RNH}_2$ , $\text{R}^1\text{R}^2\text{NH}$	$\text{RSH}$ , $\text{RSR}'$ , $\text{R}_3\text{P}$
$\text{NH}_3$ , $\text{RMgBr}$ , $\text{RLi}$	$\text{Br}^-$	烯烃, 芳环

不光亲核试剂可用软硬来分类，亲电试剂也可以。例如， $\text{H}^+$  是一个非常硬的亲电试剂，因为它体积小且带电荷；而  $\text{Br}_2$  是一个软的亲电试剂，因为它的轨道分散，而且不带电。您在本章的早期又见到了烯烃与  $\text{Br}_2$  的反应，我们在 Chapter 5 中阐释了，这个反应仅仅由于轨道相互作用而发生：因为并没有电荷参与。

#### ● 软/硬反应性

- 硬的物种的反应由电荷和静电效应支配。
- 软的物种的反应由轨道效应支配。
- 硬亲核试剂倾向于与硬亲电试剂反应。
- 软亲核试剂倾向于与软亲电试剂反应。

这和硫醇共轭加成又有什么关系呢？嗯，一个  $\alpha,\beta$ -不饱和羰基化合物 会不寻常地有两个亲电位点，一个更硬，一个更软。羰基在羰基碳上有更高的部分电荷，并倾向于与硬的亲核试剂，例如有机锂和格氏试剂，这种在亲和碳原子上也有很高的部分电荷的试剂反应。相反地， $\alpha,\beta$ -不饱和羰基体系的  $\beta$  碳并不具有很高的部分电荷，但这里却是 LUMO 最大的轨道系数所在的位点；这使得  $\beta$  碳是一个软的亲电试剂，因此很可能与硫醇这样的软的亲核试剂很好地反应。

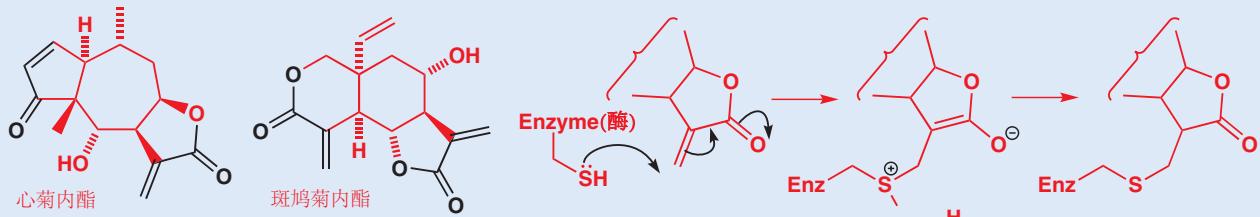
#### ● 软/硬——共轭/直接 加成

- 硬的亲核试剂倾向于在烯基酮的羰基碳（硬）上反应。
- 软的亲核试剂倾向于在烯基酮的  $\beta$  碳（软）上反应，导致共轭加成。

### 利用硫醇的共轭加成的抗癌药物

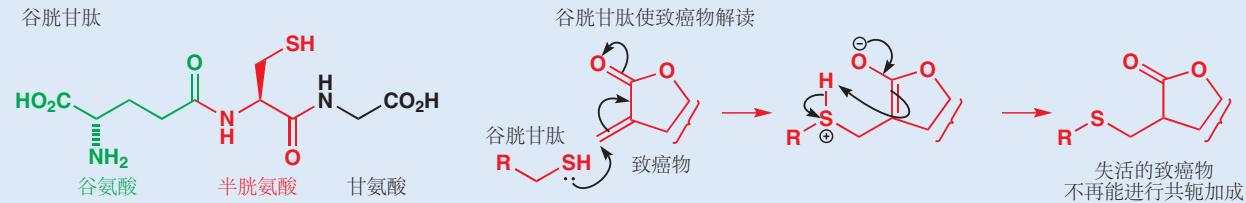
抗癌药物作用于一些列的生物化学途径，其中最常见的是作用于癌细胞迅速增殖所需的过程。其中一类进攻的是 DNA 聚合酶，这种酶用于产生新细胞所需的 DNA 的复制。心菊内酯 (Helenalin) 和斑鸠菊内酯 (vernolepin) 就属于这类化合物，如果您仔细观察它们

的结构，您应该能发现，它们中的每一个都含有两个  $\alpha,\beta$ -不饱和羰基。生物化学就是在很小的容器，即细胞中进行的化学；DNA 聚合酶与这些药物的反应即是硫醇 (该酶半胱氨酸残基上的 SH) 和不饱和羰基的反应。反应是不可逆的，并完全停止该酶的功能。



也正是因为这个原因，任何共轭加成的受体化合物都对生命体有潜在的危险。即使是像丙烯酸乙酯这样的简单化合物都被标记为“可疑致癌试剂”。它们通过对巯基、氨基的共轭加成进攻酶，尤其是参与细胞分裂的 DNA 聚合酶。幸运的是，人体中大多

数组织都包含一种可以起到一定程度的保护作用的重要化合物。这个化合物是谷胱甘肽 (glutathione)，一种三肽——由三个氨基酸形成的化合物。本书中我们还会更加细致地讨论这类化合物 (Chapter 42)，但在此时，请注意这个化合物可以在酰胺键处拆分为三个氨基酸。

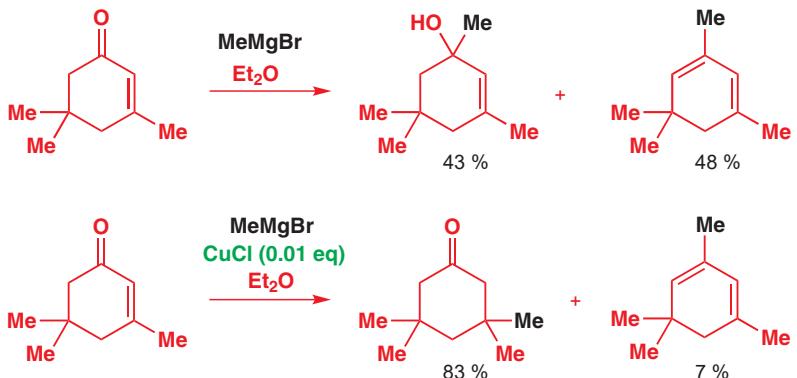


谷胱甘肽发挥作用的一端是巯基 (SH)，通过共轭加成清扫了致癌化合物。如果我们以一种“外亚甲基内酯 (exomethylene lactone)”——一种高活性的 Michael 受体——作为例子，并用  $RCH_2SH$  代表谷胱甘肽，您会理解所发生的失去。如果通常很充裕的谷氨酸被

氧化 (Chapter 42) 去除了，那么毒素就不再能被清除，有机体也继而变得危险。这是像维生素 C 这样的“抗氧化剂”有益的原因之一——它们可以清楚离群的氧化剂，并保护谷胱甘肽的供应。因此请继续吃水果和蔬菜！

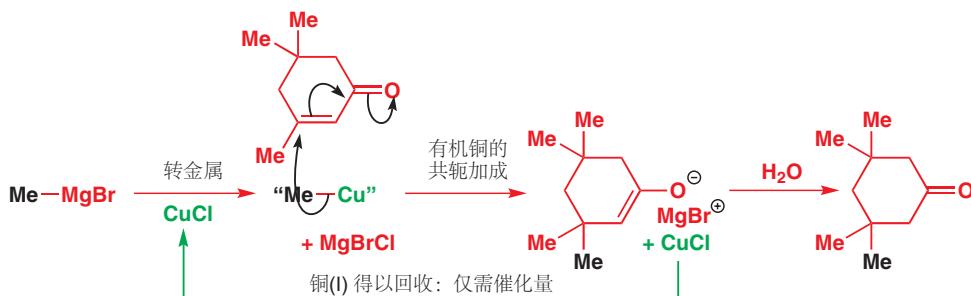
### 用铜(I) 盐促进共轭加成

格氏试剂对  $\alpha,\beta$ -不饱和醛酮 的加成通常直接发生在羰基上，并给出烯丙基醇：您已经看到了不少此事的例子，而现在您可以解释说，格氏试剂是硬的亲核试剂，倾向于进攻较硬的  $C=O$  而不是较软的  $C=C$  亲电中心。下面是一个延伸例子—— $MeMgBr$  对一个环状酮的加成，给出烯丙基醇，和一些通过这种醇脱水得到的双烯。而在这个例子下面的例子，仅加入了非常少量 (仅 0.01 当量，即 1%) 的 氯化铜(I)。亚铜盐产生的效果是激动人心的：它使格氏试剂参与共轭加成，而仅生成痕量的双烯。



## 有机铜试剂参与共轭加成

亚铜盐通过格氏试剂的转金属过程 (*transmetalation*), 生成有机铜试剂——仅是将镁换成了铜, 来发挥作用。有机铜比格氏试剂更软, 并以对较软的 C=C 双键的共轭方式加成。一旦有机铜加成完成, 重新生成的亚铜盐就又可以用于更多格氏试剂的转金属, 因此仅需催化量。

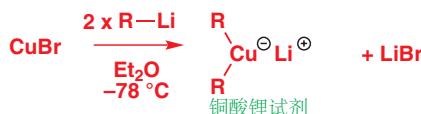


这里的有机铜被表示为 “ $\text{Me-Cu}^+$ ”, 这是因为它的精确结构还尚未得知。但也有其他的有机铜试剂同样进行共轭加成, 并且更好理解。最简单的一种是在低温下, 由两当量的有机锂与一当量的铜(I) 盐, 例如  $\text{CuBr}$  在乙醚或 THF 溶剂中产生。所生成的铜酸锂 lithium cuprates ( $\text{R}_2\text{CuLi}$ ) 并不稳定, 必须立即使用。

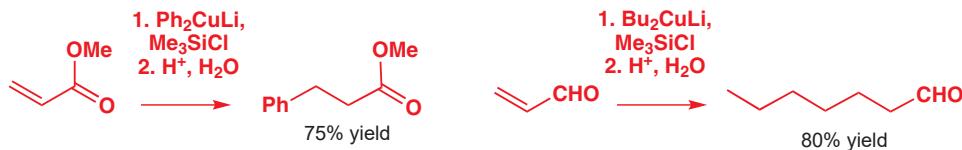
■ 有机铜比格氏试剂更软, 是因为铜的电负性比镁小, 因此  $\text{C}-\text{Cu}$  键相比  $\text{C}-\text{Mg}$  键极化得也少, 于是碳原子的部分负电荷也少。

电负性:  $\text{Mg}, 1.3; \text{Cu}, 1.9$ .

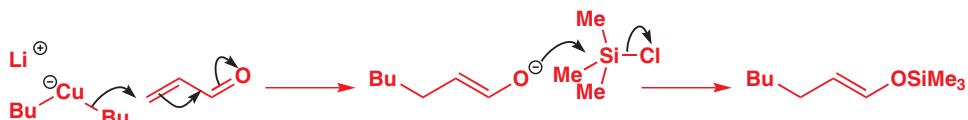
■ 和其他很多有机金属化合物一样, 有机铜的确切结构比我们这里说明的要复杂得多: 它们可能是四聚体 (四个  $\text{R}_2\text{CuLi}$  紧密连接), 但简单起见我们将其画作单体。我们有一章单独讨论有机金属 (含有金属–碳键的化合物, Chapter 40).



如果在反应中加入三甲基氯硅烷, 则铜酸锂对  $\alpha,\beta$ -不饱和酮的加成会进行得更好——我们马上会解释其原因。下面是两个铜酸锂加成的例子。



硅通过与共轭加成产生的带负电的中间体反应, 给出烯醇硅醚——我们在 Chapter 20 遇到的一类分子, 以发挥作用。下面是一个在  $\text{Me}_3\text{SiCl}$  的存在下,  $\text{Bu}_2\text{CuLi}$  和一种  $\alpha,\beta$ -不饱和醛的反应。



## 总结: 控制共轭加成的因素

在这里, 我们有必要评估一下控制对  $\alpha,\beta$ -不饱和羰基化合物 加成的两种方式的因素。

● 共轭(1,4或Michael)与直接(1,2)加成

	有利于共轭加成的	有利于对 C=O 直接加成的
反应条件(用于可逆加成):	热力学控制: 高温、长时间	动力学控制: 低温、短时间
$\alpha,\beta$ -不饱和化合物的结构:	不活泼的 C=O 基(酰胺、酯) 无空阻的 $\beta$ 碳	活泼的 C=O 基(醛、酰氯) 有空阻的 $\beta$ 碳
亲核试剂的种类:	软亲核试剂	硬亲核试剂
有机金属:	有机铜或催化量的铜(I)	有机锂、格氏试剂

## 将反应扩展到其他缺电子烯烃

不仅是羰基可以使烯烃反常地与亲核试剂反应，其他吸电子基团也可以起相同的作用。下面是两个例子：一个带有氰基，一个带有硝基。这些种类的化合物在 Chapter 21 关于芳香取代反应的内容中也有涉及，它们会从环上吸取电子密度。同样的事情也发生于此。

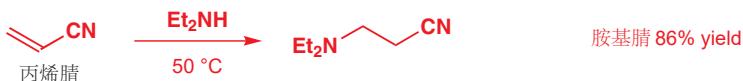
### 不饱和腈和硝基化合物

最简单的共轭腈是丙烯腈(acrylonitrile)。这个化合物可以很轻易地添加胺。想要促进在 C=C 上，而不是在 C≡N 的进攻并不需要特别的条件，这是因为氰基碳是相当不活泼的亲电位点。

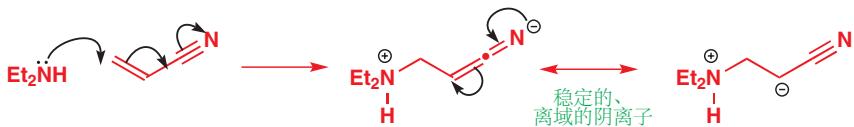
一些强亲核的试剂，也会部分地因为没有其他可以进攻的事物而进攻 C≡N—见 pp. 220 和 231.

Conjugate addition of amines to acrylonitrile

本章中，我们会几次使用分子内的机理表达质子转移的过程。本情形中，就节省了两个步骤的书写——烯醇盐的质子化，和在氮上的去质子——但很有可能这不是真实的质子转移机理。任何质子都在不停地到处跳跃，因此任何质子转移都不会严格按照字面上箭头指示的过程发生。我们在 Chapter 12, p. 267 讨论了质子转移机理可替换而又等价的几种表述。



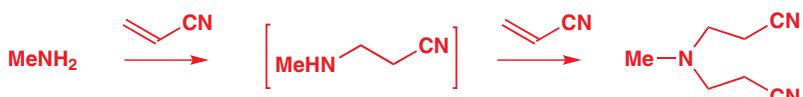
胺首先以一个经典的共轭加成进攻烯烃，并生成被邻位氰基所稳定的阴离子。这个阴离子的电荷可以画在 C 或 N 上：就像烯醇盐一样，是离域的。不要因为这种“烯醇盐”的古怪外观而感到反感。两根双键之间的点是为了提醒，这个位置有一个直线型 sp 碳原子。



在碳上的质子化复原了氰基，并给出产物——一个胺基腈(aminonitrile)。整个过程将一个 2-氰基乙基添加到了胺上，在工业上被称为氰乙基化(cyanoethylation)。



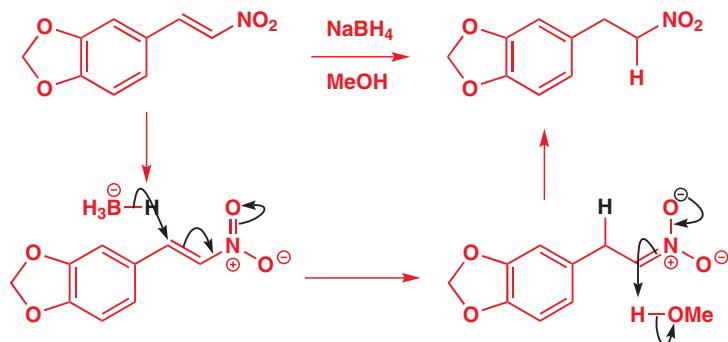
如果用伯胺，翻译不会再这一阶段停止，因为产物仍具亲核性，进而还能发生第二个加成，并将氮上的第二个氢原子替换。



其他元素，例如 O, S, 或 P 也可以加成。苯基膦可以像上个例子那样，加成两次；而醇可以加成因此。如果有第一周期（例如 N 或 O）和第二周期（例如 S 或 P）元素之间的竞争，第二周期元素一般会获胜，原因在上文已讨论（p. 507，周期数越大越软）。

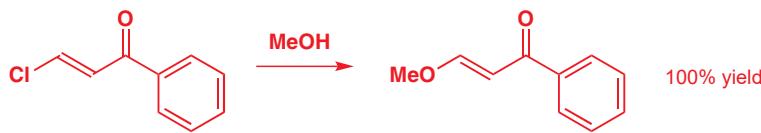


硝基 ( $\text{NO}_2$ ) 是非常吸电子的——大约相当于两倍的羰基的吸电子性。它同样是一个不活泼的亲电位点，并使得对硝基烷烃的共轭加成是一个非常可靠的翻译。在这个例子中，硼氢化钠通过共轭方式进攻  $\text{C}=\text{C}$  键，给出一个看起来很像烯醇阴离子的中间体，包含带负电的氧原子，与一个 ( $\text{N}=\text{C}$ ) 双键共轭。它也像烯醇盐那样反应，从碳上攫取质子，重新生成硝基并给出一个稳定的产物。



## 共轭取代反应

就像对  $\text{C}=\text{O}$  的直接加成 (Chapter 6) 在有离去基团存在时转变为了在  $\text{C}=\text{O}$  上的取代 (Chapter 10) 一样，如果有离去基团的存在，例如在  $\beta$  碳上有 Cl，共轭加成也会变为共轭取代 (conjugate *s*-substitution)。下面是一个例子：Cl 被  $\text{OMe}$  取代，这与我们考察过的，酰氯被取代的反应异曲同工。



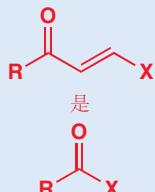
就像在  $\text{C}=\text{O}$  上的取代一样，这个看起来很简单的反应并不包含在单一的一步中对离去基团的直接取代。机理的开始与共轭加成的方式完全一样，给出烯醇中间体。



现在离去基团可以被烯醇排出：双键在一个消除反应中，回到原始的位置上——这个流程通常被称作加成-消除反应 (addition-elimination reaction)。“新”的双键有较稳定的 *E* 构型。在下一个

### 插烯 (Vinyllogous) 行为

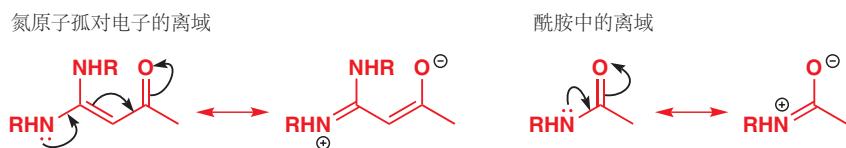
像这样的化合物被称作插烯酰胺——共轭的双键充当连接羰基与杂原子的电子桥，使其化学与光谱性质都和相应的含简单官能团的分子相同。您可以将本节开始时讨论的  $\beta$ -氯代烯基酮想成插烯的酰氯，并会与甲醇反应得到插烯的酯。



的插烯版本，  
与之反应方式相似

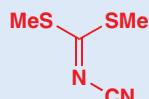
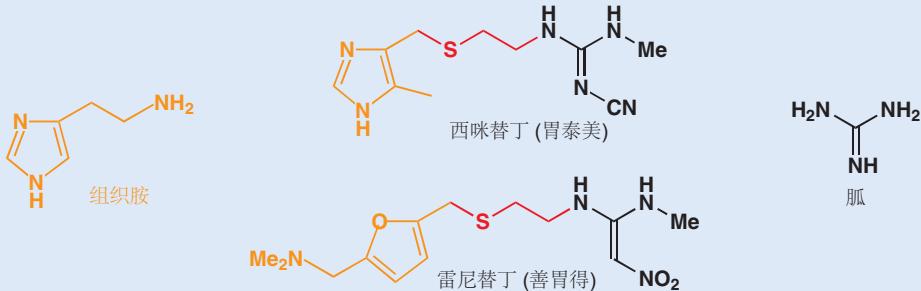


乍一看，这个产物看起来相当不稳定——对水，或痕量的酸敏感。但事实上，它对二者的反应都有明显的抗性。原因在于共轭：它事实上并不是一个胺（或二胺），因为氮原子上的孤对电子与羰基离域，非常类似于酰胺中的。这使得胺的碱性更弱，羰基的亲电性也更弱。

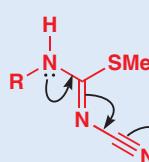


### 抗溃疡药物合成中的共轭加成

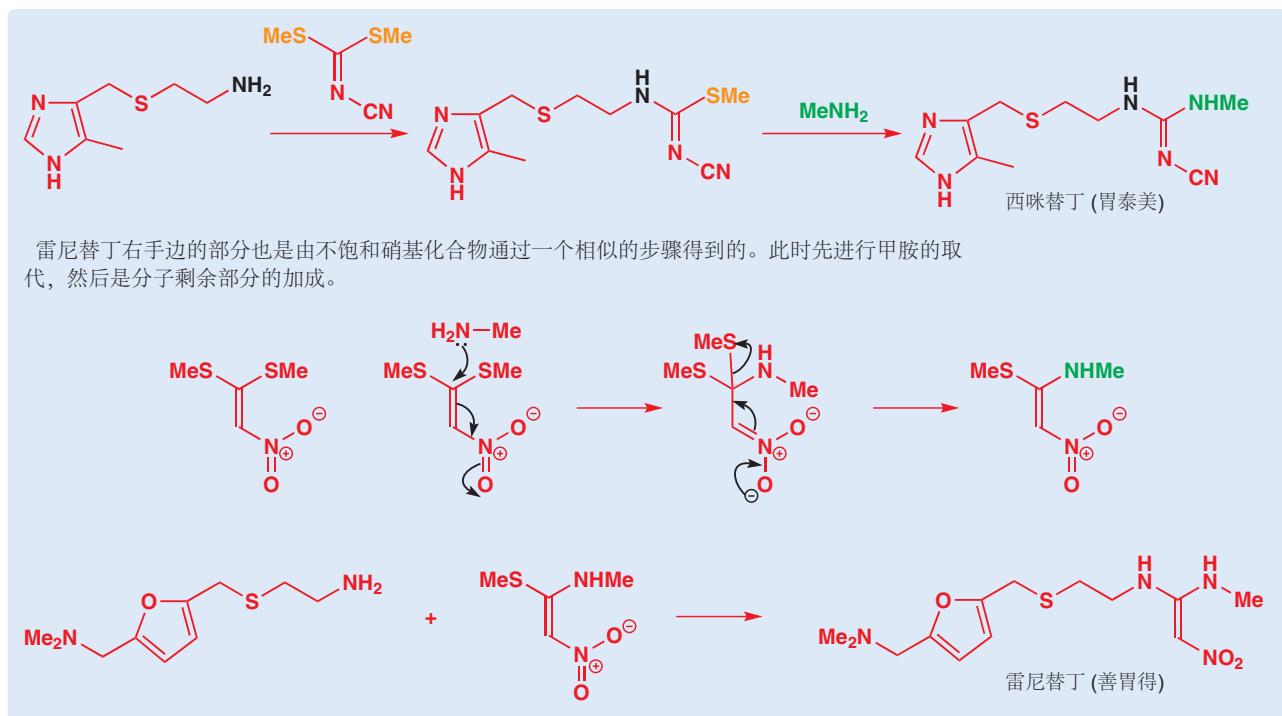
就像氰基 ( $\text{CN}$ ) 和硝基 ( $\text{NO}_2$ ) 可以引起共轭加成一样，它们也可以发起共轭取代。下面例子中的反应在两种药物的合成中起到重要作用，它们都是现代医药化学的发展中具有重大意义的药物：它们是抗溃疡化合物西咪替丁 cimetidine (商品名胃泰美 Tagamet) 和雷尼替丁 ranitidine (善胃得 Zantac)。我们在 Chapter 8 (p. 178) 中考察过了这些药物结构的一些方面，而现在我们将着眼于共轭加成在它们的合成中的应用。



最简单的氰化亚胺 (cyanimine) 位于左侧，有两个  $\text{SMe}$  基作为内置的离去基团，并能很轻易地在两个阶段与胺反应给出胍 (guanidines)。每个反应都是一个共轭加成。如果我们先用概括性的伯胺  $\text{RNH}_2$  绘制反应，那么它就会清晰很多：共轭加成，正如丙烯腈的一样，紧跟着最好的离去基团的排出。硫醇是酸性化合物， $\text{MeS}^-$  是比  $\text{RNH}^-$  更好的离去基团。



反应用于此处干净地停止，而取代第二个  $\text{MeS}^-$  基则需要更有力的条件。这是因为第一个产物相比于起始原料活性更低：新加入的氨基是给电子的，共轭也在它与氨基间建立，这钝化了面对第二次共轭取代的分子（图示位于左侧）。换用更加有利的条件，可以将一个不同的胺引入，并取代第二个  $\text{MeS}^-$  基。在西咪替丁的合成中，第二个胺是  $\text{MeNH}_2$ ，由此合成完毕。

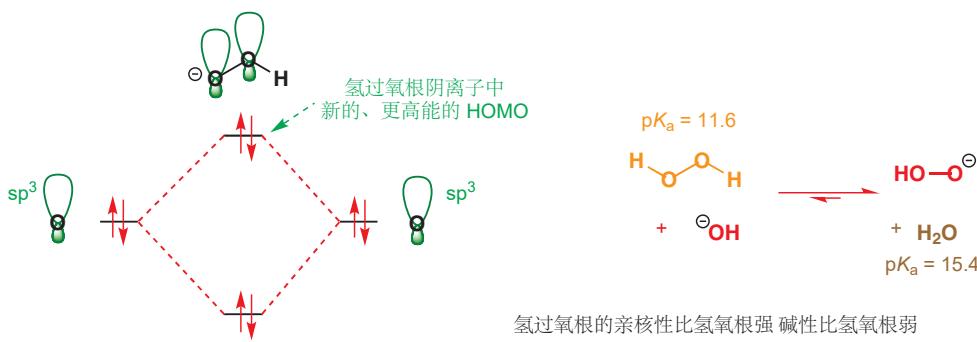
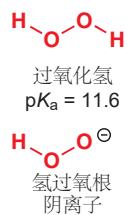


## 亲核环氧化

我们刚才所讨论的共轭取代反应依赖于带离去基团的起始原料。在本节中，我们将考察当离去基团不带在不饱和羧基化合物上，而是带在亲核试剂上时会发生的事。对于带离去基团的亲核试剂，我们会在 Chapter 38 中深入讨论，而在此刻，您需要了解的是其中最重要的一种，氢过氧根 (hydroperoxide), 过氧化氢的阴离子。

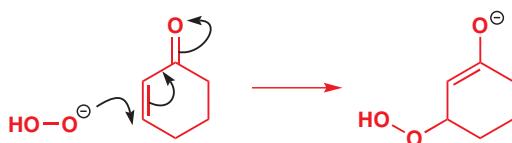
注：“氢过氧根”的翻译采取类推翻译法。“bi-”译为“某氢根”，“hydro-”译为“氢某根”。

由于  $\alpha$  效应 (alpha effect)，过氧化氢是一个很好的亲核试剂：两个相邻氧原子上孤对电子的相互作用提高了阴离子 HOMO 的能量，使其成为一个比氢氧根更好，同样也更软的亲核试剂。由于第二个氧原子的诱导吸电子效应，氢过氧根的碱性还比氢氧根弱。碱性和亲核性通常携手变化——但此处并不如此。这意味着氢过氧根阴离子可以通过用氢氧化钠的水溶液处理过氧化氢得以生成。



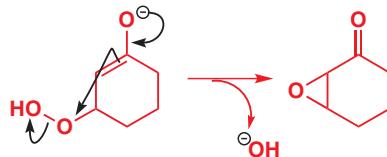
■ 这一效应也可解释为什么羟胺和肼的亲核性比氨强 (见 p. 232)。

下面是将其加入一种烯基酮时发生的变化。首先，发生共轭加成。



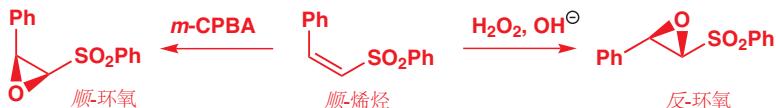
但产物并不稳定，因为常做亲核试剂的氢氧根可以从氧原子上掉下来。氢氧根在当下可以很好地作为离去基团——总之，氢氧根会通过 E1cB 消除从烯醇盐上失去，并且此时断裂的是一个弱的 O–O 键。产物是一个环氧。

Interactive mechanism for nucleophilic epoxidation



亲电的环氧化试剂，例如 *m*-CPBA，您已在 Chapter 19 中遇到，在亲核性的烯烃上可靠地工作；而对于  $\alpha,\beta$ -不饱和羰基化合物和其他缺电子的烯烃，过氧化氢——一个亲核的环氧化试剂——通常代替使用。

还有一个过氧化氢和 *m*-CPBA 的显著区别，以下面的一对反应呈现。



► 如果需要回顾术语立体专一性的含义，请见 p. 396.

*m*-CPBA 环氧化的立体专一性，是由于其一步完成的特点实现的。而氢过氧化物完成的亲核环氧化，则是一个两步的反应：阴离子中间体中存在一根能自由旋转的键，在图中已经标出；因而不管起始烯烃的几何结构如何，最终得到的都是更稳定的反式环氧。

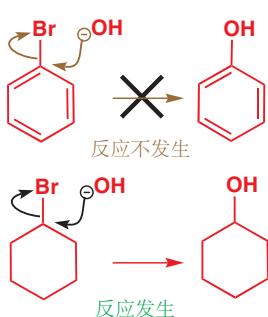


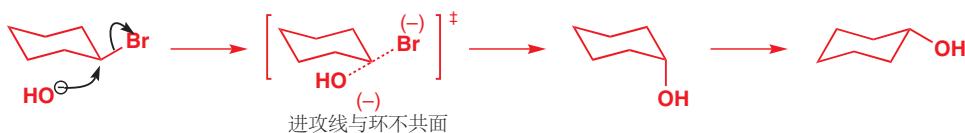
## 芳香亲核取代

在下一节中，我们将考虑一种与共轭取代相关的反应，其中的双键是一个芳环的一部分。我们在 Chapter 21 中花费了相当多的时间来解释芳环的亲核性：亲电试剂进攻它们，而经典的芳香反应性也是经历亲电取代。

通常来说，芳香卤的亲核取代反应——例如氢氧根试图取代溴的反应——**不会发生**。您可能会问“为什么？”这个反应看似很正确，如果环是饱和的，将不会有任何问题。

这是个  $S_N2$  反应，如我们所知 (Chapter 15)，进攻必须发生在 C–Br 键的正后方，也就是  $\sigma^*$  轨道最大的波瓣所处的位置。这对脂肪环来说十分完美，因为碳原子是四面体型的，C–Br 键与环也并不共面。平伏溴的取代反应如下所示：





但对于芳香化合物，碳是三角型的，C–Br 键是在环平面当中的。为了从后方进攻，亲核试剂必须在苯环内部出现，并且以一种荒唐的方式进攻碳原子。这个反应当然是不可能的。

这是此条一般规则的又一例子：



### ● $sp^2$ C 上的 $S_N2$ 反应不发生。

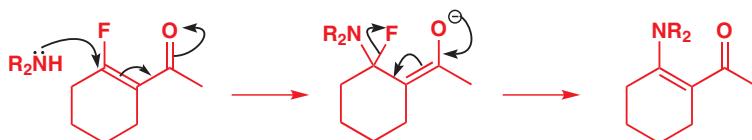
如果  $S_N2$  是不可能的，那  $S_N1$  怎么样呢？这是个可能的反应，但除非离去基团格外地好（见下面的例子），它会是非常不利的。它会包含离去基团的独自离去，和芳基阳离子的生成。任何我们在  $S_N1$  反应中见到的碳阳离子中间体（Chapter 15）都是平面型，带有空的 p 轨道的。而这个阳离子虽是平面型，但 p 轨道是充满的——它是芳环的一部分——于是空轨道是在环外部的  $sp^2$  轨道。

但是一些芳香化合物确实发生亲核取代反应。就像通常亲核的烯烃，在带有吸电子取代基的情况下同样可以发生共轭取代一样；通常亲核的芳环也可以在有适当的取代基是表现亲电性。它们经历亲核取代反应的机理与您刚刚看到的共轭取代机理十分相似。

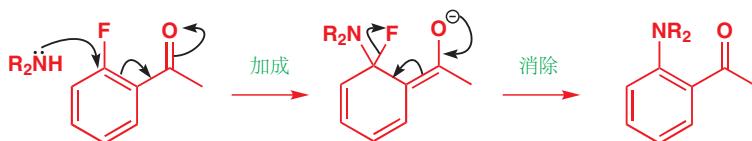


## 加成-消除机理

想象一个环状的  $\beta$ -氟代烯基酮与一个仲胺发生共轭取代反应的过程。通过一般的加成形成烯醇盐，紧跟着负电荷的返回以排出负离子，并给出产物。



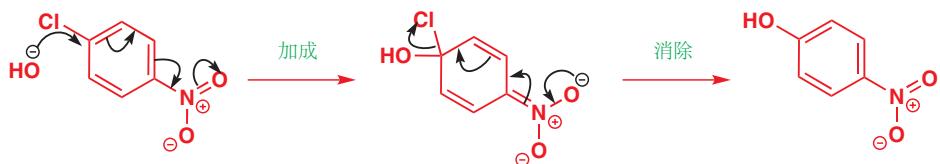
现在请想象仅将两根额外的双键添加到环上的同一反应。它们在我们的机理中不起任何作用；仅仅是使一个脂肪环变成了芳香环。共轭取代也转变为了**芳香亲核取代** (nucleophilic aromatic substitution)。



这个机理包含亲核试剂的加成，以及离去基团的消除——故被称作 **加成-消除机理** (addition-elimination mechanism)。羰基不是必要的——任何吸电子基团都可以完成工作——唯一的要求是，电子必须能脱离环，进入这个阴离子稳定基中。下面是一个对应硝基参与的例子。

■ 机理也被缩写作  $S_NAr$  (即取代、亲核、芳香 Substitution, Nucleophilic, Aromatic)。

 Interactive mechanism for aromatic addition-elimination



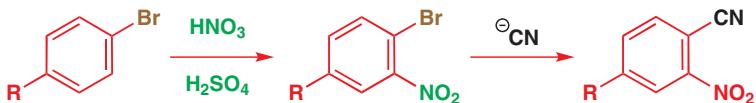
在这个例子中，所有情景都发生了变化——包括亲核试剂 ( $\text{HO}^-$ )、离去基团 ( $\text{Cl}^-$ )、阴离子稳定基 ( $\text{NO}_2$ )，乙基阴离子稳定基所处的位置 (对位)——但反应仍然进行。亲核试剂的亲核性很好，负电荷可以一直推到硝基的氧原子上，氯离子是一个比  $\text{OH}$  更好的离去基团。

#### ● 典型的芳香亲核取代包含：

- 一个基于氧原子、氮原子的，或氰根亲核试剂；
- 一个卤素作为离去基团；
- 离去基团的邻和/或对位有一个羰基、硝基或氰基。

由于硝基通常可以通过芳香亲电取代 (硝化反应, Chapter 21) 引入到卤素的邻对位。如下是一个常见的流程，先硝化，随后亲核取代。

如果您将阴离子稳定基置于间位，那么这个反应将不能工作。您不能画出将电子推到氧原子上的箭头。试试看。



这个流程的实用之处还在于，硝基的引入只能在卤代后、亲核取代前，因为其他情况会导致硝基的位置错误。氰基是间位定位的，而烷基 (R) 则是邻对位定位的。

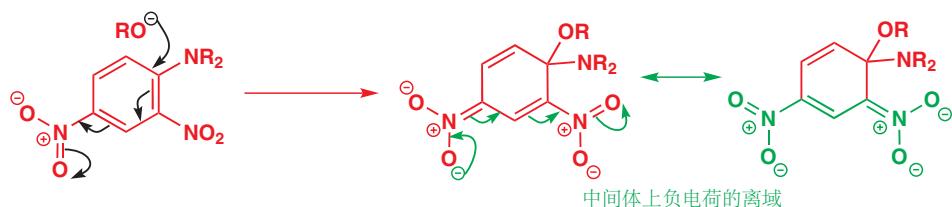
有两个吸电子的活化基 (硝基) 的苯比只有一个的更好，因此氯苯的二硝化可以得到一个非常亲电的芳基卤。它可以与肼反应给出一个非常有用的试剂。

有用，但也十分有毒！这个化合物——2,4-二硝基苯肼——是致癌的。它会和羰基化合物形成带颜色的亚胺晶体 (腙)——在光谱法出现前，它被用于检验醛和酮 (并不能区分醛酮，见 p. 232)。

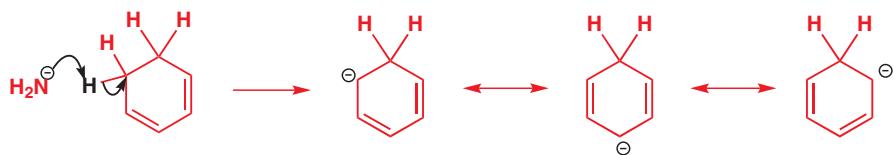


#### 加成-消除机理的中间体

有什么证据证明本节中我们讨论的中间体存在？当上一个反应的例子发生时，通常会在反应混合物中出现紫色，随后紫色消失。在一些情况下，紫色是持久的，这被认为是中间体导致的。下面的  $\text{RO}^-$  攻击硝基苯胺的例子就是这样的情况，因为可能的离去基团 ( $\text{NR}_2$  或  $\text{OR}$ ) 都不是很好。



中间体的特点是什么？本质上讲，它是一个离域在六元环中的五个  $sp^2$  杂环碳原子上的阴离子（第六个碳原子，即亲核试剂进攻的碳原子是  $sp^3$  杂化的）。通过环己二烯的去质子也能得到它的一个简单的同系物。离域的阴离子生成如下三个结构。



我们从前使用过的， $^{13}\text{C}$  NMR 光谱可用于揭示电荷分布，这个阴离子的  $^{13}\text{C}$  NMR 光谱细节如下所示，也一并有苯本身的，和苯的质子化得到的阳离子的（回忆 Chapter 21，芳香亲电取代生成得中间体）。

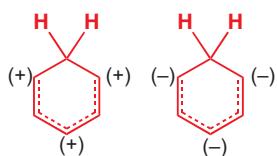
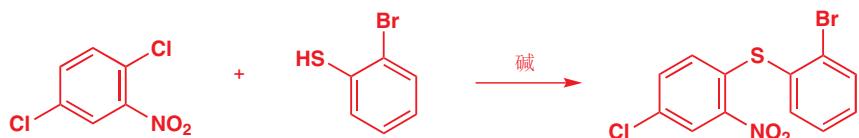


■ 回顾：较大的位移意味着较少的电子屏蔽，较小的位移意味着较多的电子屏蔽。

结果非常显著。两个离子间位的位移与苯本身的差距都很细微（均为大约 130 ppm）。而阴离子中邻位和对位的碳进入高场区，位移大大减小，暗示更高的电子密度；与之对照的，阳离子的邻对位碳进入低场区，位移大大增大。

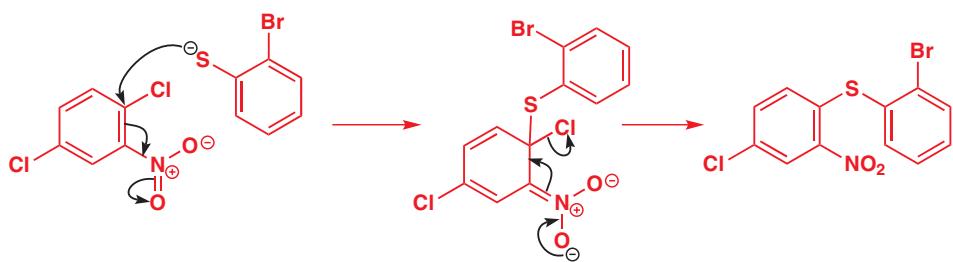
差距十分大——阳离子与阴离子几乎相差 100 ppm！从这些光谱上能十分明显地得知，两种情形中的离子电荷几乎都完全离域于邻位和对位。边栏的可替代结构展示了这一离域。

这意味着，在阴离子的情形中，如硝基或氰基的稳定基，只有处于被亲核试剂进攻的位点的邻对位碳上才能发挥作用。下面的选择性取代的例子很好地说明了这一点，亲核试剂仅取代两个氯原子中的一个，即硝基邻位的氯原子失去了，而间位的一个得以保留。



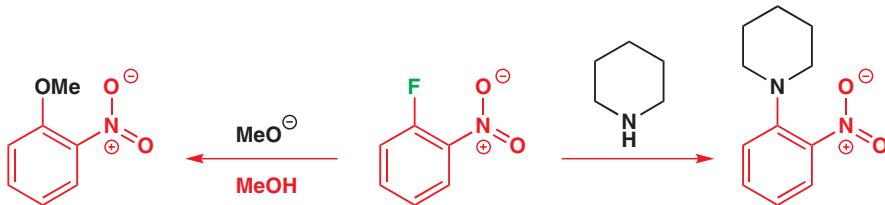
■ 记住，括号中的部分电荷显示了一个电荷所分成的主要组成部分（在这里 ca. 1/3）。对照  $\delta$ ，这意味着更小的极化。

如果亲核试剂（硫醇衍生的阴离子）进攻带有硝基邻位氯原子的碳时，机理可以很好地工作，因为负电荷可以推到硝基上。如果进攻另一个氯原子，则不能做到这一点。这个例子是一个真实反应，它被用作一种镇定剂的批量生产。

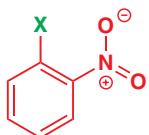


### 离去基团和机理

我们向您展示的首个芳香亲核取代中，离去基团就是氟离子。氟离子在这些反应中能很好地运作，包含氟离子的简单的化合物，如 2-氟代硝基苯可以很有效地与大量的亲核试剂作用，如下例子。



2-卤代-1-硝基苯  
在芳香亲核取代中的活性

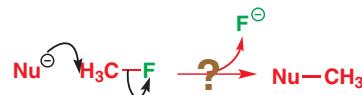


$F >> Cl \sim Br >> I$

其他 2-卤代-1-硝基苯你也可以完成相同的反应，但并没有氟化合物有效。氟化合物的反应比氯或溴代化合物的速度快  $10^2\text{--}10^3$  倍，而碘化物甚至更慢。

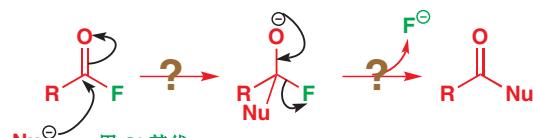
这应该令您感到惊讶。当我们提到其他亲核取代反应，例如羰基化合物上的，或饱和碳原子上的时，我们从不使用氟作为离去基团！C–F 键非常强——所有与碳成的单键中最强的——它很难断裂。因此，下面这些反应的前途并不好：

从不使用的反应:



用 Cl, Br, 或 I (I 是最好的) 替代

很少使用的反应:



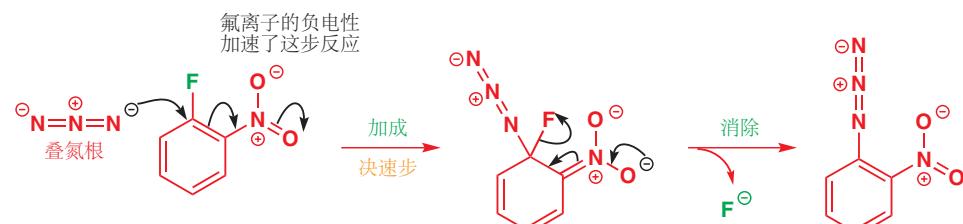
用 Cl 替代

► 您在 Chapter 15, p. 354 遇到了叠氮阴离子。

那么为什么氟在芳香亲核取代反应中运作得如此好，而在其他反应中却恰恰相反呢？您会注意到，我们并没有说氟在芳香亲核取代中是一个较好的离去基团。它不是！而解释建立在对这个反应机理更好的理解上。我们将以叠氮根阴离子作为亲核试剂，因为它已经被很好地研究过，也是最好的亲核试剂之一。

机理与我们一直讨论的完全相同——一个两阶段的 加成–消除 流程。在两步机理中，第一步很慢，也是决速的；而第二步对速率不重要。您可能已经猜到，芳香亲核取代第一步较慢的原因是它干扰了芳香性；而第二步反应则因为芳香性的恢复而较快。氟和其他离去基团（对芳香亲核取代）的效果仅来源于它对第一步反应的影响。离去基团的离去性并不重要：离去性仅影响第二步反应的速率——氟离子离去的困难性，对总反应速率没有影响。

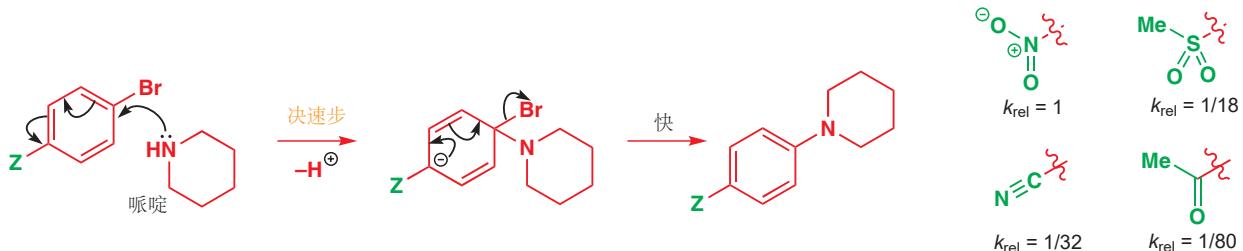
■ 仔细地记住，这里是诱导效应：氟离子吸电子的方式不能用箭头表示——仅仅是通过 C–F 键向氟本身极化体现。请于（主要）通过共轭吸电子的硝基对比。



氟离子通过诱导效应加速第一步的发生。它是电负性最大的元素，并可以稳定阴离子中间体，帮助苯环接受电子。

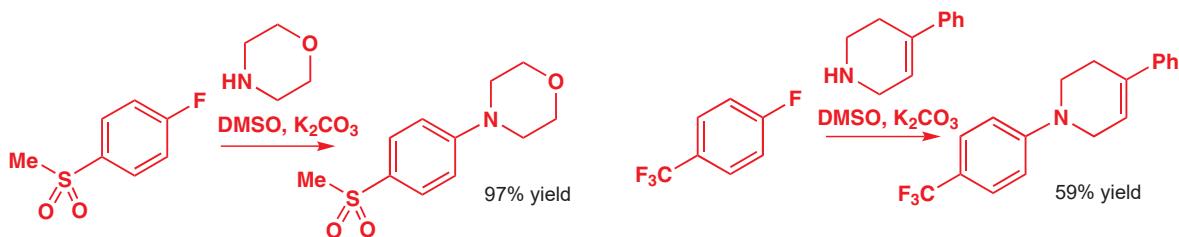
## 阴离子稳定活化基

目前为止我们已经多次使用硝基，因为它们在稳定阴离子中间体的职务上是最好的。其他可以工作的包括羰基、氰基，基于硫的砜和亚砜。不同的 Z 基团可以通过比较它们对溴代（这个例子中通过仲胺哌啶）的帮助（相对速率常数）以直接比较好坏。



其他所有化合物都比硝基化合物反应得慢。我们从前就提及过硝基强大的吸电子能力（Chapters 8 和 21）——此处又出现了它能力的又一量度。砜比其慢 18 倍，氰基慢 32 倍，酮慢 80 倍。

硝基是最好的活化基团，而其他的也都很好，尤其是与作为离去基团的氟，而不是溴结合使时。下面是两个选用其他阴离子稳定基的，在制备意义上很好地工作的反应。注意，三氟甲基运作时所用的仅有其强大的吸电子诱导效应。



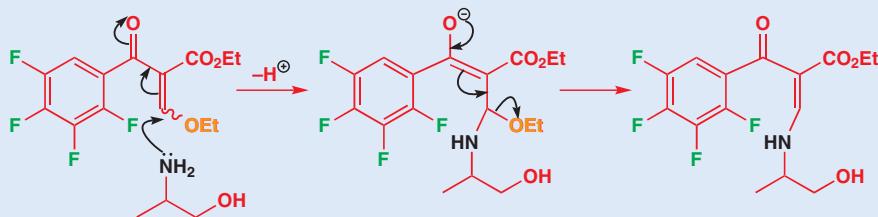
### ● 总结

在潜在的离去基团邻对位添加阴离子稳定基（吸电子基）可促进芳香亲核取代反应。

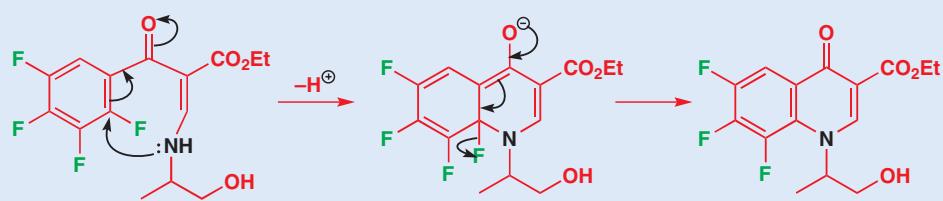
## 共轭取代和芳香亲核取代的使用：一种抗生素的合成

我们想让您相信，化学是有用的，包括在一些复杂分子中，因此我们将描述一种抗生素，氧氟沙星（oxacin）制备中的一部分。流程始于一个带有四个氟原子的芳香化合物。其中三个被亲核试剂循序地取代，而最后一个在抗生素本身中。

第一个反应是一个对用橘色标出的甲氧基的共轭取代。用一种氨基醇作为亲核试剂，此时是亲核性更强的氨基（而不是羟基）加成到烯烃（烯基酮）上。



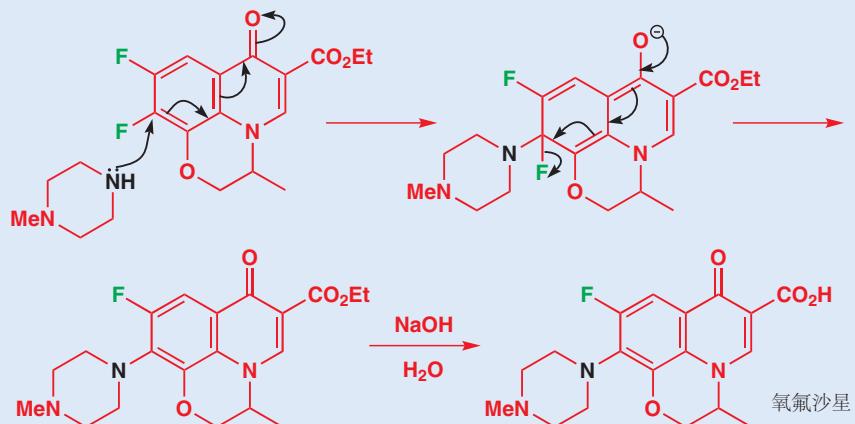
现在轮到第一次芳香亲核取代了。氨基进攻羰基的邻位，并形成烯醇盐中间体（被羰基稳定的阴离子）。消除后第一个氟被排出。



现在用碱处理 (可用  $\text{NaH}$ ) 可以将  $\text{OH}$  基转化为烷氧基阴离子，并参与下一次芳香亲核取代。这个反应中，进攻位点为酮的间位，因此我们不能将负电荷推至氧原子上。起稳定阴离子作用的是剩下三个氟原子的诱导效应。



现在只剩下两个氟原子，其中一个会被外来的亲核试剂——一个胺所取代。胺进攻的位点现在由带电中间体，即一个烯醇盐所需的稳定化因素决定了。



现在所剩下的就是在碱的水溶液中水解酯，以释放酸 (Chapter 10). 整个复杂的流程所包含的都是您曾学过的简单反应，这说明简单的有机机理也能以其强大的能力让化学家合成重要的救命化合物。

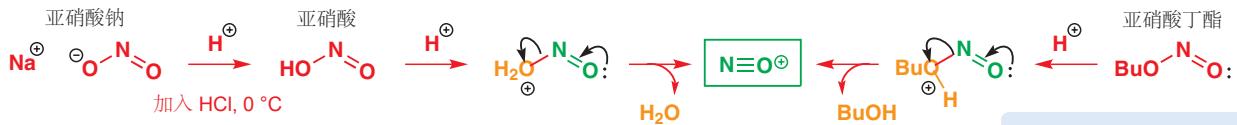
芳环上的亲核取代反应也能通过其他可替代的机理实现，这是我们下面要讨论的内容。

## 芳香亲核取代的 $S_N1$ 机理：重氮化合物

如果我们果真想用亲核取代反应制备芳香化合物，而且想要一种通用方法，那么当然这种方法所要用到的是最好的离去基团——氮气。事实上，下面的重氮化合物 (diazonium compound) 是芳香亲核取代中十分好的亲核试剂，即便没有吸电子活化基也可以有很好的效果。加热时，氮气分子离开，剩下一个阳离子以被亲核试剂捕获，此情形中为水分子。它让您回忆起  $S_N1$  反应了吗？我们希望如此。



在我们更详细讨论这类芳香 S<sub>N</sub>1 反应前，让我们先来看看如何制备重氮盐。我们需要的试剂是活泼的氮亲电试剂 NO<sup>+</sup>。您在 Chapter 20 中已经遇到过 NO<sup>+</sup>，再次提醒您，它是通过用酸在 0 °C 左右处理亚硝酸阴根离子（通常是亚硝酸钠）获得的。亚硝酸阴根的质子化给出亚硝酸，HONO；继续质子化则给出阳离子，随后阳离子离去水形成 NO<sup>+</sup>。亚硝酸丁酯（或其他亚硝酸烃基酯）也可被用作 NO<sup>+</sup> 源。



当 NO<sup>+</sup> 与一个胺反应时，重氮盐就会生成。胺上的孤对电子进攻 NO<sup>+</sup> 阳离子，并失去水。这个机理事实上相当简单，但它包含了很多电子转移过程。当然，有一个阴离子与重氮阳离子关联，这通常是形成 NO<sup>+</sup> 时所用的酸的共轭碱（通常是 Cl<sup>-</sup>）。这个反应被称作重氮化（diazotization）。



如果胺是仲胺，水不能消去，形成的是亚硝胺（nitrosamine）。



如果胺是一个烷基胺，重氮盐会非常不稳定，立即失去氮气并给出平面型碳阳离子，继而通过 S<sub>N</sub>1 过程与一个亲核试剂反应（Chapter 15），通过 E1 过程脱去质子（Chapter 17），或者发生重排（Chapter 36）。例如，它也许会与水反应给出醇：



如果胺是一个芳香胺，本节开头的反应就会发生，并形成苯酚。这事实上是一个相当有用的反应，因为我们很难通过一般的亲电取代向苯环添加氧原子：没有好的提供 OH<sup>+</sup> 的试剂。而氮原子则可以轻易地通过硝化加入，随后的还原和重氮化提供了用羟基取代硝基的方法。

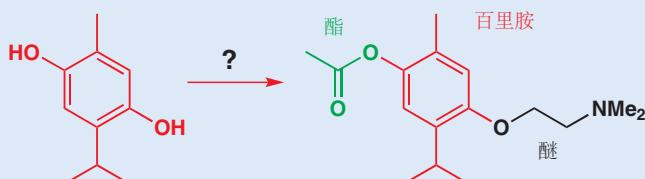
Interactive mechanism for formation of diazonium salt

我们在 Chapter 21 的结尾略微提到了这个反应。

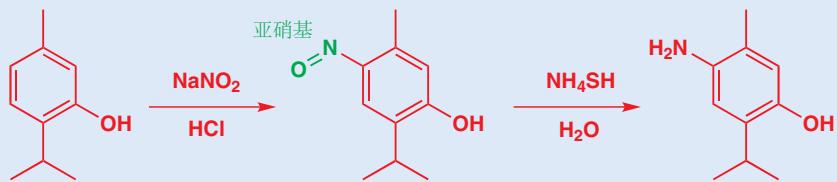


### 一种药物的合成中的取代反应

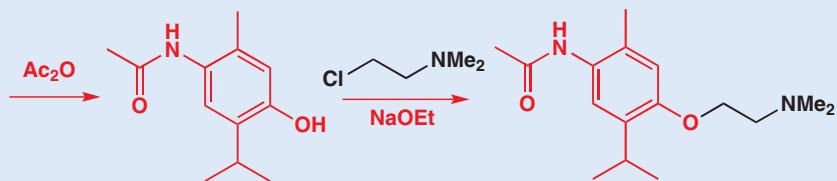
药物百里胺 thymoxamine (莫西塞利 Moxyslyte) 的合成提供了一个本反应的实际应用。



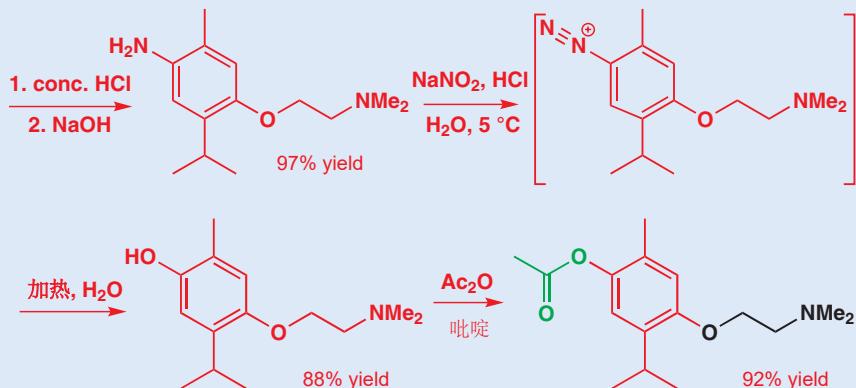
放眼看去，也许很明显这个反应可以用二羟基苯的烷基化和酰化制备，但我们如何保证酰化和烷基化都在正确的 OH 基上呢？法国的制药化学家设计了一个精巧的方案：由只有一个 OH 基的化合物开始，先烷基化，然后再用重氮盐的方法引入第二个羟基。它们引入氮原子时，用的是亚硝基（NO）而非硝基（NO<sub>2</sub>），试剂是与我们重氮化相同的试剂。下面是前两步。



NO 的还原比 NO<sub>2</sub> 简单，H<sub>2</sub>S 就足以完成这份工作。现在可将胺转化为亚胺来减弱其亲核性，以便苯酚的烷基化能干净地进行——保护（见 Chapter 23）。



最后，胺通过水解释放，然后通过重氮化和水解转化为 OH 基来参与酰化。

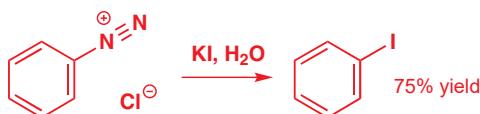


然而，一个芳基碳阳离子要比烷基碳阳离子更不稳定，因为它的空轨道是一个  $sp^2$  轨道，而不是一个 p 轨道。这使氮气的离去减慢。如果重氮化在 0 °C 左右（经典条件为 5 °C）完成，重氮盐就是稳定的，不会立即与水反应，而可以根据需要选择多种多样的亲核试剂。

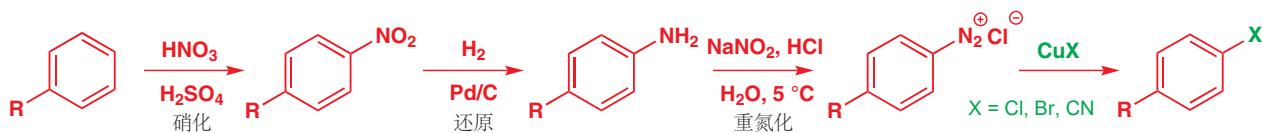
### 其他亲核试剂

芳基碘不容易通过像芳基氯、芳基溴那样的亲电取代反应制备，因为碘单质的活性不足以进攻苯环。但通过向重氮盐中加入碘化钾，则可以通过芳香亲核取代得到芳基碘。

■ 芳基碘在用 Pd 和其他过渡金属催化偶联化学中有非常广泛的用途，的见 Chapter 40。



其他亲核试剂，例如氯、溴、氰根，都可以以其 铜(I) 盐的形式很好地添加。由于芳基胺通常通过硝基化合物的还原制取，因此可以总结出如下的一般流程：



在芳香化学中，硝基经常出现，这大概归功于如上流程使其具有的多功能性——流程即为，容易通过亲电取代引入，容易还原，其重氮盐衍生物容易亲核取代。

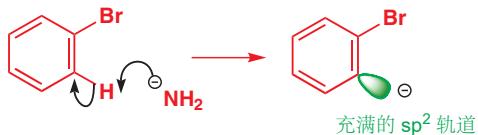
## 苯炔机理

现在我们将向您介绍最后一个芳香亲核取代的机理，而这个也会是您在目前见过的所有反应中，感到最离奇的一个机理，其中包含从来难以想象的中间体！而我们的工作，是希望让您相信，这个机理不但可能发生，而且是有用的。

在本章的早期，我们曾说过溴代苯上的溴被亲核试剂取代的反应不能发生。事实上，溴代苯的取代反应可以发生，但所需的条件十分猛烈，例如使溴代苯和 NaOH 在很高温下共熔 (fused) 用非常强的试剂  $\text{NaNH}_2$  (提供  $\text{NH}_2^-$  例子)，以相当低的温度，也可发生一个类似的反应。

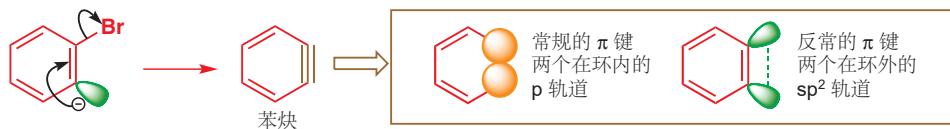


在反应历程被发现前，这个反应就已经长时间为人所知了。如我们之前解释过的，它们并不以  $S_N2$  机理反应，它们也不能以加成-消除机理反应，因为中间体中没有用于稳定负电荷的结构。找出真实机理的第一个线索是，所有以这种方式反应的亲核试剂碱性都很强。它们从移去离去基团邻位的质子开始反应。



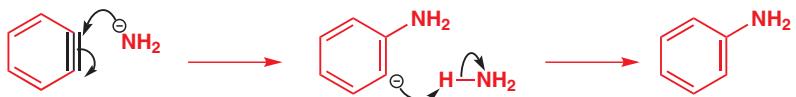
碳阴离子位于环平面上的  $sp^2$  轨道中。委实，这个中间体很像重氮盐在  $S_N1$  机理中生成的芳基阳离子中间体，它的  $sp^2$  轨道中没有电子；而这里的芳基阴离子则有两个。为什么是这个质子被移去，而不是其他的？由于溴原子具有负电性，而 C–Br 键位于  $sp^2$  轨道平面上，可以从其中吸取电子。尽管如此，稳定化因素都是微弱的，只有格外强的碱可以完成这一反应。

下一步是在消除反应中溴离子的失去。这一步很难想象，因为我们假定其所生成的中间体是看起来不可能存在的。轨道对于消除反应也是不利的——处于顺叠(顺式共平面)而非反叠(反式共平面)。但它还是发生了。



这个中间体被称作苯炔 (benzyne)，它是一个有位于苯环中的三键的炔烃。但这根三键意味着什么？它不是直线型的，当然不是一个常规的炔烃。事实上其中一根  $\pi$  键是常规的——它正好是芳环的一部分。另一根  $\pi$  键——新形成的一——是反常的，它是通过两个在环外的  $sp^2$  轨道的重叠形成

的。这根外部  $\pi$  键是很脆弱的，苯炔也是一个很不稳定的中间体。委实，当这个结构被提出时，但却还没有确凿的证据时，很少有化学家相信它。我们不久将了解这个证据，但先让我们完成机理的书写。不同于一般的炔烃，由于苯炔中脆弱的第三根键，苯炔具有亲电性。



整个由溴苯到苯胺的机理，包含了苯炔通过消除形成，和苯炔三键上的亲核加成。在许多方面，这个机理都如同加成–消除机理的逆序，并且有时也被称作消除–加成机理 (elimination-addition mechanism)。

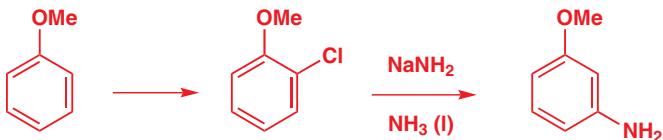
任何碱性足以移去邻位质子的亲核试剂都可以完成这个反应。已知的例子包括氧阴离子、胺阴离子 ( $R_2N^-$ )，和碳阴离子。相当碱性的烷氧基阴离子，叔丁氧基以论证，可以在使用其钾盐，并于非质子偶极溶剂 DMSO 中使活性最大化的情况下与溴苯反应。

■ DMSO (see p. 255) 可溶剂化  $K^+$  而不能溶剂化  $RO^-$ .

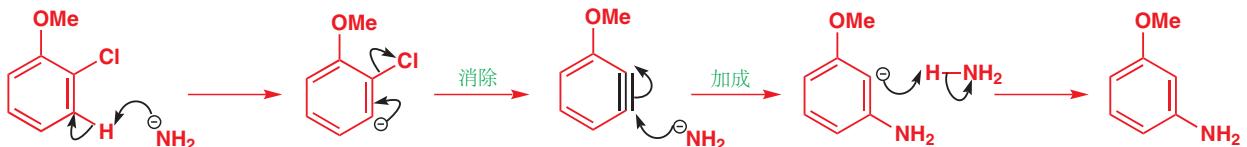


Interactive mechanism for benzene formation and reaction

这个反应有一个相当特殊的特征，这让我们确定了苯炔机理的正确性的。即在事实上，三键的两侧原则上都可以被亲核试剂进攻。这在溴苯上没有体现，因为产物都是一样的，而我们可以将三键的两侧设计的不同，进而看到一些有趣的事物。邻氯芳基醚很容易通过芳基醚的氯代制备 (Chapter 21)。而当我们在液氨中用  $NaNH_2$  处理它们时，仅以好产率得到一个单一的胺。



纵使起始物中的氯处在邻位，而产物中的氨基则处在间位。不用苯炔机理很难解释这一点。按照消除–加成流程，机理应当如下：



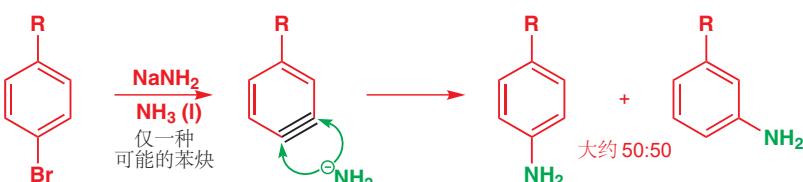
■ 空阻在亲电取代反应，和加成–消除机理的亲核取代反应中远不及如此重要。在这两个反应中，试剂都以合适的角度进攻环上的  $p$  轨道，这和邻位取代基之间是有一段距离的。

这展示了间位产物生成的历程，但为什么它应当生成呢？进攻也会发生在邻位，那为什么没得到邻位产物呢？有两个原因：电子因素与立体因素。对于电子因素，由于负电性的氧原子的吸电子诱导效应，阴离子倾向于更贴近它生成。同样的因素，氯的吸电子效应也促进了苯炔生成时，其邻位的去质子过程。对于立体因素，于其和氧原子相邻，氨基阴离子更愿意进攻远离 OMe 基的位置。苯炔上的亲核进攻发生在苯环的平面中，因为这是轨道所处的位置；因此亲核试剂进攻时必须与取代基共面，这使得这个反应对于空阻非常敏感。

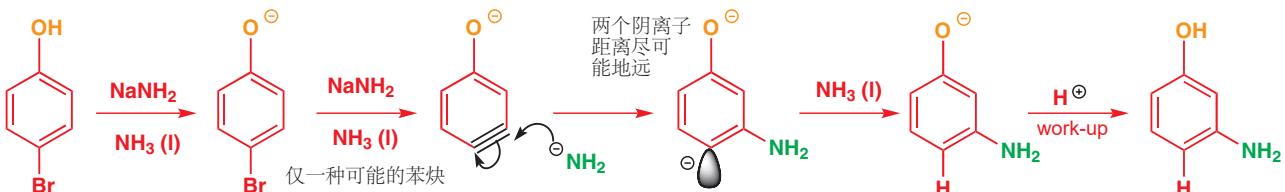


■ Oxygen is an electron-withdrawing group here because the anion is formed in the plane of the ring and has nothing to do with the benzene's  $\pi$  orbitals.

对应取代的芳基卤也可以得到单一的一种苯炔，它们中的大多数都给出产物的混合。一个简单的烷基取代基距离三键太远，很难发挥空间效应。



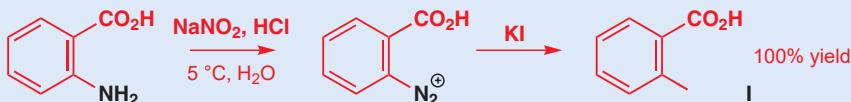
如果取代基是一个给电子基团，那么生成的就完全是间位产物，因为这样得到的产物的阴离子距离原本存在的阴离子尽可能地远。这也是有用的，可以制备两个邻对位定位基以间位相对关系出现的分子。



### 其他苯炔做中间体的证据

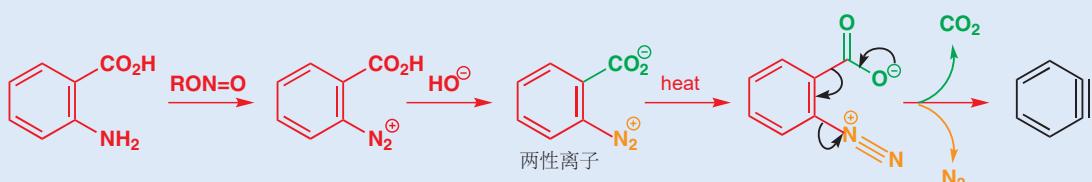
如您所料，苯炔的形成是反应中的慢步骤，因此从反应混合物中分离苯炔，甚至在光谱法上观察它都是没有希望的。然而，可以

通过在其中没有亲核试剂捕获它的其他反应制备，例如由下面的重氮化反应。



这个重氮化反应非常有效，您可以看到当用碘离子捕获重氮盐时，以定量的产率给出 2-碘代苯甲酸。然而，如果相同的重氮盐改用 NaOH 中和，则可以给出一个两性离子 (zwitterion)，在羧基上带负电荷以平衡重氮基上的正电荷。这个重氮化反应可以通过在有

机溶剂中用亚硝酸酯完成，以避免常规条件下氯离子或水做亲核试剂捕获产物。当加热两性离子，它将熵驱动地分解为二氧化碳、氮气和苯炔。



您仍不能分离出苯炔，因为它会与自己反应得到苯炔二聚体，在两个苯环之间有一个四元环。如果在质谱仪中观察两性离子，则会观察到二聚体在 152 处的峰，而更加强的峰是苯炔本身在

76 处的。质谱仪中微粒的寿命大约  $2 \times 10^{-8}$  秒，这说明苯炔在气相中至少可以存在这么长时间。



## 小结

烯烃和芳烃通常是亲核的。而本章则讨论了它们不亲核，反倒亲电的场景。记住，虽然这一章的反应很重要，但见到这些化合物，您想到的反应性原则仍应当时亲核性。

下表总结了所涉及的反应，也包含您会在本书的其余部分遇到的类似反应。

页码	烯烃类型	例子	反应
500	不饱和羰基化合物		共轭加成
510	不饱和腈和硝基烷烃		共轭加成
511	带有β离去基团的烯基酮等		共轭取代
513	不饱和羰基化合物		亲核环氧化
515	邻对位有吸电子基团的芳基氯/氟		芳香亲核取代: 加成-消除机理
520	芳基阳离子 (来源于重氮盐)		芳香亲核取代: $S_N1$ 机理
525	苯炔		芳香亲核取代: 消除-加成机理
ch. 26	烯醇盐和烯醇盐等价物作为亲核试剂		共轭加成

## 延伸阅读

F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry A, Structure and Mechanisms*, 5th edn, Springer, 2007, chapter 9 和 B, *Reactions and Synthesis*, chapter 11 也有关于芳香亲核取代的讨论。B. S. Furniss, A. J. Hannaford, P. W. G. Smith, and A. T. Tatchell, *Vogel's Textbook of Practical*

*Organic Chemistry*, Longman, 5th edn, 1989, 6.6–6.7 提供了很多芳香亲核取代的实际例子。P. Wyatt and S. Warren, *Organic Synthesis: Strategy and Control*, Wiley, Chichester, 2007, chapter 9.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 23

## 化学选择性和保护基

### 联系

#### ► 基础

- 羰基加成和取代 ch6, ch10, & ch12
- 醇的氧化反应 ch9
- 机理和催化剂 ch12
- 对烯烃的亲电加成 ch19

#### 目标

- 区域、立体和化学选择性
- 用于还原烯烃和羰基化合物的试剂
- 移去官能团
- 苯环的还原
- 用于氧化醇的试剂
- 用于氧化烯烃的试剂
- 醛、酮、醇，和胺的保护
- 肽合成

#### ► 展望

- 区域选择性 ch24
- 烯醇盐的反应 ch25 & ch26
- 硫化学 ch27
- 逆合成分析 ch28
- 环加成 ch34

## 选择性

大多数有机分子包含的官能团不止一个，大多数官能团的反应方式也同样如此，因此有机化学家通常需要预测，哪些官能团会参与反应，它们在哪里反应，以及如何反应。这些问题被我们称为选择性(*selectivity*)。

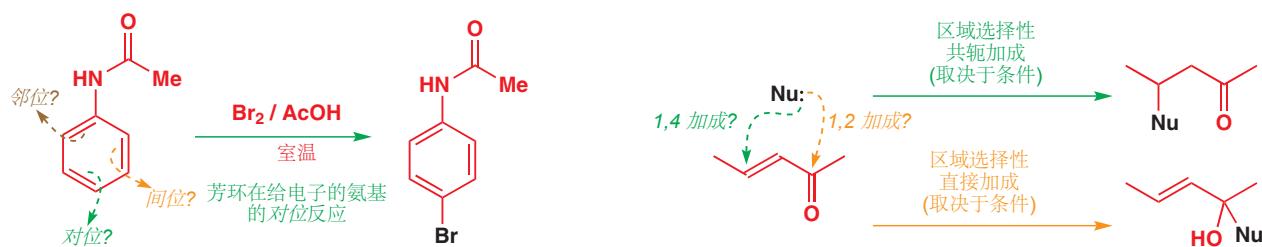
选择性可分为三种：化学选择性(chemoselectivity)，区域选择性(regioselectivity)，和立体选择性(stereoselectivity)。化学选择性描述哪些基团会反应，区域选择性描述它们在哪里反应，而立体选择性则描述为了得到产物的立体化学，官能团如何反应。

### ● 选择性

选择性主要包含三类：

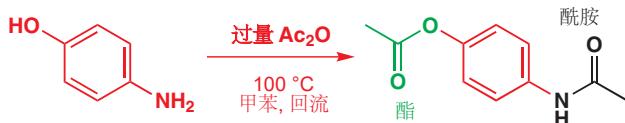
- 化学选择性：哪些官能团会反应(本章)
- 区域选择性：它们在哪里反应(Chapter 24)
- 立体选择性：它们如何反应(产物的立体化学)(Chapters 32, 33, 和 41)

在前两章中，我们已经谈论了很多关于区域选择性的内容。在 Chapter 21 中您学习了如何预测和解释从芳香亲电取代反应中得到的产物。此处的官能团是芳环：区域选择性描述它在哪里反应。在 Chapter 22 中，您见到了对不饱和酮的亲核加成，有 1,2- 和 1,4- 方式两种——哪一种真正发生(不饱和酮在哪里反应)就是区域选择性的问题。我们将在下一章中更加详细地处理区域选择性的问题。



但本章的内容是化学选择性——一个化合物会包含不止一个官能团，它们中的哪个会参与反应？

让我们由一个简单易懂的例子开始——止痛药扑热息痛的合成。4-氨基苯酚可以在氧和氮上同时与乙酸酐反应，得到一个包含酰胺和酯官能团的化合物。将其与过量的乙酸酐 ( $\text{Ac}_2\text{O}$ ) 在甲苯中加热即可得到如是结果。



但如果在碱的存在下(吡啶)仅加入一当量的乙酸酐，那么仅有  $\text{NH}_2$  基会被酰化，产物即是扑热息痛。这就是化学选择性，意料之中， $\text{NH}_2$  基比  $\text{OH}$  基的亲核性强。用氢氧化钠水解双酰化的产物，甚至也可以得到扑热息痛；酯比酰胺更活泼，更容易水解。这是另一个化学选择性的反应。

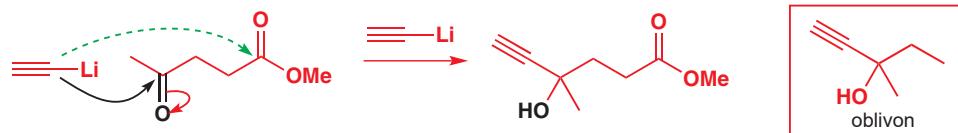
胺的亲核性比醇强，以及酯比酰胺更活泼的原因都在 Chapter 10 中有所阐述。



我们知道，面对格氏试剂和有机锂，酮的活性比酯更高，因为您不能在让酯与格氏试剂、有机锂反应时把酮排除在外。制药公司 Pfizer 中的化学家，在开发与镇静剂 *oblivon* 相关的抗惊厥药物时利用了这一点。将乙炔锂加入酮中，它们可以在另一个酯基的存在下，化学选择性地与醇反应给出叔醇。

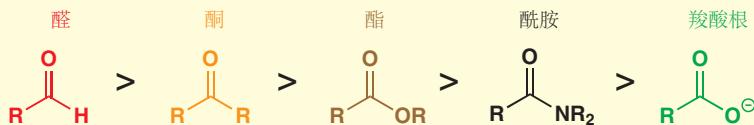
在 Chapter 10 中，我们用一些时间考察了可以用什么与有机金属化合物反应得到酮 (p. 218)。

酮比酯更加亲电



前两个反应都能发生，因为虽然每个起始原料都包含两个羰基，但面对亲核试剂 (前一个中为  $\text{OH}^-$ ；后一个中为乙炔锂)，其中一个比另一个活泼。我们可以将羰基化合物排出如下序列，通常可以在右侧的某一项存在的情况下在左侧的某一项上反应。

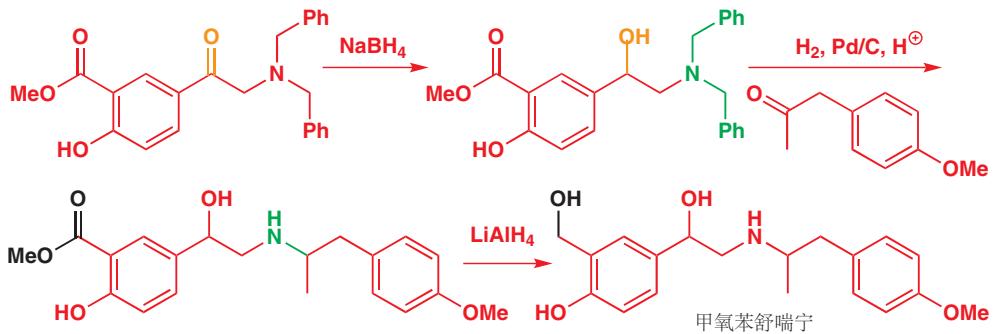
### ● 对亲核试剂的反应性



我们已经在 Chapter 10 中讨论了这一序列，即羧酸衍生物的反应性——请确保您理解 酯 > 酮 > 羧酸根 这一顺序的原因。此处我们向表中添加了醛 (最活泼，由于空间因素——空阻最小) 和 酮 (比酯更活泼，因为羰基不因与孤对电子共轭而稳定；注：但与烷基有超共轭，不如醛活泼)。

## 还原剂

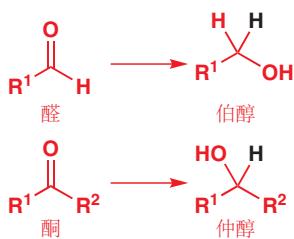
葛兰素 (Glaxo) 的化学家在平喘药物甲氧苯舒喘宁 salmefamol (畅销药沙丁胺醇 salbutamol 的姊妹药物) 的合成中利用了这一选择性序列。流程中加入了三种还原剂：硼氢化钠 ( $\text{NaBH}_4$ )，钯催化剂上的氢气，和氢化铝锂 ( $\text{LiAlH}_4$ )。



### 为什么不从始至终使用 $\text{LiAlH}_4$ ?

通常来说，用可行的条件下最温和的完成反应是最好的——减少潜在的不需要的副反应发生。另外， $\text{NaBH}_4$  比  $\text{LiAlH}_4$  容易处理很多——例如，它可以溶解在水中，而  $\text{LiAlH}_4$  潮湿时就会着火。既是  $\text{LiAlH}_4$  也可还原醛和酮，但通常这些工作由  $\text{NaBH}_4$  完成。

■ 值得注意的是，本节描述的所有对羰基的还原剂，都是硼或铝的氢化物 (负氢)。



## 羰基的还原

现在，我们应当更详细地考察羰基化合物的还原反应，其中我们会介绍几种专门的还原剂。然后我们会回到甲氧苯舒喘宁所用的另一种还原方法——催化氢化。

### 如何将醛和酮还原为醇

我们不需要在此耗费太多时间——您在 Chapter 6 中遇到的硼氢化钠，就能很好地做到这一点。硼氢化钠的还原反应，只会在质子溶剂中 (通常是乙醇或甲醇)，或亲电的金属阳离子，例如  $\text{Li}^+$  或  $\text{Mg}^{2+}$  的存在下发生 (例如  $\text{LiBH}_4$  可以在 THF 中使用)。所遵循的机理可以如下表示。

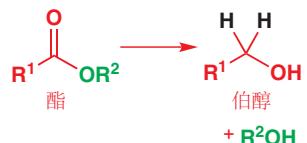


反应的本质是带着两个电子的氢原子，由硼到碳的转移 (称为 **氢负转移** **hydride transfer**)，但反应

中并不涉及真正的氢负离子)，在氧上出现的负电荷被醇质子化，所得的烷氧基阴离子在反应时，或紧跟在反应后添加到硼上。副产物，烷氧基氯合硼阴离子，本身是一个还原剂，可以继续还原三个羰基化合物分子，渐进地转移它的氢原子。

### 如何将酯还原为醇

$\text{LiAlH}_4$  通常是最好的试剂，按我们在 Chapter 10 (p. 217) 中讨论的机理得到醇。更温和的替代品（由于对  $\text{LiAlH}_4$  的不慎处理，已经引发了无数次失火），醇溶液中的硼氢化锂可以还原酯——事实上，它对酯的选择性高于酸或酰胺，而  $\text{LiAlH}_4$  并无此选择性。硼氢化钠对大多数酯的还原非常缓慢。

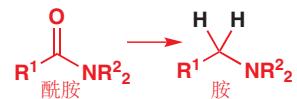
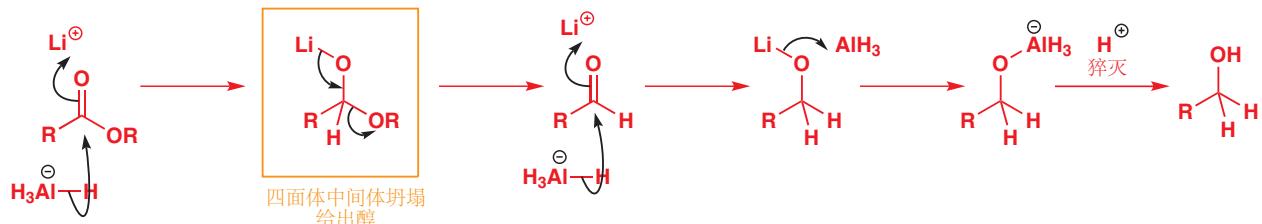


■ 为什么不写出这个机理以确保您理解了呢，然后您可与 p. 217 页对照。稍后，我们将向您展示一个稍稍复杂的版本，其中我们将说明 Li 和 Al 物种的命运。

### 如何将酰胺还原为胺

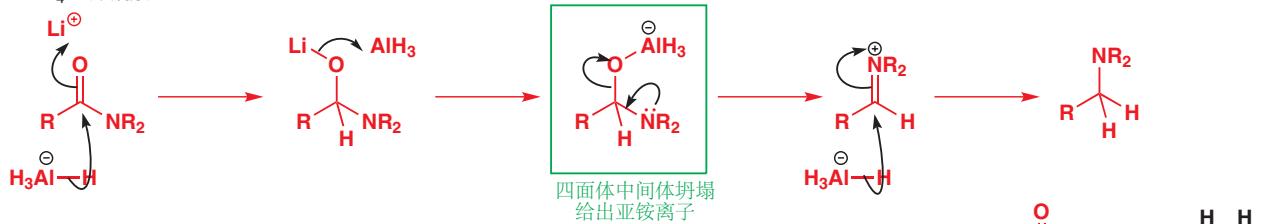
再一次， $\text{LiAlH}_4$  是完成这种转换的一个好的试剂。其机理与酯还原机理遵从相似的过程：下方都已详细地给出，关键的区别在橘色和绿色框出的步骤。橘色框中，四面体中间体失去烷氧基，形成醛，并继续参与还原。酰胺中则并非如此，它会失去与铝配位的阴离子氧——形成一个亚铵离子。酰胺到胺的还原反应还有一个很好的替代方法，即硼烷 ( $\text{BH}_3$ )，下节中会有所描述。

#### $\text{LiAlH}_4$ 还原酯



■ 此处酯还原的机理，比我们在 Chapter 10 中展示给您的简化版本含有更多的细节。

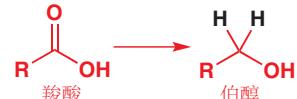
#### $\text{LiAlH}_4$ 还原酰胺



### 如何将羧酸还原为醇

这个用途最好的还原剂是硼烷， $\text{BH}_3$ ，硼烷，事实上是一种结构为  $\text{B}_2\text{H}_6$  的气体，通过与乙醚 ( $\text{Et}_2\text{O}$ )，THF，或二甲硫醚 (DMS,  $\text{Me}_2\text{S}$ ) 络合，可以将其“驯服”为液体。

虽然硼烷表面上与四氢合硼酸根相似，但它不带电，这使得它的反应性与后者完全不同。四氢合硼根与最亲电的羰基反应，而硼烷的反应性则受控于硼的空  $p$  轨道想接受一对电子的渴望。受控于。在羰基还原的领域，这就意味着富电子羰基最快地被硼烷还原。酰氯和酯都相对缺电子 (Cl 和



当  $\text{BH}_3$ ，一个 Lewis 酸从醚或硫醚——一个 Lewis 碱处接受一对电子时，这些络合物得以形成。Lewis 酸、碱的描述在 p. 180.

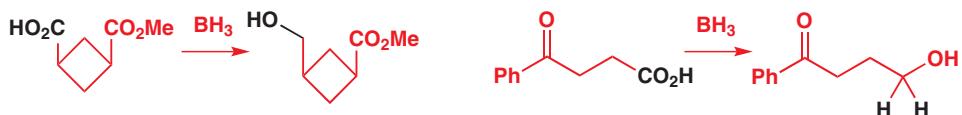
OR 都非常负电性); 于是硼烷不会与酰氯反应, 并只会很缓慢地还原酯。但它对羧酸和酰胺的还原却非常有效。

■ 酸酐比酯活泼, 也是由于其孤对电子需要“分享”给两个共轭基团(见 p. 206)。

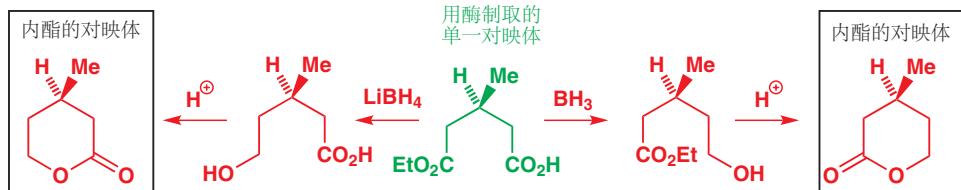
硼烷与羧酸的反应, 首先形成三酰基硼烷, 同时放出氢气。酯的亲电性通常弱于酮, 这是由于酯中的羰基与  $sp^3$  杂化的氧原子上的孤对电子共轭所导致——但在这些硼酯中, 硼旁边的氧原子上的孤对电子, 既需要分享给羰基, 又需要分享给硼的 p 轨道, 因此它们相比于普通的酯来说, 相当地活泼。



硼烷是在其他可还原的官能团, 例如酯, 甚至酮的存在下, 高化学选择性的羧酸还原试剂。



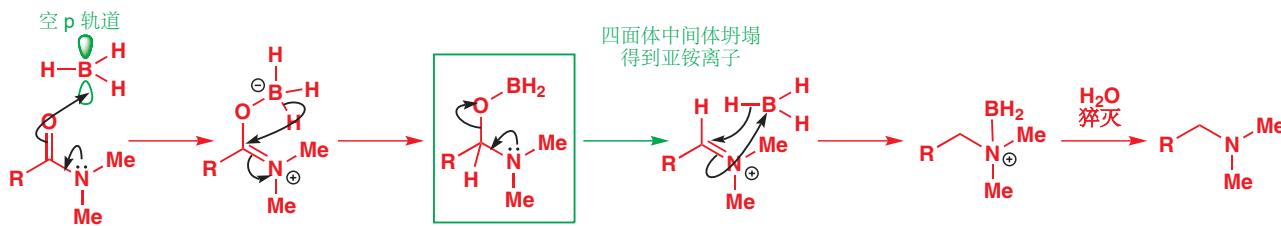
硼烷和硼氢化锂是最实用的一对还原剂, 其选择性正相反。日本化学家用酶制取了如下单一对映体的酸, 并既能够用硼氢化锂, 选择性还原酯, 也可以用硼烷选择性还原羧酸, 如此得到的两种内酯(黑色框中的)是一对对映体。



因为硼烷会与富电子羰基很好地反应, 它也被用作选择性还原酰胺的试剂 ( $LiAlH_4$  的方法没有这种选择性), 这种选择性可在酯的存在下体现:

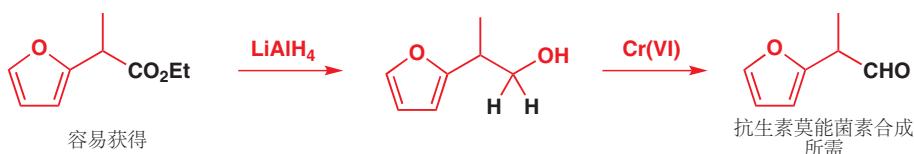
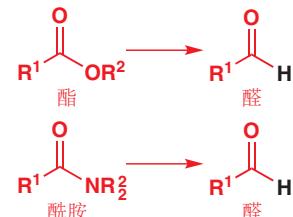


由于来自离域的 N 孤对电子的电子密度, 酰胺的羰基是富电子的。因此它可与 Lewis 酸硼烷上的空 p 轨道很好地结合。然后就可以发生由阴离子硼到亲电的碳原子上的氢负迁移。所得的四面体中间体坍塌为亚铵离子, 继而再被硼烷还原为胺。



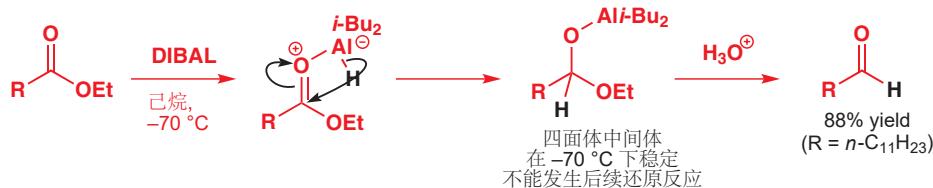
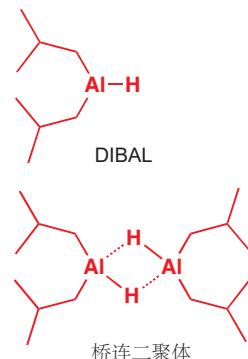
### 如何将酯或酰胺还原为醛

p. 531 中的图表显示，酯的还原（橘色四面体中间体的坍塌）给出醛。但由于醛比酯更容易被还原，因此还原反应不会终止，而是继续发生到醇氧化程度。那么如何将酯还原成醛呢？这是合成化学上的实际问题——如下的酯，可以通过您会在 Chapter 25 中遇到的办法容易地制备，但抗生素莫能菌素 (monensin) 一个重要的合成则需求其衍生的醛。



在这个例子中，化学家决定简单地忍受事实，用  $\text{LiAlH}_4$  将其还原为醇，再用 铬(VI)，您在 Chapter 9 (p. 194) 中遇到的氧化剂将其氧化回醛。然而，有一种试剂有时可以将这份工作在一步内完成，但这种您必须牢记，这并不是一个通用反应。这个试剂是 DIBAL，亦称 DIBALH——二异丙基氢化铝 (diisobutyl aluminium hydride),  $i\text{-Bu}_2\text{AlH}$ 。

DIBAL 是一种铝烷 (alane): 它的结构如边栏所示。它的化学性质在很多方面与硼烷相像——它以桥连二聚体存在，它仅在形成 Lewis 酸–碱 络合物时才可参与还原，并且它对富电子的羰基还原得最快。DIBAL 可以在甚至  $-70^\circ\text{C}$  下还原酯，在这个温度下，通过由铝到碳的氢负迁移形成（如下所示）形成的四面体中间体也许是稳定的。只有当用水溶液后处理时，它才会坍塌为醛；后处理时过量的 DIBAL 也被破坏，因此不进行后续的还原反应。



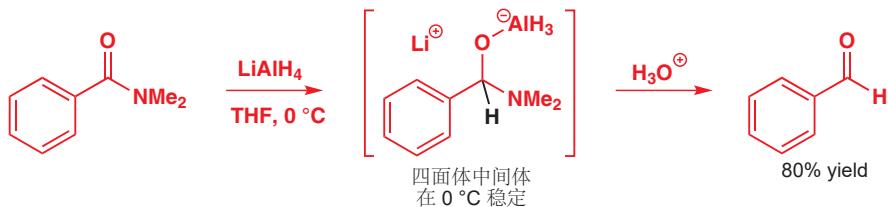
### 由内酯制备内半缩醛

内酯被还原时更有可能生成稳定的四面体中间体，因为环状的半缩醛比开链的更稳定。DIBAL 是将内酯还原为环状半缩醛（也被称为内半缩醛 lactols）最可靠的办法，如下这个反应来源于 E. J. Corey 对前列腺素的合成。



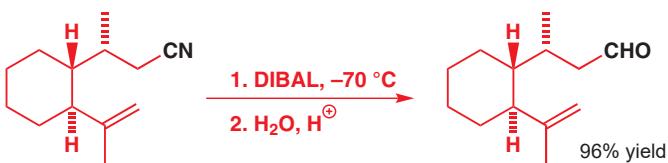
■ 亚铵的坍塌需要高温促进。

在 p. 533 所示的酰胺还原中，绿色框出的步骤给出亚铵例子。在亚铵离子形成前使反应停下，如果沒有铝的存在，四面体中间体会坍塌为醛，这也就会成为由酰胺制备醛的方法。由于酰胺还原中的四面体中间体相比于酯还原中的来说，相当地稳定，因此，仅仅在 0 °C 下进行反应，并用水猝灭即可实现。



DIBAL 也可很好地用于将腈还原为醛。委实，将腈还原为醛和将内酯还原为内半缩醛的反应（见上文的文本框）是 DIBAL 完成得最好的工作。

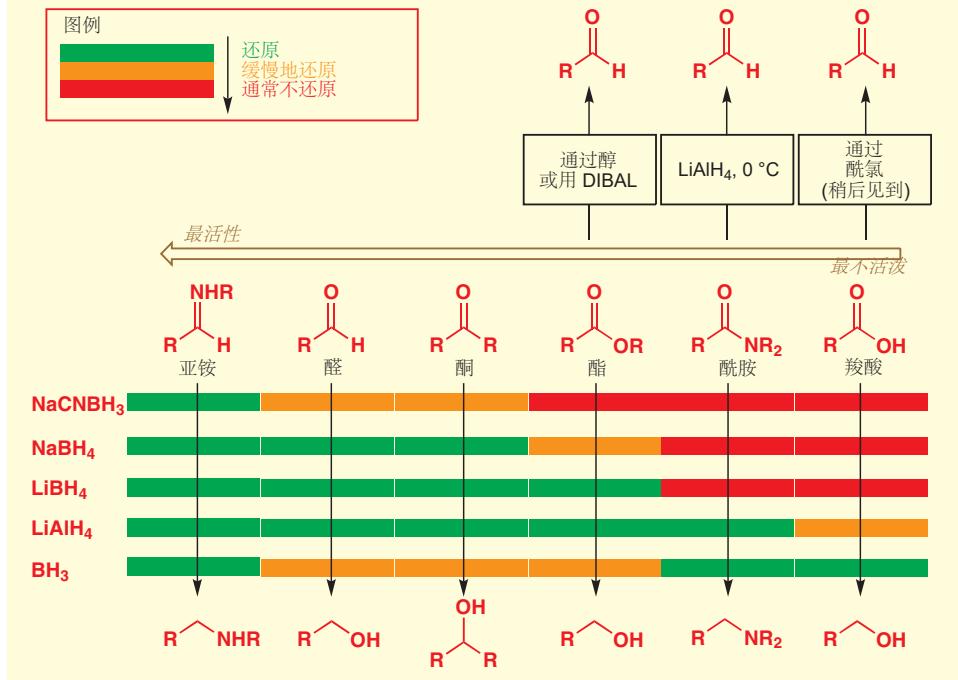
■ 羰酸也可被还原为醛，这是通过其酰氯进行的 Rosenmund 反应——见下文。



如下总结了全部这些试剂的化学选择性。

■ 也包含了您在 Chapter 11 见过的氨基硼氢化钠，它还原亚铵而不还原羰基化合物。

#### ● 对羰基的还原剂的总结

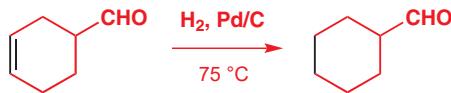


## 氢气作为还原试剂：催化氢化

► 您会在 Chapter 41 遇到一些例外。

最简单的还原试剂是氢气本身， $H_2$ 。氢气通常不能用作羰基化合物的还原试剂——它没有足够的

亲核性。然而，它可作为其他的、更弱的双键和三键，例如 C=C, C=N, C≡C 和 C≡N 的还原试剂。这些反应的进行需要一种金属催化剂，这个过程也被称作催化氢化 (catalytic hydrogenation)。氢气或由钢瓶提供，或通过气球，或通过电解制备并和底物一起泵送到催化剂上。在下面的离子中，烯烃被还原，而醛则原封不动。



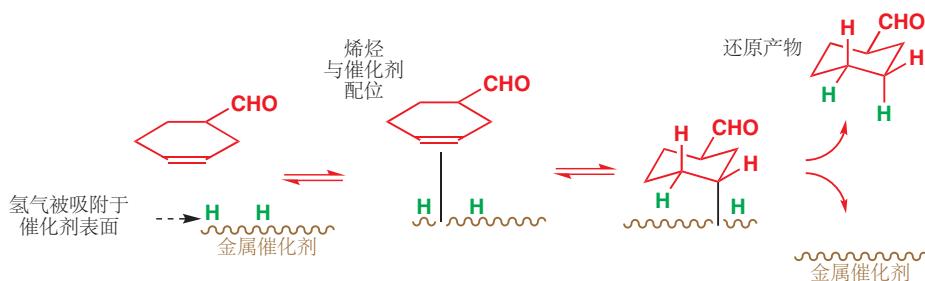
用于使氢气和双键反应的催化剂是过渡金属：通常用钯（如这个例子中）或铂，有时也用镍、铑，或钌。本节中我们将讨论几种不同的还原反应，但它们的机理彼此之间都很相似，然而却与羰基还原所涉及的那些机理大相径庭。

催化氢化在金属的表面发生。因此金属必须分散得很细小，通常是将其分散于一种惰性载体上。这就是“Pd/C”所表示的含义——钯细小地分散于碳载体上。第一步是一个氢气在金属表面的化学吸附 (chemical absorption)，这一过程导致 H–H 键的断裂，并将氢原子分散于可与有机底物反应的位置上。此时烯烃也可与金属成键，氢于是从金属转移到烯烃上。

## 钯碳

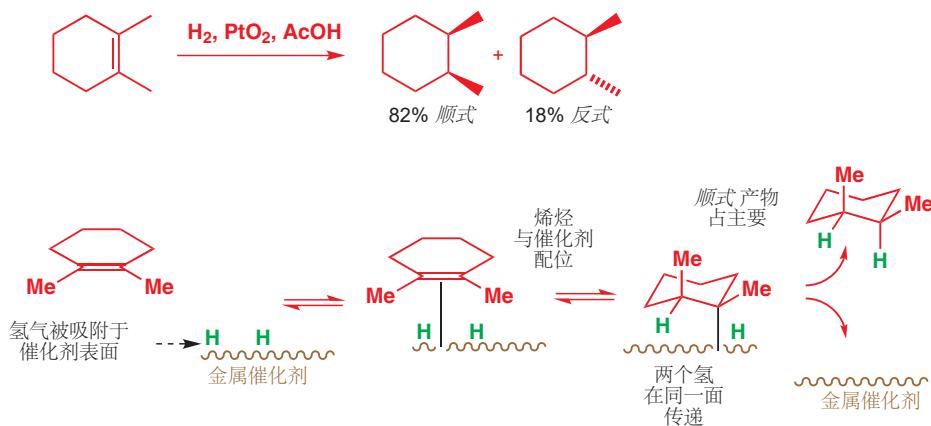
钯碳 (Palladium on charcoal, Pd/C) 以质量计的成分通常为 5–10% 的 Pd 和 90–95% 的 C。它通过将碳粉悬浮于  $\text{PdCl}_2$  溶液中，再将  $\text{PdCl}_2$  还原为金属 Pd 制取，还原过程通常用  $\text{H}_2$  气，有时也用甲醛， $\text{HCHO}$ （被氧化为甲酸， $\text{HCO}_2\text{H}$ ）。金属钯沉淀在碳上，然后可过滤和烘干。细小的 Pd 颗粒可提供催化反应发生时的最大表面积；Pd 是一种昂贵的金属，由于 Pd/C 不溶性，可以通过过滤回收。

► 我们将在 Chapter 40 更详细地考察烯烃与金属成键的方式。



## 如何将烯烃还原为烷烃

钯或铂催化的氢化反应是还原烯烃最常用的方法。您可能认为我们示出的机理不尽人意，但用弯曲箭头表示此处涉及的反应是很困难的。然而，大量的证据都表明氢化反应按此方式发生，例如下面烯烃的氢化产物主要为两个氢原子在分子同一侧的一种——这正是我们从反应在表面发生可以料到的结果。

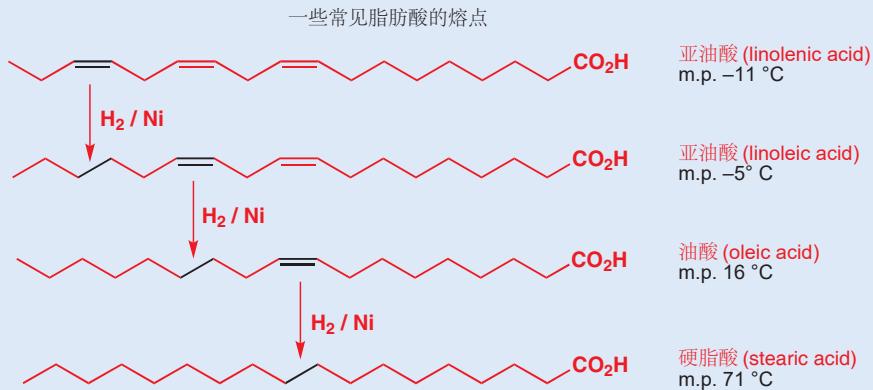


►  $\text{PtO}_2$ ，二氧化铂，被称作 Adam 催化剂 (Adams' catalyst)。实际发挥催化作用的是氢化过程中  $\text{PtO}_2$  被还原产生的金属 Pt，而不是氧化物本身。

## 氢化植物油

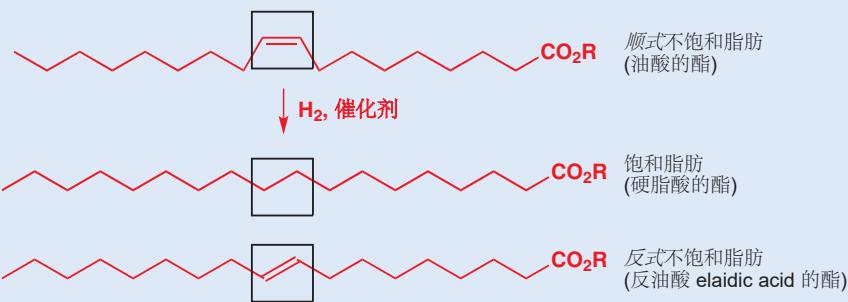
大豆、油菜籽、棉籽和向日葵等植物是食用植物油有用的来源，但这些油不适合作为黄油的替代品，因为它们的熔点太低。它们比动物脂肪低的熔点，很大程度上是由于顺式双键干扰了固态中

烷基链的排列。将粗植物油用金属催化剂上的氢气处理，可以移去一些这种双键，增加油中饱和脂肪的比例，提高其熔点，使其适于制造人造黄油。



当然，反应通常会在所有双键都被氢化前停止：人造黄油厂商极力地告诉我们，他们的产品仍“富含不饱和脂肪酸”。很多还

宣称“反式不饱和脂肪酸含量低”，这是因为人们认为冠心病的发生率和反式不饱和脂肪酸的摄入量有联系。

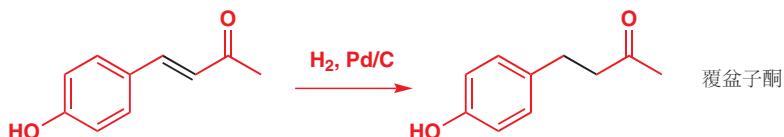


那么这些反式双键是从哪里来的呢？嗯，部分氢化过程会导致

显著的双键异构化，既包括区域异构体，也包括几何异构体。

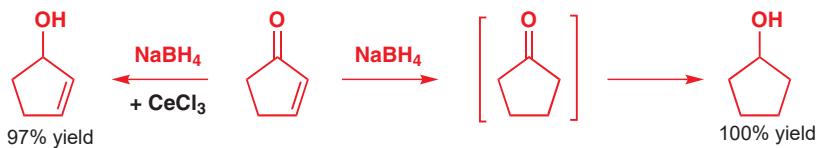
## 如何还原 $\alpha,\beta$ -不饱和羰基化合物

不出您意料地，催化氢化可以很好地完成  $\alpha,\beta$ -不饱和羰基化合物 C=C 双键的还原，因为 C=C 键相比 C=O 键更易受氢化反应的影响。调味剂覆盆子酮 (raspberry ketone) 就通过这种方法制取。



► 见 Chapter 22 关于  $\alpha,\beta$ -不饱和羰基化合物 反应性的讨论。

但如果想选择性地还原 C=O 基该怎么办？您可能立刻会想到 NaBH<sub>4</sub>。但在 Chapter 22 中我们指出，氢化物还原剂通常不是用于不饱和羰基化合物 C=O 键的选择性还原的好选择，因为它们同样倾向于加成双键，先给出饱和羰基化合物，然后再将其还原为醇。选择性还原羰基的方法是在硬的、Lewis 酸性的金属盐，例如 CeCl<sub>3</sub> 的存在下使用 NaBH<sub>4</sub>。这种试剂的结合被称作 **Luche 还原 (Luche reduction)**。



### 如何将苯环还原为环己烷

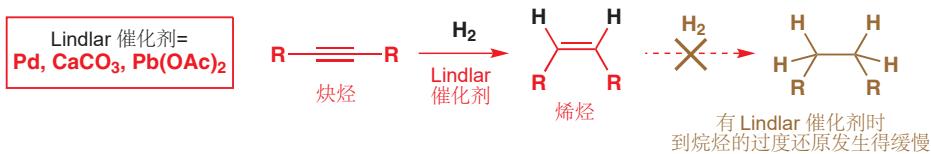
甚至是芳环，都可以在 C=O 基的存在下被氢化：这些例子中，苯基被还原为环己基，而酯和酸仍存活。



每个还原反应所用的催化剂都需要反复试错，很难预测哪种金属是最成功的——通常用于芳烃的是 Pt, Rh, 或 Ni.

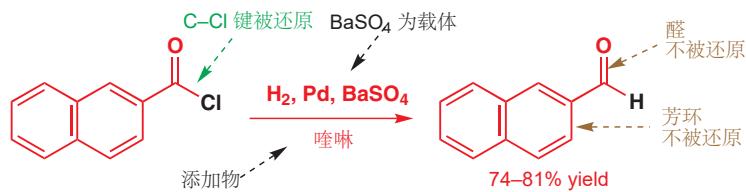
### 如何将炔烃还原为烯烃

有一种被称作 **Lindlar 催化剂** (林德拉催化剂, Lindlar's catalyst) 的催化剂可被用于将炔烃还原为烯烃，但却不容易将烯烃还原为烷烃 (您会在 Chapter 27 再一次遇到)。这需要相当微妙的化学选择性：烯烃氢化通常发生得至少和炔烃一样快，因此我们需要确保反应在烯烃一经生成时就停止。Lindlar 催化剂是故意用铅使之中毒钯催化剂 ( $\text{Pd}/\text{CaCO}_3$ )。铅减弱催化剂的活性，并减缓烯烃产物发生的后续还原反应：大多数钯催化剂会将烯烃一直还原至烷烃。如果同时向反应中加入喹啉，选择性则会最好，并且炔烃到烯烃的还原反应也可用  $\text{Pd}/\text{BaSO}_4 + \text{喹啉}$  催化进行。即便如此，Lindlar 反应通常也需要仔细地监控，以确保不发生过度还原。



### 如何将酰氯还原为醛

催化氢化通常作为对 C=C 基超过对 C=O 基化学选择性的还原方法被选用，一个重要的氢化反应包含羰基化合物，事实上并不是对于 C=O 双键的还原，而是由酰氯得到醛的反应，它被称作 **Rosenmund 反应** (Rosenmund reaction)——是一个 C–Cl 键的氢解 (hydrogenolysis) 过程。



这是一个将羧酸氧化程度的化合物还原为醛氧化程度的好方法，这就是为什么我们将其纳入了 p. 534 羰基还原的总结表中。同样需要喹啉中和反应产生的 HCl，并使催化剂活性适度，阻止过度还

氢化反应有时需要高压氢气——左侧的反应需要 100 大气压。这些反应于一个被称作 Parr 氢化器 (Parr hydrogenator) 的密闭容器中进行，或使用电解生成的氢气在高压下在流动系统中泵送。

### Raney 镍

镍通常以被称作 Raney 镍 (兰尼镍，雷尼镍, Raney nickel) 的细小分散形式用于催化氢化。Raney 镍由镍-铝合金制取，用浓氢氧化钠水溶液处理，可将铝溶解，留下以细小的粉末存在的镍。铝溶解的过程会释放 H<sub>2</sub>，一些氢原子仍会吸附在镍催化剂上。这意味着一些氢化反应，尤其是对于本章后面要遇到的 C–S 键的氢化反应，可以用新制的 Raney 镍直接进行，不需要外加 H<sub>2</sub>。Raney 镍缩写作 RaNi——注意，与镭无关。



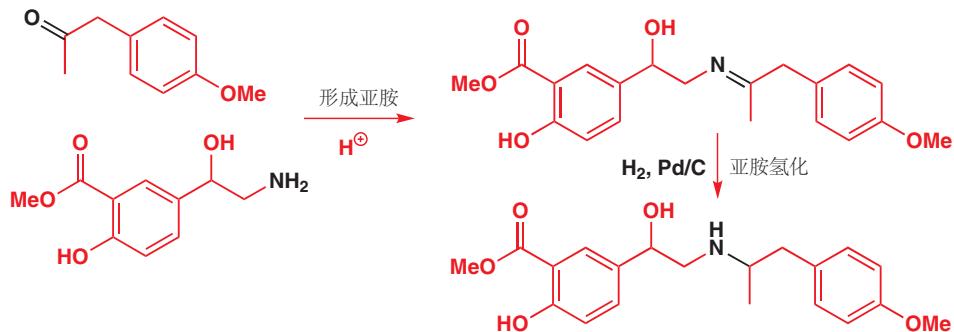
■ 您会注意到，催化剂的载体发生了变化： $\text{Pd/BaSO}_4$  而非  $\text{Pd/C}$ .  $\text{BaSO}_4$  (和  $\text{CaCO}_3$ ) 对于较容易被还原的底物是常用的载体，因为它们会让产品迅速从催化剂处逃离，以阻止过度反应 (使催化剂中毒)。

原。

### 通过催化氢化进行的还原胺化反应

羰基对于催化氢化的不反应性允许我们像用氰基硼氢化钠那样，用催化氢化进行胺和羰基化合物的还原胺化 (reductive aminations) 反应。例如我们在 p. 530 展示的甲氧苯舒喘宁的合成中，其中一步就涉及胺和酮在酸、氢气，和钯催化剂的存在下形成亚胺的过程。亚胺 (以质子化的亚铵形式) 会被氢化，产出胺，而酮 (和芳香体系) 都毫发无损。

► 您在 Chapter 11, p. 234 遇到了用氰基硼氢化钠进行的还原胺化。



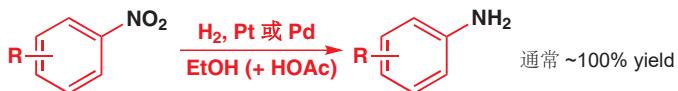
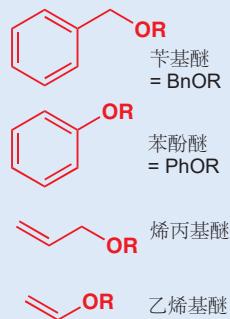
### 如何将硝基还原为氨基

► 对于硝基芳烃在芳香化合物合成上的用途，请见 pp. 521 和 576.

在 Chapters 21 和 22 中，我们见到了对芳环紧跟着硝化的还原是得到芳香胺的有效途径。硝基的还原可以通过  $\text{Sn}/\text{HCl}$  进行，但催化氢化要简单得多。这个反应通常在乙醇中，有  $\text{Pd}$  或  $\text{Pt}$  催化剂下进行，可能需要加入弱酸，以防止产生的胺使催化剂中毒。超过  $\text{Sn}/\text{HCl}$  方法的优势在于后处理上：无需分离和处置大量有毒的锡残留物，简单地过滤除去催化剂，然后蒸发、结晶，或蒸馏即可得到胺。

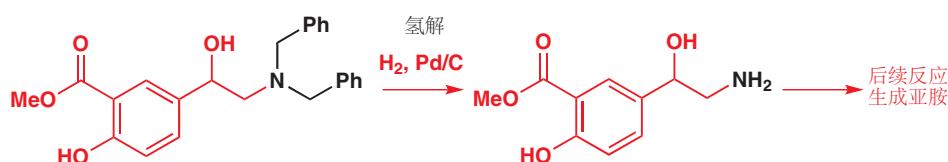
### 苄基和烯丙基

这是一个好的机会，以提醒您这几个基团的区别，苄基和烯丙基都是通过一个  $\text{sp}^3$  C 原子相连的，而苯基和乙烯基则直接与  $\text{sp}^2$  C 原子成键。您在 Chapter 2, p. 42 第一次遇到它们。

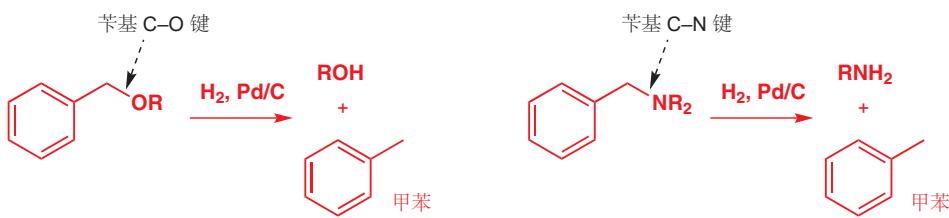


### 氢解：断裂 C–O 和 C–N 键

在如上所示的还原胺化例子中，我们略去了甲氧苯舒喘宁合成中起始胺带有两个苄基的事实 (回看 p. 530)，它们实际上会在氢化过程中消失。

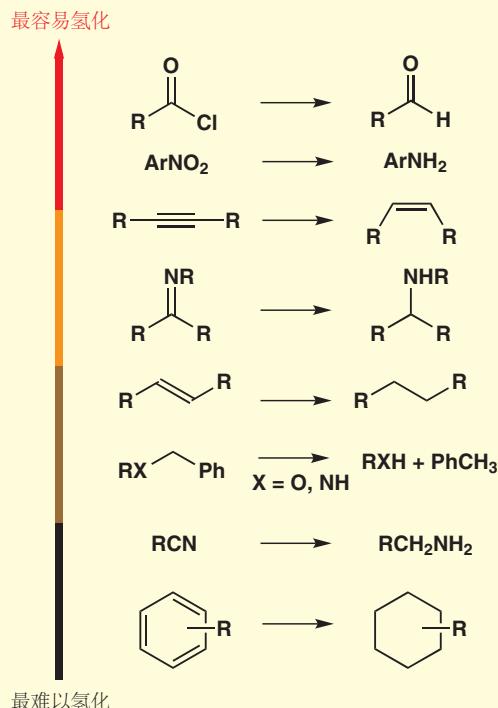


它们发生的变化是一次氢解 (hydrogenolysis)——当一个杂原子 (尤其是 O 或 N) 与与苯环相连的碳原子相连时，换句话说就是苄胺，苄醇及苄醚，容易在催化氢化的条件下发生这种反应。



氢解与烯烃氢化反应在相似的条件下发生，但所包含的是 C–O 或 C–N  $\sigma$  键的断裂，而不是 C=C  $\pi$  键的断裂。它对于苄基保护基的脱除尤为重要，我们稍后就会着眼于该问题。

- 我们可以绘制出对于氢化反应的反应性的序列。用不同催化剂得到的确切排序是不同的，一些催化剂对于某种特定类别的化合物尤其有选择性——例如，Pt, Rh, 和 Ru 会在在苄基 C–O 键的存在下选择性地氢化芳环，而 Pd 催化剂下苄基 C–O 键则还原得更快。



## 赶走官能团

官能团在用于组合分子时十分重要，但它们往往在最终产物中并不被需要。我们需要赶走它们的方法。烯烃的氢化是您已经看到的其中一种。由炔烃到烷烃的氢化十分有用，因为我们可以用炔烃的烷基化构建碳原子长链，然后再通过氢化隐藏证据：



■ 氢化反应当使用 Pd/C，而非 Lindlar 催化剂，因为我们想要它一直还原到烷烃。

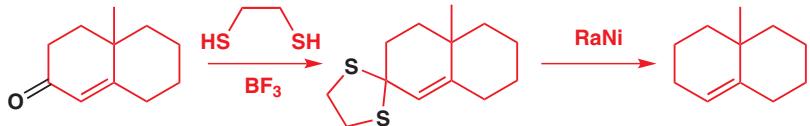
醇的去除，既可以通过先消除为烯烃，再氢化；也可以通过碘酰化，再用提供亲核氢原子的硼氢化物取代实现。

■ 此处使用了三乙基硼氢化锂——它能很好地用于  $S_N2$  取代反应——但那些强的氢化还原剂也同样可以工作。



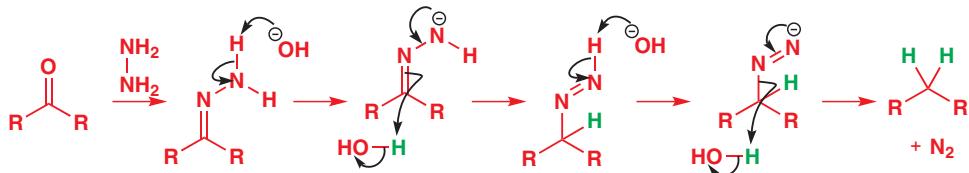
羰基的去除是相对困难的，但仍有几种可行的方案。C—O 键很强，而 C—S 键却弱得多，通常可被 Raney 镍容易地还原。我们可以通过将醛酮羰基制成 **硫缩醛 (thioacetals)** 然后再去除，硫缩醛是缩醛的硫代类似物，可通过类似于缩醛形成的反应（见 Chapter 11）消除，使用二硫醇和 Lewis 酸催化剂。新制的 Raney 镍带有足够的  $\text{H}_2$  (p. 537) 可在无外加氢气的条件下还原硫缩醛。

■ 这个反应有时被称作 **Mozingo 反应 (Mozingo reaction)**。



还有另一种稍微更有力的方法，被称作 **Wolff–Kishner 还原 (Wolff–Kishner reduction)**，由腙消去氮气驱动。热的浓氢氧化钠溶液可为腙去质子，继而失去氮气以形成烷基阴离子，烷基阴离子立即被水质子化。

Interactive mechanism for Wolff–Kishner reduction



第三种方法是最简单的方法，但它的机理是最复杂的。**Clemmensen 还原 (克莱门森还原, Clemmensen reduction)** 是相当暴力的方法，当化合物只有一个官能团（羰基）时才可合理地选用。它使用溶解在浓盐酸中的金属锌。当金属溶解时，会释放出两个电子——没有其他事可以做时，这两个电子会将酸中的  $\text{H}^+$  还原为  $\text{H}_2$ ，即得到  $\text{ZnCl}_2$  和  $\text{H}_2$ 。但在羰基化合物的存在下，这两个电子可以前去还原  $\text{C=O}$  键。

■ 您在 Chapter 21 中见过此反应，我们将其作为可将容易通过 Friedel–Crafts 酰基化制备的酰基芳烃转换为难以用 Friedel–Crafts 烷基化制备的烷基芳烃的实用方法。

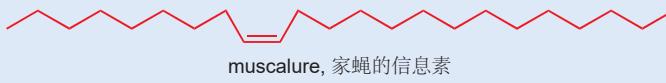


这个反应的机理与一大类还原反应有许多共同之处，Clemmensen 还原是 **溶解金属还原 (dissolving metal reductions)** 的成员之一。我们现在会将其作为还原剂的第三种重要类别（前两个是氢化物和催化氢化）展开讨论。

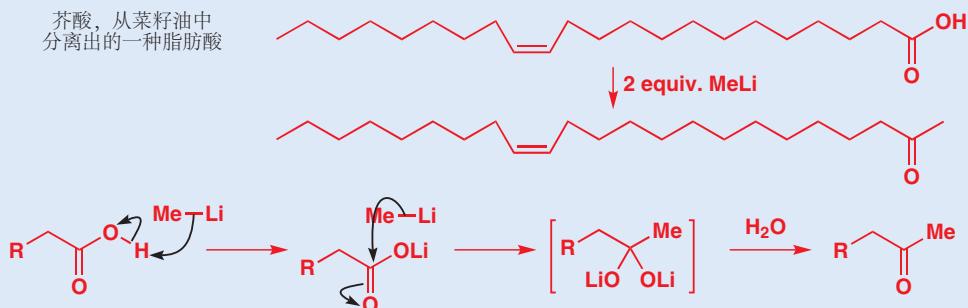
### Muscalure—家蝇信息素的两条合成路线

许多昆虫通过分泌一种被称为信息素 (pheromone) 的挥发性有机物来吸引配偶。信息素对物种有高度的特异性/专一性，因此对于害虫防治也有巧妙的意义：将一块浸过雄性信息素的棉花放入陷阱中，所有的雌性害虫都会落网——由此防止下一代。如果昆虫控制依赖于信息素，那么信息素需要被合成——从昆虫中大量提取是不现实的。

一种非常常见的昆虫——家蝇——非常简单的信息素的两种合成路线，分别为我们刚刚描述的还原方法中的两种提供了说明。这种被称为 muscalure 的信息素，是一种 Z-烯烃。



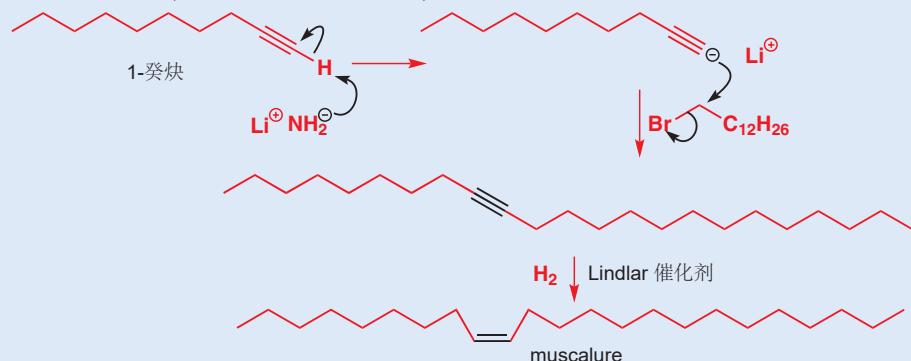
美国化学家在 1970s 初使用了一种非常简单的方法。这些化学家注意到了 muscalure 和一种名为芥酸 (erucic acid) 的，富含于菜籽油中的脂肪酸在结构上的相似性，并决定由芥酸制取 muscalure。它



下一步是移去酮官能团。选用的方法是 Wolff-Kishner 反应，我们在 p. 540 中叙述了这个反应：制取腙，并在碱的存在下加热。所



后来，一些俄罗斯化学家用另一种不同的路线制取了相同的化合物。它们引入 Z 双键的方法是炔烃在 Lindlar 催化剂上的催化氢化反应 (p. 537)。为了制备所需的炔烃，它们用 LiNH<sub>2</sub> 处理 1-癸炔，



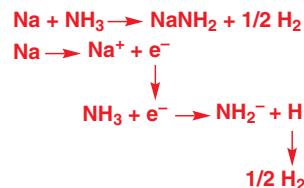
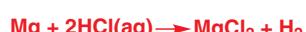
们首先将芥酸与两当量的甲基锂反应——第一当量用于酸去质子形成羧酸锂，第二当量用于与羧酸锂反应给出酮 (见 p. 219)。

## 溶解金属还原

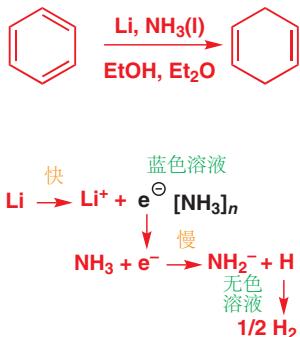
很多金属会与酸反应，放出氢气并同时得到盐，这一观点对您来说非常熟悉。侧边栏就是其中一个例子。金属阳离子 (这个例子中为 Mg<sup>2+</sup>) 由金属失去电子得到，这些电子将  $2 \times \text{H}^+$  还原为 H<sub>2</sub>。

如果金属非常活泼 (比如钠、钾)，这个反应即使在很弱的酸中也能进行 (水、醇，甚至液氨)。您可以将其过程想象为如下两步：第一步中钠释放电子，电子被 NH<sub>3</sub> 中质子捕获，质子变为 H，继而形成 H<sub>2</sub>。乙醇钠 (NaOEt) 和氨基钠 (NaNH<sub>2</sub>, p. 171) 都是通过将金属分别溶于乙醇、液氨而制取的。

但如果，我们不仅仅用电子还原溶剂放出氢气，而是通过给予一个更容易被还原的底物来利用它们。结果便是一次溶解金属还原 (dissolving metal reduction)：注意 dissolving (进行的)。金属溶解时释放的电子必须被捕获，否则它们会仅仅还原溶剂，得到 H<sub>2</sub>。



■ 事实上您已经见到了很多溶解金属还原，例如用于硝基还原的 Sn, HCl (p. 495) 和上文提及的 Clemmensen 还原。



■ 氨基钠， $\text{NaNH}_2$ ，您在本书中之前遇到过的一种碱，就是通过将 Na 溶于液  $\text{NH}_3$  并等到溶液不再显蓝色而制得的。

最终产物的立体化学（无取代基时）取决于最后的质子化步骤——阴离子本身，当然可以离域在两个位置上，即可以给出一个更稳定的共轭双烯产物。但为什么它在中间攫取质子，而给出一个较不稳定的异构体呢？戊二烯基阴离子与亲电试剂动力学控制的反应通常在中心碳原子上发生，这是轨道相互作用所致。更多的信息，请见本章结尾的延伸阅读。

► 术语本位、邻位、间位和对位的定义位于 Chapter 18, p. 416.

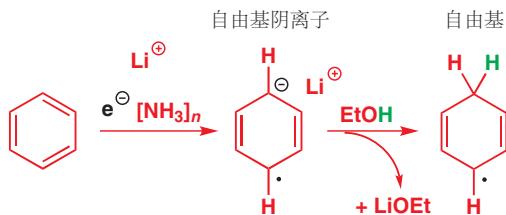
溶解金属还原的工作原理，是活泼金属形成可溶性阳离子时，释放的电子可以被利用于其他用途的还原反应。电子是最简单的还原剂，它们会还原羰基化合物、炔烃或芳环——事实上任何有低能  $\pi$  轨道的官能团都是电子的目标。

### 芳烃的 Birch 还原

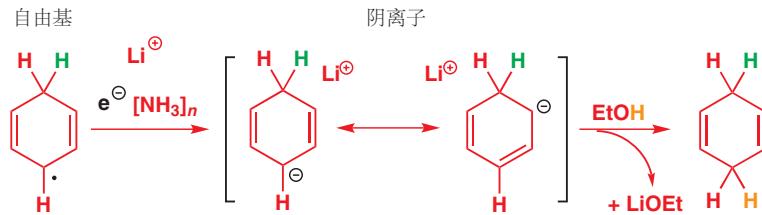
我们会以芳烃的溶解金属还原，即 **Birch 还原**（**伯奇还原**，Birch reduction）还原开始论述。边栏显示了苯与液氨中的锂的反应。您第一眼可能认为它是荒谬的，因为一个苯环最终变为了不共轭的双烯。这种区域化学，以及反应就此停止的原因——换句话说就是芳环比烯烃更易被溶解锂还原的原因，都可以通过机理得以解释。

需要注意的第一件事是当锂或钠溶解在液氨中时，会得到一种深蓝色（intense blue）溶液。蓝色是溶剂化电子（solvated electrons）的颜色：这些第 1 族金属离子化会给出  $\text{Li}^+$  或  $\text{Na}^+$  和  $\text{e}^-(\text{NH}_3)_n$ 。随着时间的迁移，蓝色会褪去，这是由于电子将氨还原为  $\text{NH}_2^-$  和  $\text{H}_2$ 。

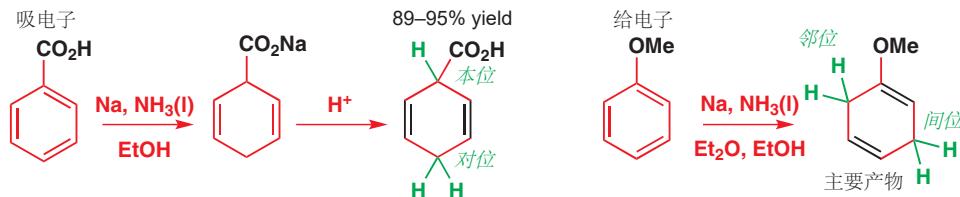
Birch 还原所用的是那种蓝色溶液，带有作为还原剂的溶剂化电子。由  $\text{NH}_3$  到  $\text{NH}_2^-$  和  $\text{H}_2$  的还原反应很慢，更好的电子接受体则会在蓝色溶液中被率先还原。对于苯，电子进入最低能的反键轨道（苯的 LUMO）。由此得到的物种可以以很多种方式表示，它们都是自由基阴离子 radical anions（含有一个附加的未成对电子的分子）。自由基阴离子碱性非常强，可从反应混合物中的乙醇上攫取一个质子。



分子已不再是阴离子，但仍是自由基。它可以攫取另一个电子，与自由基成对，以得到一个阴离子，继而又被质子源（乙醇）猝灭。整体上，我们通过循序地添加两个电子和两个质子，达到了添加两个 H 原子的目的。



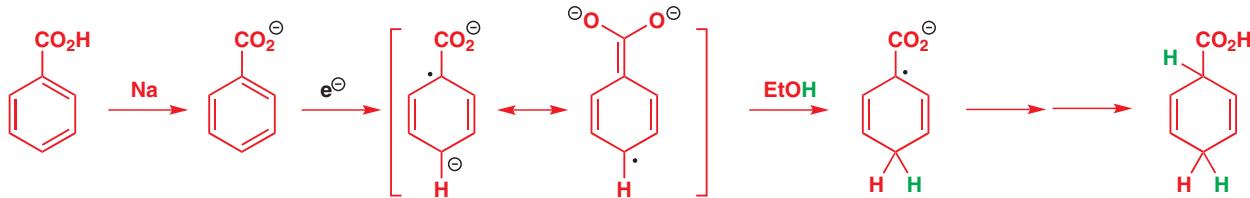
当芳香环上有取代基时，会引发更多的区域选择性烷烃。如下是两个例子。



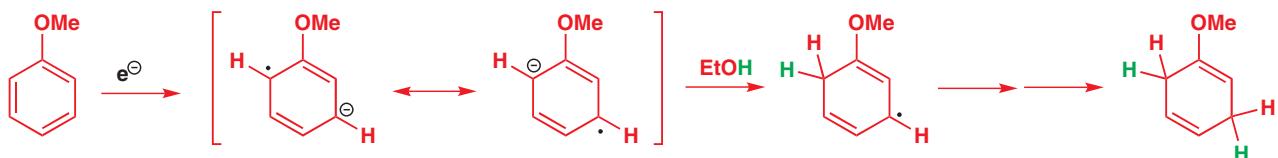
这些例子服务于说明一个普遍的原则：

- 吸电子基促进本位、对位的 Birch 还原。
  - 给电子基促进邻位、间位的 Birch 还原。

这一原则的解释建立在自由基阴离子中间体的电子密度分布上。吸电子基稳定本位和对位的电子密度，并在对位发生质子化。



而给电子基则稳定邻位和间位的电子密度：

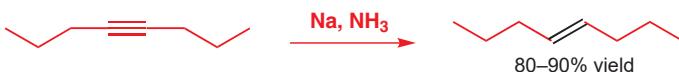


如果您想要共轭双烯作为产物，那么简单地用酸催化剂使之异构化即可。事实上，如上的苯甲醚在反应中也会产生少量的共轭产物（大约 20%）。对于苯胺，则难以阻止异构化在反应进行时发生，它的 Birch 还原往往给出共轭双烯胺。



炔烃的 Birch 还原

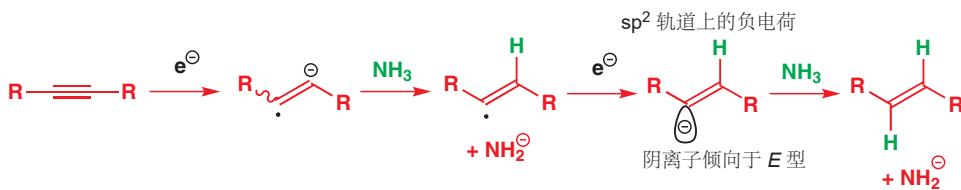
Birch 还原也可用于炔烃，并可将其还原为反式烯烃。



机理遵从与芳环还原相同的过程，但烯基阴离子的碱性足以让氨去质子，因此不需要额外的质子源。烯基阴离子在几何上也不稳定，并且选择 *E* 型。再次，两个绿色的 H 原子来源于两个电子和两个质子。

- 确保您可以写出异构化为共轭结构的机理。提示。将其想作烯醇醚，机理由烯醇醚在碳上的质子化开始。此为您在 Chapter 20 所学。

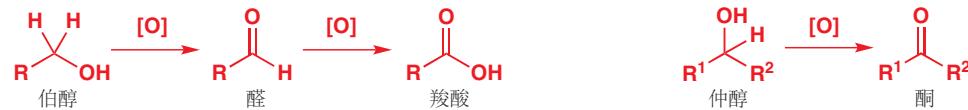
- 注意这个反应的区域选择性，正好与在 Lindlar 催化剂上氢化 (p. 537) 的选择性互补。



## 氧化反应中的选择性

如果您需要回顾醇的氧化，请回到 p. 194 (Chapter 9 章末)。

■ [O] 代表不特指的氧化剂。



那以后，您又遇到了许多其他氧化剂，尤其在 Chapter 19 中有：

- p. 429: 过酸氧化 C=C 双键，给出环氧。
- p. 442: 四氧化锇 ( $\text{OsO}_4$ ) 氧化烯烃，给出邻二醇。
- p. 443: 臭氧 ( $\text{O}_3$ ) 通过臭氧化，裂解烯烃，给出羰基化合物。

与 Cr(VI) 不同的是，这些试剂中没有一个是氧化羟基的：它们是对于 C=C 双键化学选择性的，并不会与羟基反应。与之对比，Cr(VI) 则氧化醇，而不氧化烯烃。

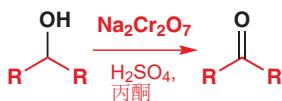
### 还原剂

对于 C=C 双键化学选择性	对于醇或羰基化合物化学选择性
过酸， $\text{RCO}_3\text{H}$ (Chapter 19)	Cr(VI) 化合物
四氧化锇， $\text{OsO}_4$ (Chapters 19 和 34)	Mn(VII) 化合物
臭氧， $\text{O}_3$ (Chapters 19 和 34)	一些高氧化态卤素、N, 或 S 化合物

本节中，我们将会着重考察醇和羰基的氧化剂；并且尤其会着眼于伯醇的氧化中，选择性地停在醛的阶段，或继续氧化为羧酸的方法。

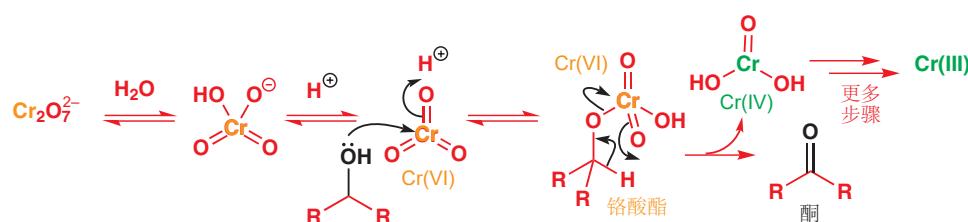
醇的氧化中最常用的方法，都以高氧化态金属为基础，通常是 铬(VI) (您在 Chapter 9 中遇到的) 或 锰(VII)，您还会发现在机理上它们是很相似的——它们都依赖于羟基和金属键键的形成。另一类氧化反应，基使用高氧化态的卤素、硫，或氮的反应，则将会相对简短地处理。

## 如何将仲醇氧化为酮



Interactive mechanism for chromium(VI) oxidation of alcohols

我们在 p. 195 讨论了这个机理。

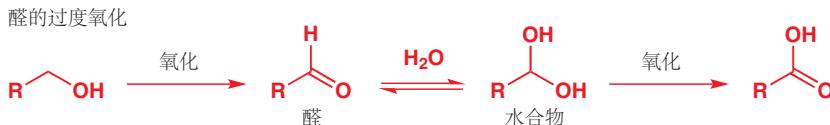


对于敏感酸性的醇，铬酸是最好的选择。另一种替代试剂是 PCC (氯铬酸吡啶𬭩/吡啶氯铬酸盐)，可以在二氯甲烷中使用。



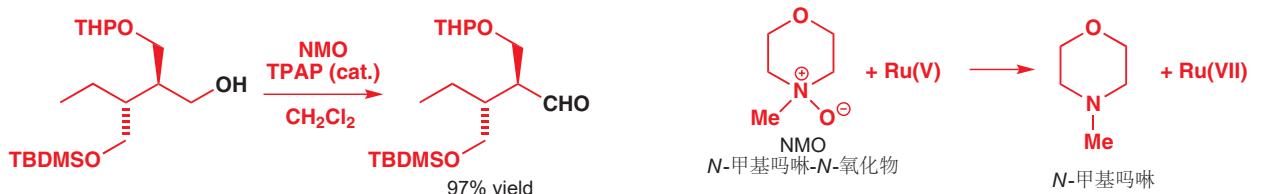
### 如何将伯醇氧化为醛

水溶液方法，例如 Jones 氧化不适用于此，因为形成的醛会通过其水合物被进一步氧化。氧化剂将其水合物视作醇处理，将其氧化为酸。



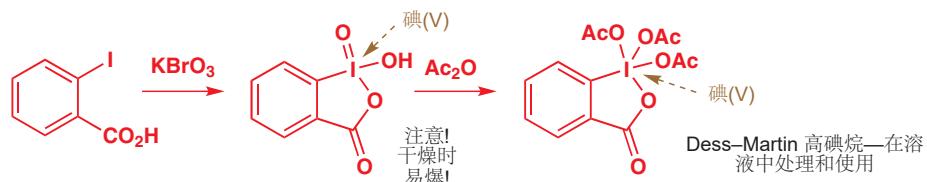
关键在于避免水，因此二氯甲烷中的 PCC 可以很好地工作。相关的试剂 PDC (重铬酸吡啶𬭩) 也尤其适用于醇到醛的氧化。

一些非常温和的氧化剂，在非常敏感的醛的合成中，也被越来越广泛地使用。其中一个被称作 TPAP (过钌酸四正丙基铵/四正丙基过钌酸铵, tetra-*n*-propylammonium perruthenate, 读作“t-ee-pap”)。TPAP 可以作为催化剂使用，避免大多数铬氧化剂生成的大量的有毒重金属副产物。这个反应中按化学计量的氧化剂是 NMO (*N*-甲基吗啉-*N*-氧化物)，可以被还原为胺，将钌重新氧化为 Ru(VII)。



另一种重要的温和氧化剂是一种高价的碘化合物，被称为 Dess–Martin 高碘烷 (Dess–Martin periodinane)。它可以由 2-碘苯甲酸制备。

► 缩写 THP 和 TBDS 将会在本章中阐述 (p. 550)。



它可用于将非常敏感的醇氧化为羰基化合物——例如，侧边栏中展示了其将一个 顺-烯丙基醇 氧化为 顺- $\alpha,\beta$ -不饱和醛 的例子，中途不会使之异构化为反式，或产生其他的副产物，这一点很少有氧化剂能做到。

我们将把另一种方法的详细讨论移至后面的 Chapter 27，因为它的机理包含您会在那里系统学习的硫化学；而现在我们则将介绍它在合成上的重要性。这个反应是 Swern 氧化 (斯文氧化, Swern oxidation)，它使用一种亚砜 [硫(IV)] 作为氧化剂，亚砜被还原为硫醚时，醇被氧化为醛。



► 更多关于 Swern 氧化的细节，及其机理，见 p. 667。



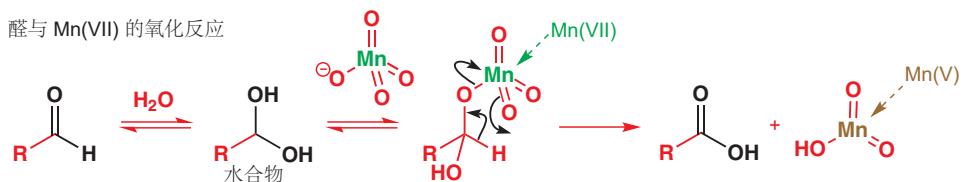
### 如何将伯醇或醛氧化为羧酸

有时，我们在将伯醇氧化为醛时努力要避免的所谓“过度氧化”，也有可能是您事实上需要的反应。它很容易通过 Cr(VI) 或 Mn(VII) 的水溶液完成。酸性或碱性的高锰酸钾水溶液即使一个好选择。在酸性溶液中，由醇反应的机理与与铬酸反应的基本一致，由醛反应的机理也很相似。

高锰酸钾是一个很强的氧化剂，也会将苯型甲基（即甲苯衍生物）氧化为羧酸。您在 p. 486 糖精的合成中见过了此反应的应用。



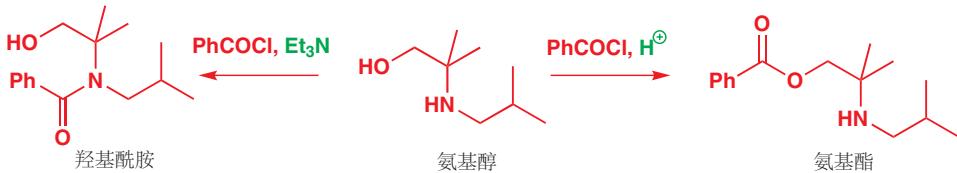
醛与 Mn(VII) 的氧化反应



### 竞争反应性：选择反应的基团

我们希望如上关于氧化、还原中的重要方法的概述，能让您明白，您可以通过选择合适的试剂，来达到仅让自己想让的某个基团发生反应。这些化学选择性，都是动力学化学选择性——由于在一处反应比其他处快而引起的。

而现在我们将着眼于一种在酸性下，用苯甲酰氯完成的一种氨基醇的酰胺化反应（事实上，是一种止痛药 isobucaine 的合成）。羟基被酰基化形成酯。但如果在碱性下反应，选择性则很不相同，得到的是酰胺。



关于选择性逆转的原因的一条线索如下所示——事实上，仅仅在酸性下处理酰胺，或在碱性下处理酯，都可以实现相互转化。



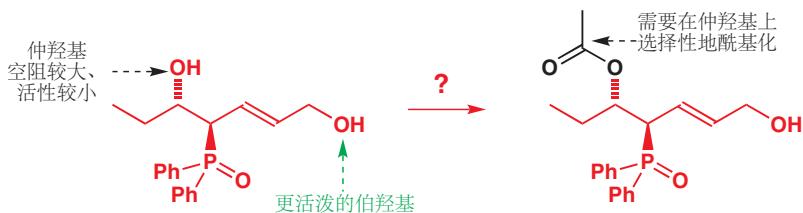
我们在 Chapter 12 (p. 264) 中讨论了热力学和动力学控制，而在 pp. 435 和 505 又涉及了它们。

这个反应的选择性是热力学化学选择性。在酯和酰胺存在平衡的条件下，获得的产物是其中更稳定的一个，并不一定是生成得快的一个。在碱性下更稳定的酰胺会占主要；而在酸性下由于酯中有可被质子化的胺，胺质子化后可将酯移出平衡，于是使之占主要。

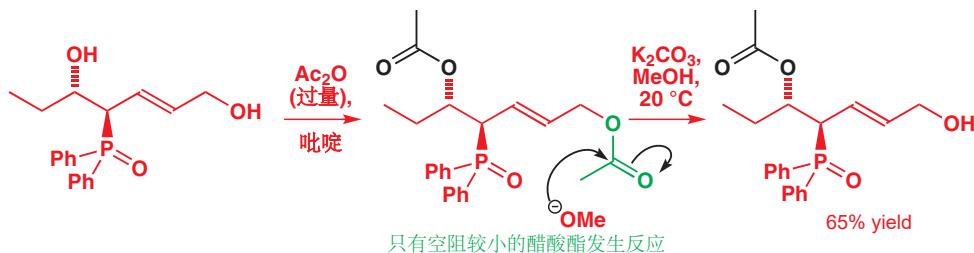


## 如何在较不活泼的基团上反应 (I): 先都反应, 再“不反应”一个

刚才给出的例子中, 通过在热力学控制下进行反应, 醇和胺的相对活性可以被颠覆。在动力学控制下, 在一对官能团——例如基于羰基的几种官能团——中较活泼的一个上, 发生化学选择性的反应是很简单的。那么如果您想在这一对官能团中较不活泼的一个上反应呢? 有两种常用的解决方案。第一种可以通过剑桥大学的化学家学习环氧化合物时需要的一个化合物说明。它们可以制得下面的二醇, 但只想在空阻较大的仲羟基上反应。



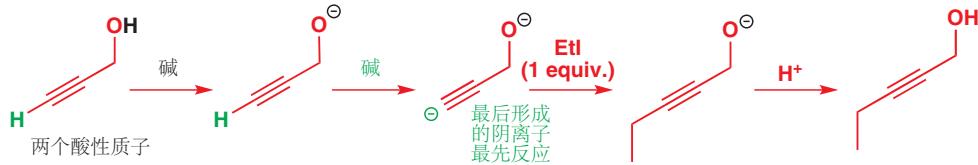
用一当量的酰基化试剂处理, 结果并不会理想, 因为伯羟基较为活泼; 相反, 化学家会先将两个羟基都酰基化, 然后再用温和的碱性乙醇 ( $\text{K}_2\text{CO}_3$ ,  $\text{MeOH}$ ,  $20^\circ\text{C}$ ) 处理所得的双醋酸酯, 只有较小空阻的醋酸氧基 (acetoxymethyl,  $\text{OMe}$ ) 发生反应, 并以 65% 的产率给出我们所需的化合物。



换句话说, 先让两个基团都反应, 然后再倒退, 让反应逆向进行, 但仅限于两个基团中的一个。由于两个基团的区别是空阻, 那么就意味着在较不活泼的基团上, 发生的较不有利的反应, 其逆反应也同样是较不容易的。

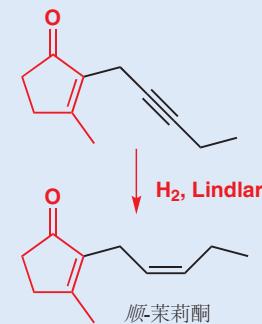
## 双阴离子反应的化学选择性

与之相似的观点也是双阴离子引起的, 一种实用的化学选择性的中心。1-炔丙醇可在强碱下被两次去质子——第一次在羟基上去质子, 得到烷氧基阴离子 ( $\text{OH}$  的  $\text{p}K_a$  大约 16); 而第二次, 则在炔烃上去质子, 得到双阴离子 ( $\text{p}K_a$  大约 25)。(当然, 后引入的负电荷是更活泼的), 因此当这个双阴离子与亲电试剂反应时, 往往在炔基阴离子上反应, 而不是烷氧基阴离子上反应。

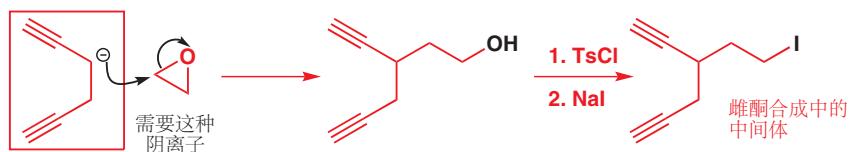


- 双阴离子的反应性  
最后生成的阴离子最先反应。

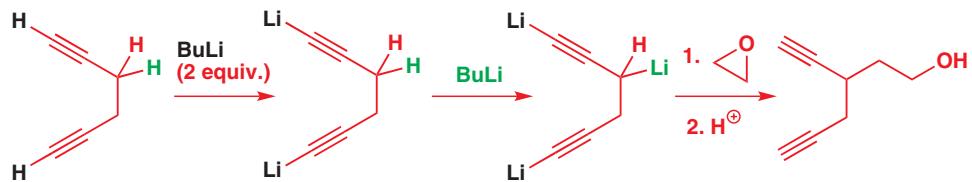
这个反应在香水化合物 顺-茉莉酮 (*cis*-jasmonate) 的合成中是重要的。炔烃是顺-茉莉酮的烯烃侧链的前体。



Vollhardt 将这种化学选择性用在了他在 1977 年关于雌性激素雌酮 (oestrone) 的合成上。合成中需要一种烃基碘，可通过一种二炔烃的一种阴离子与环氧乙烷制取。



虽然炔烃旁边可以直接地形成阴离子，但分子中另有两个酸性质子（黑色）会先于绿色质子被碱拔去。然而，用三当量的叔丁基锂则可以移去全部三个质子，所得的三阴离子可以与环氧乙烷在其最后形成的阴离子中心反应，给出所需的化合物。

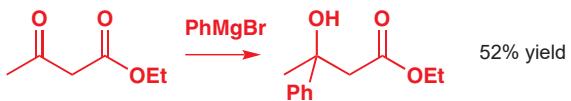


### 如何在较不活泼的基团上反应 (II): 保护基

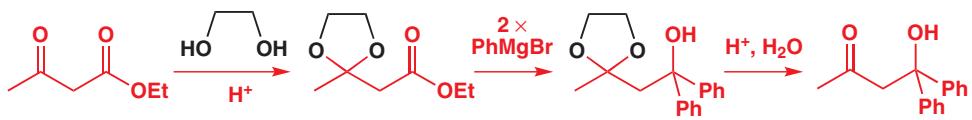
为达到在较活泼的基团存在下，使较不活泼的基团反应的目的，更惯常的方法是使用**保护基 (protecting group)**。例如，如果我们使溴化苯基镁在如下酮酯（乙酰乙酸乙酯）的酯上，而不是酮上反应，则会得到一种叔醇。



如您所料，仅仅将溴化苯基镁加入乙酰乙酸乙酯中，则主要会加成在较亲电的酮上。



制取我们想要的醇的一种方式，通过亲核试剂将其掩蔽，以**保护**酮不受进攻。所用的是一种缩醛保护基（黑色所示）。



第一步是将保护基放在（较亲电的）酮羰基上，使其不再具有对亲核加成的反应性。然后格氏试剂加成到酯上，经过一个“脱/去保护 (deprotection)”步骤，即缩醛的酸催化水解，可将酮恢复。缩醛在这里是一个理想的选择——缩醛在碱性下（我们想做的反应中）稳定，但在酸性下却容易断开。

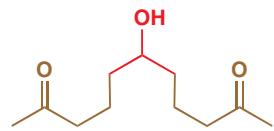
- 像这种的五元环缩醛也被称作二氧戊环 (dioxolane-s)。在 Chapter 11 关于缩醛形成和水解的讨论中，您首次遇到他们。

## 保护基纵览

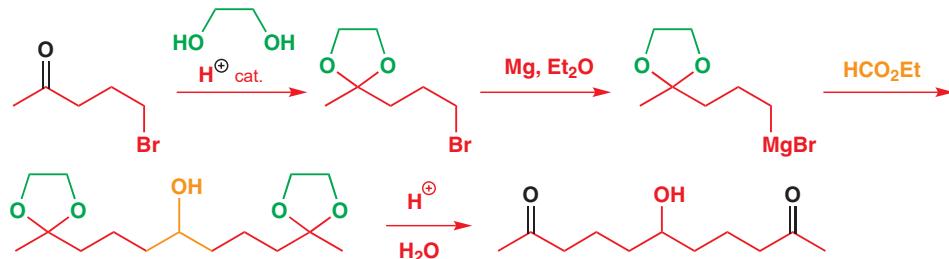
二氧戊环可以在非常强的碱性亲核试剂下，保护醛和酮。这也是我们将在下面的几页中讨论的内容，保护基，中的首个例子。

保护基	结构	保护对象	面对	保护方法	脱保护方法
缩醛(二氧戊环)		酮、醛	亲核试剂、碱		H+, H <sub>2</sub> O

通过对像酮这样的敏感基团的保护，使我们能够制备除此之外会不稳定的试剂。在天然产物 porantherine 的合成中，需要基于如侧边栏所示的一种结构的化合物。由于它是一个对称的仲醇，我们会想到用甲酸乙酯被格氏试剂加成两次的方法制备(见 p. 216).

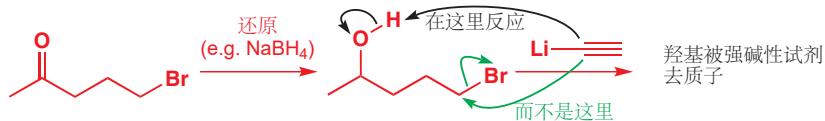


但，当然，一个带有酮的格氏试剂是不可能的，因为它会发生自缩合，因此选用的是缩醛保护的化合物。加成后。再酸催化水解两个绿色的二氧戊环，会重新得到二酮。



像格氏试剂、有机锂这样的强亲核试剂，同样也是强碱，因此不但亲电的羰基需要保护，酸性质子也应当被保护。其中最麻烦的莫过于羟基上的质子。当一些美国化学家想制备一种抗病毒剂 Bre-feldin A 时，他们需要侧边栏中的一种简单炔醇。

一种合成路线可以由与上文相同的溴代酮开始：还原给出醇后，它与炔基阴离子的烷基化就不可能发生了，因为炔基阴离子会先使羟基去质子。

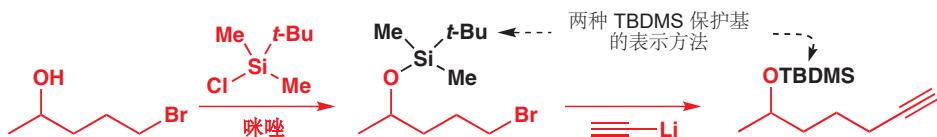


咪唑 =  
(一种弱碱)



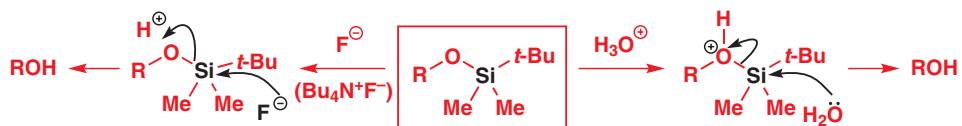
答案是，先用一个对碱有抗性的基团保护羟基，这里选择的基团是硅醚 (silyl ether)。这种醚可通过将醇与三烷基氯硅烷/三烷基硅基氯 (这里所用的是叔丁基二甲基氯硅烷 *tert*-butyldimethylsilyl chloride, 简写作 TBDMSCl) 在弱碱下反应制得，弱碱常用咪唑，一种也作为亲核催化剂的物质 (Chapter 12)。

您在 p. 178 见过了咪唑。



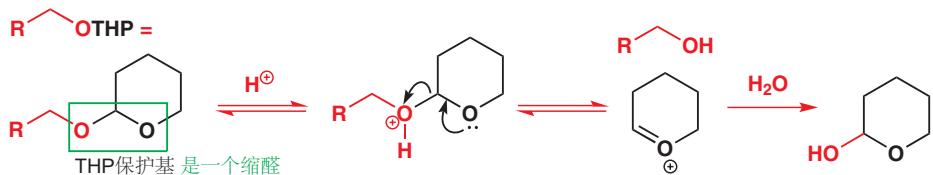
硅对负电性元素，尤其是 O, F, and Cl, 有很强的亲和性 (affinity)，所以三烷基硅基醚会被氢氧根离子、水，或氟离子进攻（脱保护），但对碳碱、氮碱，或其他亲核试剂则较稳定（起到的保护作用）。它们的去除，通常使用酸的水溶液或氟盐，尤其是可溶解在有机溶剂中的  $\text{Bu}_4\text{N}^+\text{F}^-$  (氟化四正丁基铵/四正丁基氟化铵, tetra-*n*-butylammonium fluoride, 缩写作 TBAF 读作“tea-baff” )。事实上，TBDMS 是三烷基硅基保护基家族中的一员，而这类保护基面对各种各样亲核试剂的相对稳定性由硅带有的三个烷基决定。最不稳定的，三甲基硅基 tri-methylsilyl (TMS)，仅仅用甲醇处理即可去除；而最稳定的则需要用氢氟酸脱除。

■ 虽然不重要，但我们还是应提及，这里的取代反应不是简单的，它们看起来也许像是  $\text{S}_{\text{N}}2$  反应 (Chapter 15). 亲核试剂先加到硅上，形成五价阴离子，继而分解失去醇。



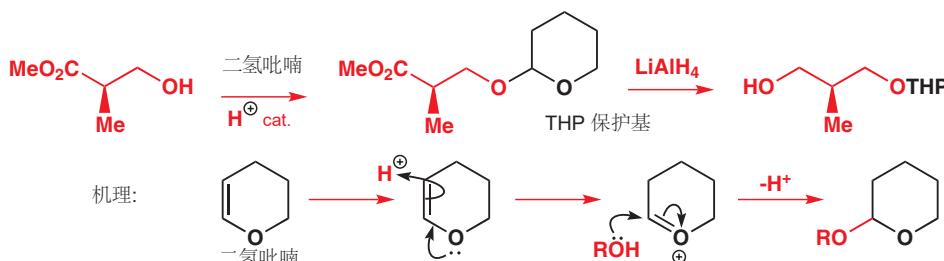
保护基	结构	保护对象	面对	保护方法	脱保护方法
三烷基硅基 $\text{R}_3\text{Si}-$ , e.g. TBDMS	$\text{RO}-\text{SiMe}_3$ $\text{RO}-\text{SiMe}_2\text{t-Bu}$	醇 (OH 一般而言)	亲核试剂, C 或 N 碱	$\text{R}_3\text{SiCl}$ , 碱	$\text{H}^+$ , $\text{H}_2\text{O}$ , 或 $\text{F}^-$

为什么我们不能直接用简单的烷基 (比如甲基) 来保护羟基呢？得到醚并没有任何问题，并且它能在大多数反应中存活——但有一个问题就是，如何脱去醚。这是保护基化学常常要思考的一个问题——您想得到的是一个能在您要做的任何反应的条件下 (上述离子中的强碱和亲核试剂) 都保持稳定的基团，但与此同时，也得是一个能在温和的条件，即不会导致敏感分子分解的条件下轻易脱去的基团。因此我们所需的醚要有阿喀琉斯之踵 (唯一的致命伤)——易受某些特定试剂进攻，或在特定反应条件下易被进攻。这样的基团中，其中一种是四氢吡喃 (tetra hydropyran, THP) 基。作为醚，它在碱性下稳定；但它还是个缩醛，第二个氧原子的存在就是它的阿喀琉斯之踵，使 THP 保护基易在酸性下水解。您可以看到，第二个氧原子上的孤对电子作为为了仅在酸存在下会松开的保险栓。



► 在 Chapter 20 有更多关于烯醇醚的化学。

THP 缩醛的制取需要用一种陌生的方法完成，因为通常的“羰基加两个醇”的方法不适于此 (思考为什么！)。用一种烯醇醚，即二氢吡喃在酸催化剂下处理，即可使醇得以保护。注意氧盐中间体 (通过 Chapter 12 涉及的一个熟悉的机理形成)——与一般的缩醛形成反应中的一致。这个例子中，THP 基的作用是防止羟基干扰酯的还原。

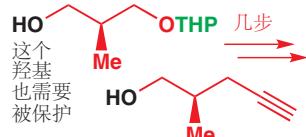
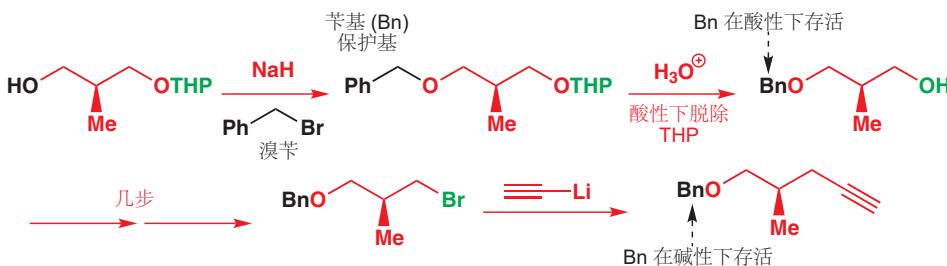


保护基	结构	保护对象	面对	保护方法	脱保护方法
四氢吡喃 (THP)		醇 (OH 一般而言)	强碱		H+, H2O

进一步的审视会展现给您，这里的 THP 基团不但阻止了 OH 对  $\text{LiAlH}_4$  还原的干扰，同时对化合物手性的保留也是至关重要的。粗浅形键告诉您，起始原料是一个单一对映体：如果不对其中一个羟基进行保护，那么手性中心将会出现两个完全相同的基团，并不再具有手性。THP 基团通过引入一个额外的手性中心使情况更加复杂，由此会出现两个潜在的非对映体，我们会忽略。

上方 THP 所保护的化合物，被用作一种杀虫剂米尔倍霉素（也称倍脉心，milbemycin）合成中的中间体。它需要被转化为侧边栏所示的炔烃——三键通过碱性下炔基锂的反应得到，因此另一个羟基也需要被保护。

然而，这一次，不能使用 TBDMS 保护基，因为随后 THP 保护基的脱去需要酸性环境（会脱去硅基）！另外，这种保护基也需要能在这种杀虫剂合成的剩下几步中所需的酸性条件下存货。因此答案是选用第三种羟基保护基，苄醚。苄基（Benzyl, Bn）保护基用强碱（通常是氯化钠）加溴苯上保护，并在酸性和碱性下都稳定。



您在 Chapter 15 中见到了这种用  $S_N2$  反应制取醚的方法。

### 苄基和苯甲酰基

注意苄基醚， $\text{ROCH}_2\text{Ph}$  的缩写是  $\text{ROBn}$ 。请与苯甲酸酯， $\text{ROCOPh}$ ，也许会被缩写作  $\text{ROBz}$  对比。

苄醚的阿喀琉斯之踵是芳环，并且阅读本章的上半部分后，您应当能想到脱去它的条件：钯催化剂上的氢化（氢解），可断裂苄基 C—O 键。



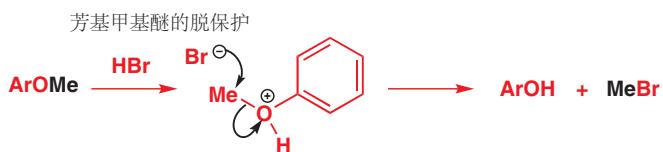
■ 必须用钯催化剂——铂则会先催化氢化芳环。

苄醚有时也可通过带有亲核的共轭碱的酸去除。例如  $\text{HBr}$  可以去除苄醚，因为  $\text{Br}^-$  是一个对于（也仅仅对于）苄基中心的  $\text{ROH}$  的取代足够好的亲核试剂。

保护基	结构	保护对象	面对	保护方法	脱保护方法
苄醚 (OBn)		醇 (OH 一般而言)	几乎任何事	NaH, BnBr	H <sub>2</sub> , Pd/C, 或 HBr
甲醚 (ArOMe)		酚 (ArOH)	碱	NaH, MeI, 或 (MeO)2SO2	BBr3, HBr, HI, Me3SiI

我们之前说过，简单的烷基醚不容易脱去，因而不适合做 OH 的保护基。这通常是正确的，但不包括 OH 为酚羟基的情况——ArOH 是一个比 ROH 好的离去基团，因此 HBr 也会从芳基甲基醚上脱去甲基。

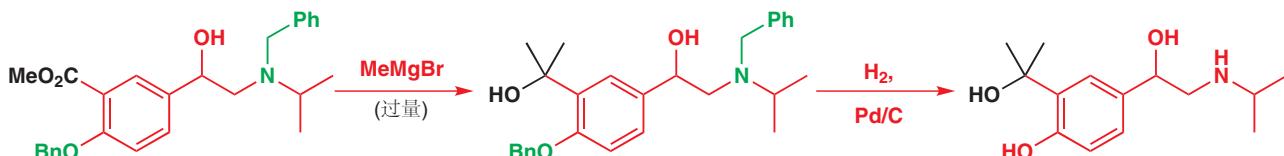
■ HBr 可用 BBr<sub>3</sub> 替代，而通常最称心的试剂是 HI 和 Me<sub>3</sub>SiI。



保护基也许是有用的，但它们也是一种浪费——对时间和原料的浪费，使用它们需要两个额外的步骤（上保护和脱保护过程），并且这些步骤可能都不是 100% 产率。下面是一种避免使用它们的方法。在定喘药物沙丁胺醇（salbutamol）的后续开发中，需要如下的三醇。由于大量的沙丁胺醇已经可以获得，最直接的制备方法看似就是直接在由叔丁胺醇得到的酯上添加溴化苯基镁。不幸的是，这种酯也包含三个酸性质子，看起来所有的羟基和氨基都需要被保护。但事实上，仅仅通过加入大量的格氏试剂——足够移去所有酸性质子，并加成到酯上的量——则可以进行这个反应。



尝试这种策略很容易，因为格氏试剂并不值钱（您可以买到瓶装的 PhMgBr），远比先放上保护基，再脱去它们实惠得多。但这并不总能工作——除非在实验室亲自尝试，否则没有任何方式能说明它是否能工作。如下这个十分相近的反应，同一拨化学家尝试时发现，他们需要先以苄基醚保护苯酚羟基（另一个醇 OH 则无需保护），并用苄基胺保护胺 NH。这两者都在随后的氢化步骤中脱去。



苄基是在也许可将仲胺去质子的强碱下保护仲胺的一种方式。但造成化学选择性问题的通常是胺的亲核性而不是 NH 基的酸性。在合成生物分子中最重要的类别之一，肽时，这个潜在的隐患会

更加尖锐。

## 肽合成

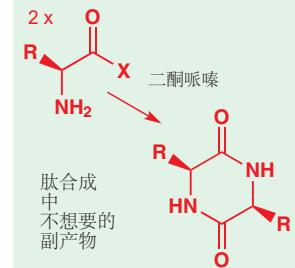
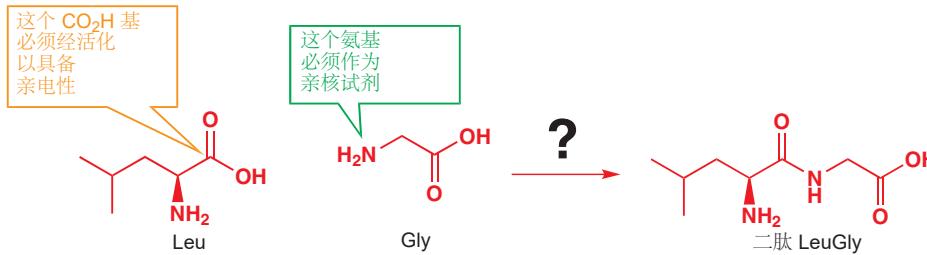
肽合成已经成为了实用有机化学 (practical organic chemistry) 中可靠并且可预测的领域之一，原则上是因为保护基在其中运用的效果所致。由于这个原因，肽也是为数不多的可被机器例行制造的复杂有机分子种类之一，右图所示是一种多肽合成仪，我们将要讨论的内容中大多是在没有人为干预下发生的。

生理上，肽和蛋白质是通过 20 或更多种氨基酸选择性地偶联得到的。在实验室中完成相同的工作，则需要面对很多困难。我们将从如何让两个氨基酸反应在一起，以得到二肽 (dipeptide) 开始——如亮氨酸和甘氨酸的组合。如果我们想让甘氨酸的  $\text{NH}_2$  基与亮氨酸的  $\text{CO}_2\text{H}$  基反应，那么我们首先就得活化亮氨酸中的羧酸面对亲核取代的能力——如将其做成酰氯，或某种异乎寻常的酯，以  $\text{RCOX}$  表示。



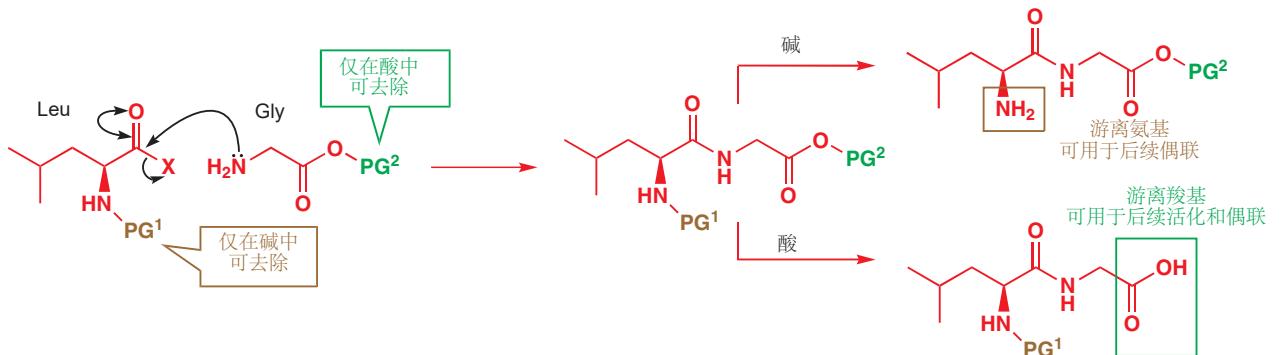
■ 在 p. 554 有关于用于组成大多数肽的全部氨基酸的名称、结构和缩写的列表。

■ 事实上，肽合成并不使用酰氯，因为酰氯的使用会导致很多潜在的副反应，包括外消旋化和二聚(生成名二酮哌嗪的产物)。



将甘氨酸加入其中后，主要的问题出现了，也就是，甘氨酸游离的  $\text{CO}_2\text{H}$  能与  $\text{COX}$  基反应形成酸酐，并且两种分子都有游离的氨基，会同时给出 LeuLeu (我们所不需要的) 和 LeuGly (我们所需要的)。

面对这个问题，我们需要保护亮氨酸的  $\text{NH}_2$  基和甘氨酸的  $\text{CO}_2\text{H}$  基。它们需要变为哪类保护基呢？它们完成自己的工作后，我们还需要能轻易地将它们脱除，因此毫无疑问的是：如果用酰胺来保护胺，我们就会在之后面临在两个酰胺存在下选择性脱除其中一个的难题。并且我们不仅希望保护基可以在温和条件下被脱除，而且还希望两个保护基 ( $\text{NH}_2$  的和  $\text{CO}_2\text{H}$  的) 的脱除发生在不同条件下。这样我们就有机会随心所欲修饰二肽的任意一端了。



对于这对脱保护条件，一个好的选择或许是酸性和碱性——我们或许会用一个只能在碱性下去除的保护基来保护  $\text{NH}_2$  基，并用一个只能在酸性下去除的保护基保护  $\text{CO}_2\text{H}$  基。

### 氨基酸

供参考，如下给出了大多数肽结构中出现的全部氨基酸，附带有可描述它们的缩写符号。侧链都以黑色展示，侧链官能团以绿色展示。更多氨基酸的化学会在 Chapter 42 中给出。

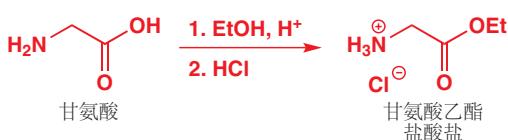
名称	三字母缩写	单字母缩写	结构
甘氨酸 (glycine)	Gly	G	
丙氨酸 (alanine)	Ala	A	
缬氨酸 (valine)	Val	V	
亮氨酸 (leucine)	Leu	L	
异亮氨酸 (isoleucine)	Ile	I	
苯丙氨酸 (phenylalanine)	Phe	F	
色氨酸 (tryptophan)	Trp	W	
脯氨酸 (proline)	Pro	P	
丝氨酸 (serine)	Ser	S	
苏氨酸 (threonine)	Thr	T	
酪氨酸 (tyrosine)	Tyr	Y	

名称	三字母缩写	单字母缩写	结构
半胱氨酸 (cysteine)	Cys	C	
甲硫氨酸 (methionine)	Met	M	
组氨酸 (histidine)	His	H	
赖氨酸 (lysine)	Lys	K	
精氨酸 (arginine)	Arg	R	
天冬氨酸 (aspartic acid)	Asp	D	
天冬酰胺 (asparagine)	Asn	N	
谷氨酸 (glutamic acid)	Glu	E	
谷氨酰胺 (glutamine)	Gln	Q	

### Cbz 保护基—催产素



前文我们举出了二肽 LeuGly 的例子，这是由于它出现在多肽激素催产素 (oxytocin) 的一端。催产素合成的第一步确实就是甘氨酸（由其氨基）与亮氨酸的偶联。下面是 du Vigneaud 和 Bodanszky 完成这一步的方法。首先，甘氨酸的羧基被用乙酯保护。成酯是防止  $\text{CO}_2\text{H}$  作为酸或亲核试剂干扰反应很明显的方法。然而，简单的甲酯、乙酯可能也会引发问题——它们仍能和像胺这样的亲核试剂反应。因此氨基酸的乙酯仅在  $\text{NH}_2$  基被保护时稳定。甘氨酸乙酯可用以其盐酸盐的形式储存： $-\text{NH}_2$  基被“保护”为  $-\text{NH}_3^+$ 。

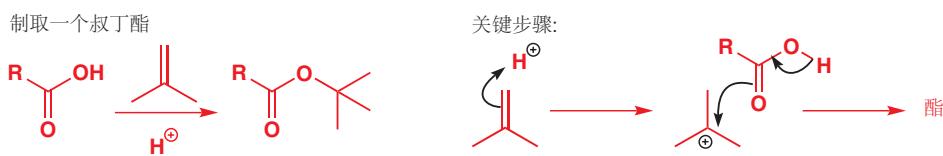


催产素是在对女性分娩开始，和随后乳汁分泌的控制中所涉及的一种激素。它是第一种被合成的多肽类激素，与 1953 年被 du Vigneaud 合成，他也因多肽合成上的工作而获得 1955 年的诺贝尔奖。这种激素的“合成”版本（和自然界中分离得到的当然完全相同，但不具有生物污染的危险）在现代产科学中经常被用作为过期分娩的女性引产。

一个更常用的羧基保护基是面对亲核进攻相当稳定的叔丁酯。叔丁酯可用通过羧酸与异丁烯在硫酸中生成的阳离子反应制取。

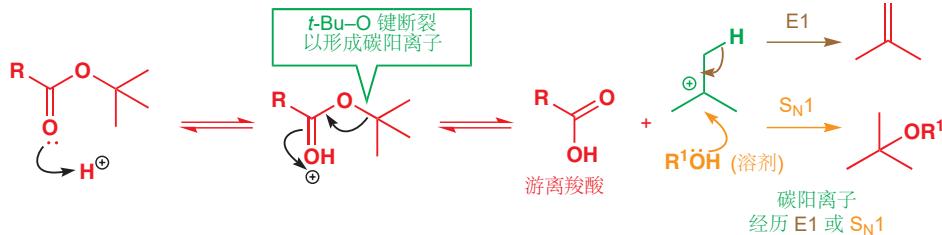
■ 这是比通常的方法，即酰氯加醇（见 Chapter 10）更受欢迎的方法，因为受空间影响，与叔丁醇的反应会非常缓慢。

► 您在 Chapter 15, p. 558 和 Chapter 17, p. 384 中看到过这个反应。



叔丁酯的大空间意味着，在羰基上的亲核进攻受到阻碍，这也包含在碱性下的水解 ( $\text{HO}^-$  的亲核进攻)。但它在酸性下水解则相对容易，因为叔丁酯在酸性下水解的机理很不同。它并不经历对羰基的亲核进攻，而是通过一个稳定碳阳离子的失去进行的，这个碳阳离子会被溶剂捕获，发生  $\text{S}_{\text{N}}1$  反应，或失去一个质子发生  $\text{E}1$  反应。

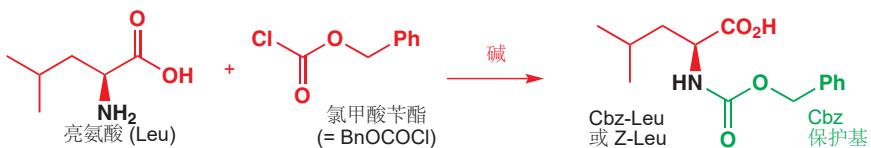
叔丁酯在酸性下水解：



保护基	结构	保护对象	面对	保护方法	脱保护方法
叔丁酯 ( $\text{CO}_2\text{t-Bu}$ )		羧酸	亲核试剂	异丁烯, $\text{H}^+$	强酸

不过到头来，在催产素的合成中，甘氨酸的羧基最后还要被做成伯酰胺，即需要能与氨反应。因此化学家需要一个在温和的酸性下稳定的基团——因此他们最终选择的是乙酯。

而对于亮氨酸一侧，则需要使其  $\text{NH}_2$  基在碱性下稳定的保护基保护，这是因为甘氨酸盐酸盐释放  $\text{NH}_2$  基的过程在碱性下进行。所选用的基团是最重要的氮保护基之一，被称作 Cbz 基 (Cbz 代表苄氧羰基 carboxybenzyl)。Cbz 基通过氯甲酸苄酯 benzyl chloroformate ( $\text{BnOCOCl}$ ) 和碱的处理上保护。

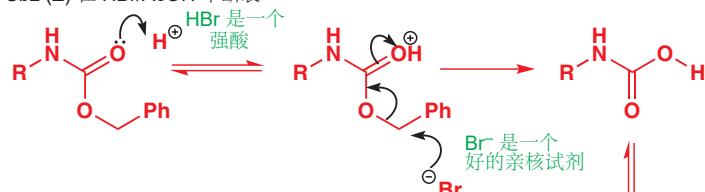


■ 氨基甲酸酯是酯和酰胺的结合，它们的化学性质大多与酰胺相近。

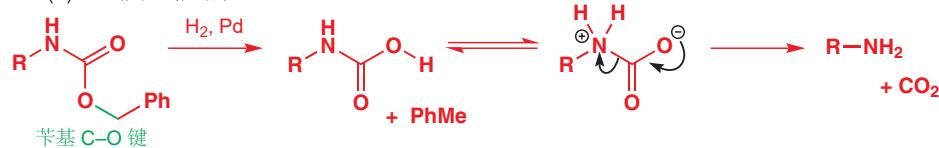


Cbz 保护的胺事实上是氨基甲酸酯 (carbamates)：与酰胺相似，不再具有亲核性，因为氮原子的孤对电子被束缚在了和羰基的共轭中。它们对于酸的水溶液和碱的水溶液都具有抗性，但类比于我们从前发展的一种阿喀琉斯之踵——苄基，释放保险栓并脱去 Cbz 的方法，正是苄醚脱保护的两种方法 (p. 551)：

Cbz (Z) 在 HBr/AcOH 中断裂



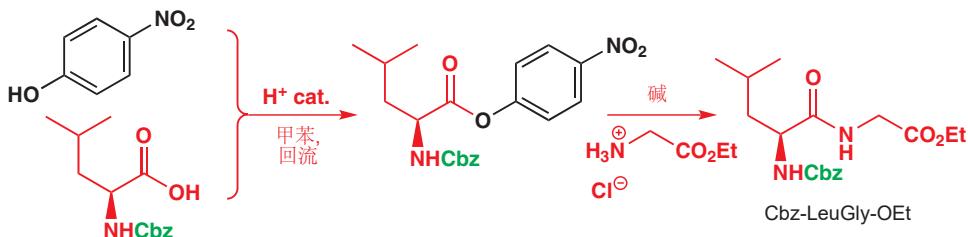
Cbz (Z) 通过催化氢化断裂



保护基	结构	保护对象	面对	保护方法	脱保护方法
Cbz (Z) ( $\text{OCO}^{\text{Bn}}$ )		胺	亲电试剂	$\text{BnOCOCl}$ , 碱	HBr, AcOH; 或 $\text{H}_2$ , Pd

Cbz 保护的亮氨酸上的羧基接下来需要被活化，以与甘氨酸反应。酰氯太不稳定，不适合做这份工作，肽化学中的一个替代方法是制成 对硝基苯酚酯或 2,4,6-三氯苯酚酯。酚氧基阴离子，尤其是当它们带有吸电子取代基时，可用作为一个很好的离去基团。Cbz-亮氨酸对硝基苯酚酯与甘氨酸乙酯盐酸盐在弱碱的存在下反应 (三乙胺，用于释放甘氨酸的  $\text{NH}_2$  基).

■ 酚较低的  $pK_a$  使酚氧基阴离子成为比烷氧基好的离去基团；而一个缺电子的酚氧基阴离子则更好 (see p. 173).



■ 注意这一步中的化学选择性——甘氨酸的  $\text{NH}_2$  基带有三个可选择反应的羰基，但仅与最亲电的一个——离去基团离去性最好的一个反应。

现在二肽的偶联就完成了——但仍然被保护着。氨基的脱保护 (HBr/AcOH) 可给出 LeuGly 乙酯的 HCl 盐，以进行在亮氨酸一侧继续连接的后续反应。多肽的余下部分可通过大致相同的方式游刃有余地构筑——每个氨基酸都通过 Cbz-保护的对硝基苯酚酯引入，产物经酸性脱保护继续用于下一次偶联，直到催产素的全部九个氨基酸都被引入。

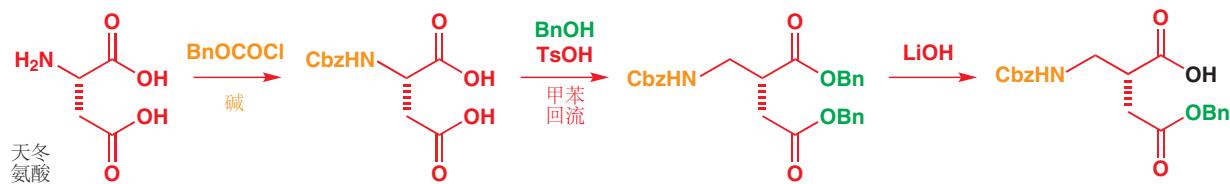
## Boc 保护基—胃泌素和阿斯巴甜

胃泌素 (Gastrin) 是一种由胃分泌的激素，用于控制消化过程。对于这种激素的早期工作表明，只有多肽中 C-端/羧基端的四个氨基酸 (C-端四肽) 对它的生理学或许是必要的。

**H<sub>2</sub>N-Tyr-Met-Asp-Phe-CONH<sub>2</sub>**  
胃泌素 C-端四肽

合成开始于两种新的氨基酸的偶联：天冬氨酸 (由羧基) 和苯丙氨酸 (由氨基)。如您所料，苯丙氨酸的羧基被保护，这次所用为甲酯；而天冬氨酸的  $\text{NH}_2$  基则被保护为 Cbz 衍生物。由于天冬氨酸含有两个羧基，而其中末端羧基恰恰需要反应，而侧链羧基恰恰不需要反应。保护的方法如是一一首先用 Cbz 基保护氨基，然后将两个羧基都被保护为苄醚，然后再水解其中一个苄醚。此处的化学选择性水解是出人意料的，不在实验室亲自尝试是无法预测这种结果的。

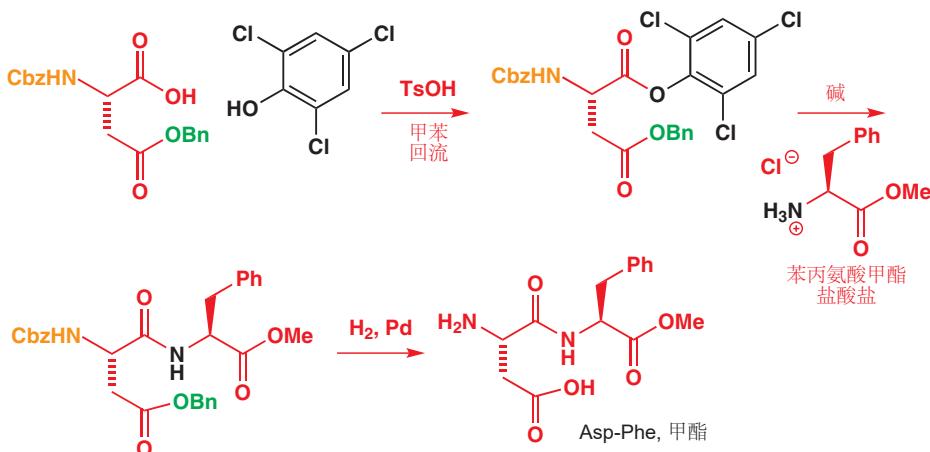
C-端 (terminus) 意为多肽带有末端  $\text{CO}_2\text{H}$  基的一端。另一带有  $\text{NH}_2$  基的端，为 N-端。习惯上，端往往写在左侧而 C-端写在右侧。



### 意外的阿斯巴甜

在 Searle, 现已倒闭的美国制药公司的实验室中, 一次对该四肽的合成, 做到此时此刻, 有了惊人的发现。实验员意外发现 AspPhe 单甲酯尝起来是甜的——大约是蔗糖甜度的 200 倍。AspPhe 单甲酯现在被称为阿斯巴甜 (aspartame), 并以商品名 NutraSweet 出售。尽管这个非凡的发现正出于此, 但在实验室中品鉴任何事物, 无论有意无意都是不明智、欠考虑、绝对危险的。唐纳德·拉姆斯菲尔德 (Donald Rumsfeld, 政治家) 曾是 Searle 的首席执行官。

被保护的酸随后被活化为 2,4,6-三氯苯酚酯, 并已准备好与苯丙氨酸甲酯在碱中反应。现在您可看出, 为什么要选用苯醚来保护 Asp 的侧链羧基——通过氢解, 可用使 Cbz 基和苯醚同时断裂。



多肽中的下一个氨基酸是甲硫氨酸, 理所当然, 它需要 N-上保护 和 C-活化。这回使用的 N-保护基有所不同——仍是一个氨基甲酸酯, 但不是 Cbz——是 Boc, 代表叔丁氧羰基 (*t*-butyloxycarbonyl) 读作 “bock”。Boc 基团,  $t\text{-BuOCO}$ , 通过  $(t\text{-BuOCO})_2\text{O}$  即 Boc 的酸酐引入。

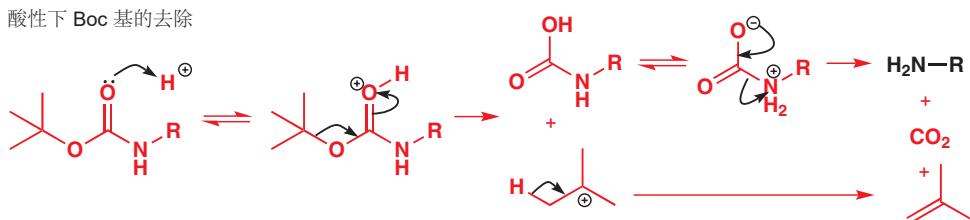
■ Cbz 基的引入所用的是氯代甲酸酯 ( $\text{BnOCOCl}$ )。而对在此处, 相应的氯代甲酸酯,  $t\text{-BuOCOCl}$  是不稳定的, 因此选用的是  $\text{Boc}_2\text{O}$ 。请自行书写反应机理, 这是个很好的练习。



与 Cbz 一致, Boc 基是一个氨基甲酸酯保护基。但与 Cbz 不同的是, 仅仅用稀酸水溶液不能去除它。只有 3M HCl 可用水解它, 再一次, 通过质子化, 叔丁基阳离子的失去, 和脱羧完成。另一方面, 碱无法触及 Boc 基——羰基空阻太大, 不能被甚至  $\text{OH}^-$  进攻, Boc 对碱性水解具有很强的抗性。

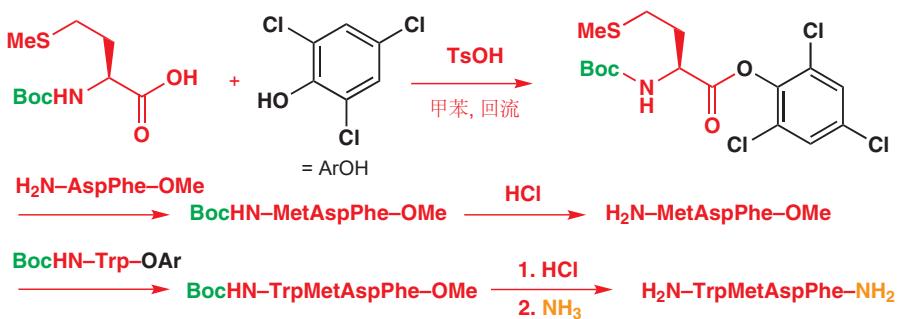
■ 您可将这个水解机理与 Cbz 基的酸催化断裂机理对比, 但在此要注意,  $t\text{-Bu}$  基以  $\text{S}_{\text{N}}1$  步骤离去 (因此任何强酸工作)。而 Cbz 基则需要好的亲核试剂,  $\text{Br}^-$  的辅助, 因为它所涉及的是  $\text{S}_{\text{N}}2$  步骤。

### 酸性下 Boc 基的去除



保护基	结构	保护对象	面对	保护方法	脱保护方法
Boc ( <i>t</i> -BuOCO)		胺	亲电试剂	( <i>t</i> -BuOCO) <sub>2</sub> O, 碱	H <sup>+</sup> , H <sub>2</sub> O

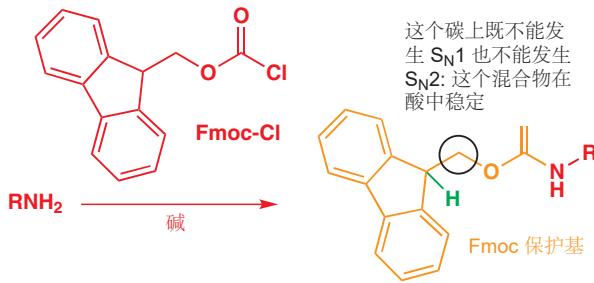
回到四肽的合成上，甲硫氨酸 (Met) 已被 Boc 保护，并准备好活化——这次是 2,4,6-三氯苯酚酯（上文缩写作 Ar）——继而与脱保护的 AspPhe-OMe 反应。酸性水溶液可在不水解肽键、酯键的情况下脱去 Boc 基。然后再用 Boc-色氨酸 三氯苯酚酯 (BocHN-Trp-OAr) 重复这一循环，最后与氨反应制得酰胺以完成四肽的合成。



### Fmoc 保护基

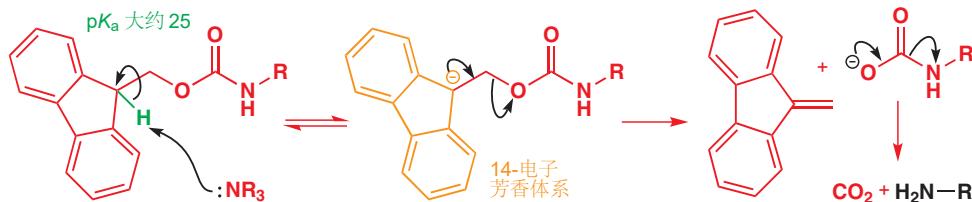
我们最后要考察的一个保护基，与 Boc 的敏感性 (susceptibility) 正颠倒。Fmoc (读作 “eff-mo-ck”)，或芴甲氧羰基 (fluorenylmethyloxycarbonyl)，是一个不能通过 Cbz 或 *t*-Boc 的取代反应的方式脱去的保护基，因为无论是 S<sub>N</sub>1 还是 S<sub>N</sub>2 反应都不能在与环相连的碳原子上进行：因为它既是伯碳，还具有很大的空阻。

► 在 Chapter 15 我们仔细地分析了有利和不利于两种取代反应的结构特征。



因此，保险栓在哪里呢？Fmoc 的阿喀琉斯之踵是它相当具有酸性的质子 ( $pK_a$  大约 25)，如绿色所示。它具有酸性的原因是，它的去质子产物具有芳香性。虽然任何时候生成的芳香阴离子浓度都非常小，但仍会经历消除反应，因此 Fmoc 保护的胺可轻易地在碱性下脱保护。

► 对这种类型的芳香性，有代表性的是 Chapter 17, p. 401 讨论过的茂离子。



本章不紧不慢地建立起来的保护基表，现在已经完成了。此时此刻，您应当能写出如下所列出的任意一个成员的结构，也应当熟悉它们的保护和脱保护所必要的条件。

保护基	结构	保护对象	面对	保护方法	脱保护方法
缩醛(二氧戊环)		酮, 醛	亲核试剂, 碱		H+, H2O
三烷基硅基 R3Si (e.g. TBDMS)	RO-SiMe3 RO-SiMe2-t-Bu	醇 (OH 一般而言)	亲核试剂, C 或 N 碱	R3SiCl, 碱	H+, H2O, 或 F-
四氢吡喃 (THP)		醇 (OH 一般而言)	强碱		H+, H2O
苄醚 (OBn)		醇 (OH 一般而言)	几乎任何事物	NaH, BnBr	H2, Pd/C, 或 HBr
甲醚 (ArOMe)		酚 (ArOH)	碱	NaH, MeI, 或 (MeO)2SO2	BBr3, HBr, HI, Me3Sil
叔丁酯 (CO2t-Bu)		羧酸	亲核试剂	异丁烯, H+	强酸
Cbz (Z) (OCOBn)		胺	亲电试剂	BnOCOCl, 碱	HBr, AcOH; 或 H2, Pd
t-Boc (OCOt-Bu)		胺	亲电试剂	(t-BuOCO)2O, 碱	H+, H2O
Fmoc		胺	亲电试剂	Fmoc-Cl	碱, e.g. 胺

化学选择性的氧化和还原方法，和帮助控制化学选择性而使用的保护基，会在本书中不断地出现，而对于肽和它们在生物上的功能，我们将会在 Chapter 42 中更详细地讨论。那以前，我们还会详细考察立体选择性 (在 Chapters 32, 33, 和 41)，而离我们最近的一章则在讨论选择性的另一方面——区域选择性。

## 延伸阅读

基础的介绍: S. Warren and P. Wyatt, *Organic Synthesis: the Disconnection Approach*, Wiley, Chichester, 2008, chapter 5.

*Molecular Orbitals and Organic Chemical Reactions: Student Edition* by Ian Fleming, Wiley, Chichester, 2009 on pentadienyl anions, pp. 126–128.

Birch 还原: P. W. Rabideau, and Z. Marcinow, *Org. React.* 1992, 42, 1. Lindlar 还原: H. Lindlar and R. Dubuis, *Org. Synth. Coll.* 1973, vol 5, 880.

肽合成: N. L. Benoiton, *Chemistry of Peptide Synthesis*, Taylor and Francis, 2005. J. Jones, *Amino Acid and Peptide Synthesis*, Oxford Primer, 2nd edn, OUP, Oxford, 2002.

保护基: 基础介绍, Jeremy Robertson, *Protecting Group Chemistry*, Oxford Primer, Oxford, OUP, 2000. 更多进阶书籍: P. J. Kocienski, *Protecting Groups*, 3rd edn, Thieme, 2003. P. G. M. Wuts and T. Greene, *Greene's Protecting Groups in Organic Synthesis*, Wiley, 2007. 一个不同的视角: T. Newhouse, P. S. Baran, and R. W. Hoffmann, *The Economies of Synthesis*, *Chem. Soc. Rev.* 2009, 38, 3010.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 24 区域选择性

## 联系

### 基础

- 化学选择性 ch23
- 芳香亲电取代 ch21
- 对烯烃的(亲电)加成 ch19
- 在饱和 C 上的取代反应 ch15
- 亲电的烯烃和芳香亲核取代 ch22

### 目标

- 由机理决定的新的一类选择性
- 试剂和底物都很重要
- 控制芳香取代基的重排
- 如何得到 邻位选择性：邻位锂化和磺酰化占位
- 自由基与离子型反应
- 烯丙基化合物的反应
- 回顾共轭加成

### 展望

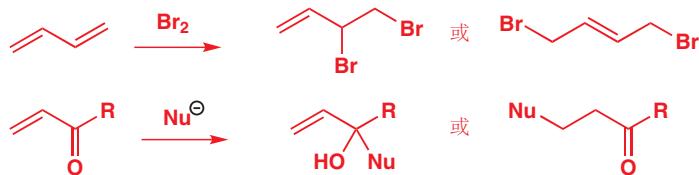
- 立体选择性 ch32–ch33
- 烯醇和烯醇盐的反应 ch25 & ch26
- 杂环的反应与合成 ch29 & ch30
- 自由基反应 ch37

## 引入

我们在上一章研究了化学选择性——哪个基团参与反应。化学选择性意味着，分子中存在两个独立的官能团，试剂必须从它们中做选择。与之相比，区域选择性 (regioselectivity) 则表明，分子中存在一个可在不同位点反应的官能团，试剂必须选择在哪里反应。简单的例子包括 HX 对烯烃的加成 (Chapter 19) 和对环氧的亲核进攻 (Chapter 15)。



区域选择性也讨论：两个官能团被结合为一个单一的共轭体系时，引发的两种（或多种）反应位点的问题。例如溴对双烯/二烯（两个烯烃共轭）的加成，和亲核试剂对不饱和羧基化合物（羧基与烯烃共轭）的加成。



对苯环亲电进攻时，邻对位还是间位取代的选择（Chapter 21）也是区域选择性研究的问题。我们将在本章中详细地讨论全部这些内容，并将研究思路拓展到更多新的反应上。

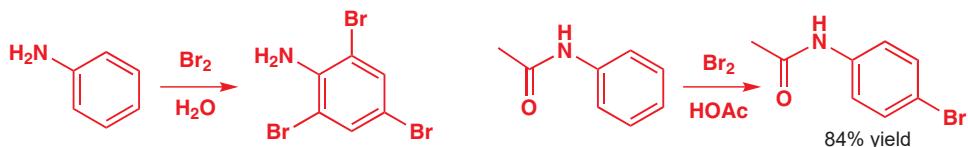


## 芳香亲电取代中的区域选择性

我们将由芳香亲电取代开始。在 Chapter 21 中我们提出了这个观点：给电子取代基有利于邻对位，而吸电子取代基有利于间位。并且，虽然间位取代的速率通常要慢于邻对位取代（因为吸电子基团同时也钝化苯环），它仍通常单一地给出间位产物。



大多数带有给电子取代基的苯环会给出邻对位产物的混合物；如果取代基非常给电子，那么还可能导致同一分子既在邻位，又在对位取代。使对位产物有利的控制，通常是通过减弱定位基的活性，并增大它的大小来完成的。



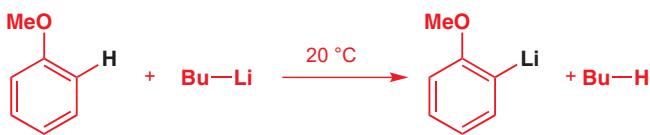
当然，如果对位被阻挡，那么邻位就是唯一的选项，这是我们稍后会回来考察的占位基（blocking substituents）的内容。但首先我们将考虑通过金属化对邻位的活化，这是将亲电试剂定位在邻位的一种一般方法。



▶ 这些例子都取自 Chapter 21.

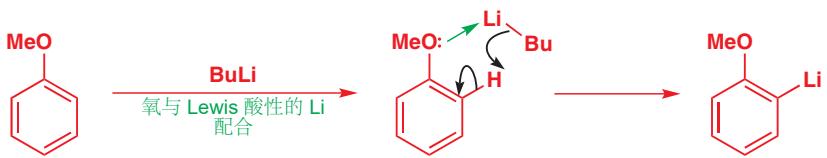
## 芳环去质子得到有机金属：邻位锂化

看向下面的反应：丁基锂给一个  $sp^2$  杂化碳原子去质子，给出一个芳基锂。这个反应能够发生，是由于  $sp^2$  碳上的质子比  $sp^3$  碳上的质子酸性更强（它们都比炔烃质子的酸性弱）。

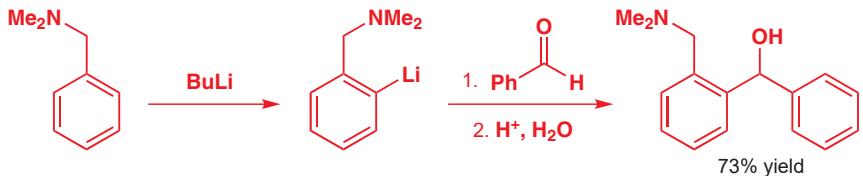


但仍需要另一个因素来解释这种专有的邻位取代，因为邻位是所有位点中空阻最大的一个。包含氧（有时还会是氮）的官能团与被移去的质子相邻；正是这个官能团“指引了”丁基锂，使其进攻邻位的质子。这一过程是通过与 Lewis 酸性锂原子形成配合物完成的，这种配合物与乙醚通过与格

氏试剂中的 Lewis 酸性金属离子配合，使之溶解的道理相似。这种机理意味着，仅有与官能团处于邻位的质子可以被移去，这个反应被称作是邻位锂化 (ortholithiation)。



下面是一个通过叔胺上的氮原子活化而完成的邻位锂化反应，用于形成新的 C-C 键。此处是氮原子定位了丁基锂的进攻，同样是通过与 Li 原子形成配合物。

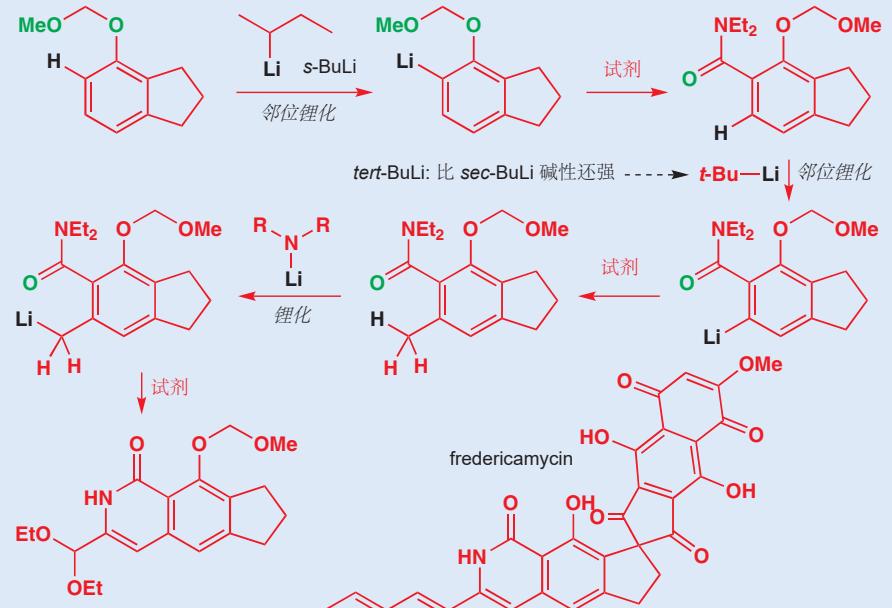


■ 与您在 Chapter 9 学过的制备有机锂、格氏试剂的方法对比——那些方法中有机金属的形成大多依赖于烷基卤或芳基卤的还原。

邻位锂化反应是一种制备活泼的有机锂试剂的实用方法，因为起始物并不需要包含一个卤原子。但它们远不及我们之前告诉过您的制备有机锂的方法通用，因为它们对于芳环上携有哪类基团有十分严格的限制。最好的邻位锂化定位基包含用于向 Li 给电子的孤对电子，并且也应是负电性的，这样才可从苯环吸电子，并帮助稳定在邻位形成的阴离子。

### Fredericamycin

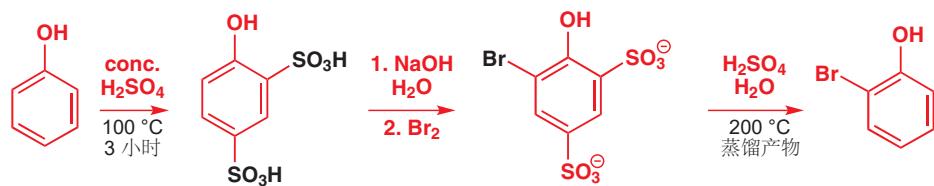
Fredericamycin 是于 1981 年从土壤细菌灰色链霉菌 (*Streptomyces griseus*) 中提取的一种古怪的芳香化合物。它是一种强大的抗生素和抗肿瘤剂。它的首次实验室合成，于 1988 年由波士顿化学家完成，合成开始于三次相继进行的锂化反应：两次是邻位锂化，第三次稍有不同。您不需要考虑与有机锂反应的试剂，仅仅考察锂化反应本身就可以了。每一次锂化反应中，都以一个或多个氧原子（绿色）定位强碱性试剂来移去邻近的质子（黑色）。它们都没有用 *n*-BuLi 本身，而是用了它更活泼的兄弟，仲丁基锂/*sec*-BuLi 和 叔丁基锂/*tert*-BuLi (见 p. 186 的表格)。第三次锂化选用了另一种不同的，与 LDA 类似的碱，通过一种胺 ( $pK_a$  大约 35) 的去质子得到。黑色质子与芳环相连，酸性较强，在第三次锂化中失去。



## 磺化可用于邻位取代

我们在 Chapter 21 中介绍了磺化 (sulfonation) 反应，但并非徒有其表，磺化反应有一些我们没有讨论过的特征使其变得很有趣。它与其他亲电取代例子的一个重要的区别在于，磺化反应是可逆的。加热芳香磺酸可以使之分解，释放气态的  $\text{SO}_3$ 。

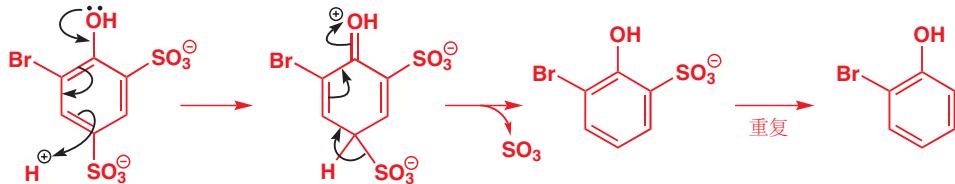
下面是一个例子，我们可以利用这一特点，在不诉诸于锂化的情况下得到对区域选择性的控制。第 1 阶段，苯酚被磺化两次——第一个磺酸基(在 OH 的对位)是吸电子的，会钝化苯环，使第二个磺酸基(OH 的邻位，同时是磺酸基的间位)的引入更难，第三个磺酸基还要更难，这就是为什么我们能分离出二磺化的苯酚。



### 磺化试剂

磺化反应中，亲电试剂的确切属性似乎随水的量变化而变化。无疑，对于发烟硫酸 (oleum, 浓硫酸中加入三氧化硫)，和三氧化硫的有机溶剂溶液，亲电试剂是三氧化硫， $\text{SO}_3$  本身。而有水环绕时，则有表明或许是  $\text{H}_3\text{SO}_4^+$  和  $\text{H}_2\text{S}_2\text{O}_7^-$ 。

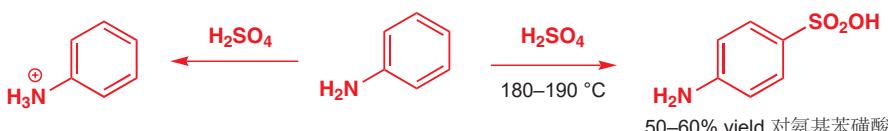
第二阶段为溴代，OH 基使之定位于邻位和对位，但溴仅能进攻唯一一个未被占据的邻位。需要使用氢氧化钠使磺酸基去质子，减弱其钝化作用。磺化反应是可逆的，而第三阶段可以通过在高温下蒸馏出相对挥发性的 2-溴苯酚以驱动反应进行。 $\text{SO}_3$  的失去包含  $\text{H}^+$  对芳环的进攻。



■ 根据我们在 p. 248 对于熵和温度的讨论，您或许能理解磺化在高温下可逆的原因。

纵观全过程，我们成功地制取了 2-溴苯酚，而苯酚本身直接溴化(在低温下)则主要会给出对溴苯酚，在较高温下溴化则会给出 2,4,6-三溴苯酚。磺酸基是一个很实用的可逆的占位基。

由于芳香胺也可进行对位磺化，相同的方法也可以用于苯胺。这或许是您没料到的，因为基本所有的胺都会在硫酸中被质子化，因而变为间位定位的铵基 ( $\text{NH}_3^+$  不再是富电子的)；不过事实上，仍然生成了对磺酸(对氨基苯磺酸 sulfanilic acid)。在高温下完成这个反应时，可能，任何间位取代的产物都重新转化回了起始原料，而对磺酸则因此积累，因为它通过离域而稳定，并且空阻也更小。



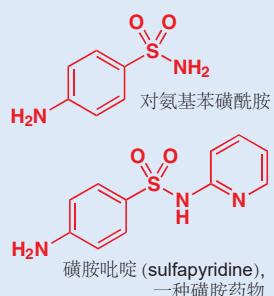
## 萘的区域选择性反应

我们在 Chapter 7 中向您介绍了萘的 10-电子芳环。如您所料，它们也可以与您在 Chapter 21 中遇到的试剂经历芳香亲电取代反应，但它的反应的选择性却与苯的“邻、间、对位”不同。萘含

■ 磺化反应的可逆性也许是甲苯与  $\text{H}_2\text{SO}_4$  的磺化反应，与其与  $\text{ClSO}_2\text{OH}$  的氯磺化反应相比，对位选择性更高的原因 (p. 485)。

### 磺胺类药物

所得的产物是重要的，它衍生的酰胺(对氨基苯磺酰胺)是首个抗生素，也是磺胺类 (sulfa) 药物之一。



在 Chapter 7 中，我们指出，中间的键比其余的几根端，也正是因为，我们建议您将萘中间的键画作双键——这使机理更为真实。

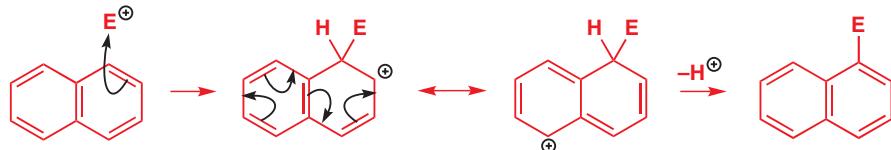


未活化的环，例如苯，溴代时需要 Lewis 酸催化：见 p. 474.

考察这两种离域阴离子的区别另一种方式是：使第一种阳离子挨着双键，并不需要破坏剩下的芳环；而在第二种中，若想得到阳离子进入共轭体系的共振式，则需要失去另一个芳环。

有 10 个碳原子：其中两个形成环的公共边，并不能发生取代反应；而另八个则分为两类，一类为  $\alpha$  (1-位，与公共边相邻) 和  $\beta$  (2-位置)。

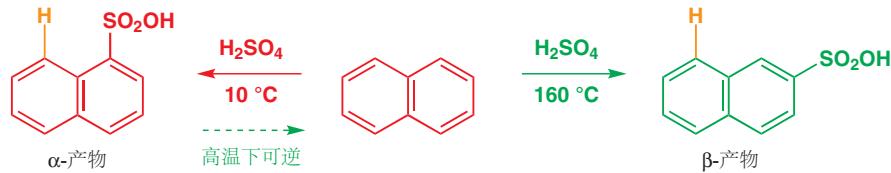
萘上的亲电取代一般发生在与公共边相邻的位点 ( $\alpha$ ) 上。这是因为，HOMO 在此处有最大的轨道系数，您可以通过一串相连的箭头将其表示/共振为一个长的、线性离域结构。长共轭体系对阳离子的稳定化作用也使萘比苯更亲核。因此，即使没有 Lewis 酸的催化，溴代也能在  $\alpha$ -位上以很好的产率发生。



在另一类位点的反应 ( $\beta$ ) 较不利，因为中间体阳离子是交叉共轭的。即阳离子虽然能在两个环上离域，但不能画出长串彼此相联的箭头的共振。

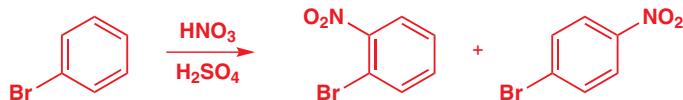


如果反应是不可逆的，则通常形成  $\alpha$ -产物。但如果反应是可逆的，比如碘化反应中，取代为点则或许会由温度决定。低温下的碘化反应通过动力学控制给出  $\alpha$ -产物，而高温下的碘化反应则通过热力学控制给出  $\beta$ -产物。 $\beta$ -产物形成得更慢，但却是更稳定的，因为其中大的磺酸基与另一个环上橘色的氢之间空阻更小。在碘化反应可逆的条件下，最终全部产物都会终止于  $\beta$ 。

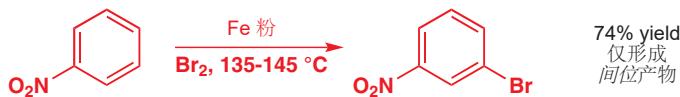


### 通过路线选择完成的区域控制

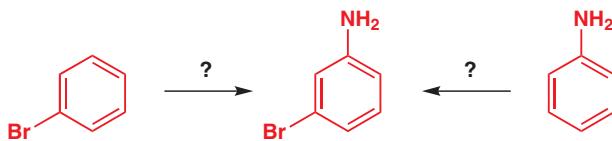
如果您想得到芳环的一种特定的异构体，那么选择合适的路径是最基本的。我们可以用溴代硝基苯的一种异构体的合成为例说明这个问题。由于溴取代基是邻对位定位基，而硝基是间位定位基，因而如果我们利用好亲电取代的区域选择性，制备全部的三种异构体都是可能的。溴代苯的硝化会给出邻对位异构体，而硝基苯的溴代则会给出间位异构体。第一个反应的选择性不是太好：溴很小，负电性并不显著，因此空阻的影响是很小的，邻位并不会被钝化。再者，邻位有两个，而对位只有一个：因此一贯会给出大约 37% 邻位，1% 间位，和 62% 对位产物。这些化合物都是工业产品，通过硝化后的分离得到。



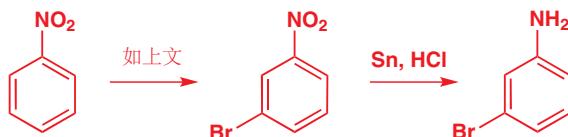
考虑到硝基苯在芳香亲电取代反应中的不活泼性，它的溴代会进行得很好。一种配方是使用铁粉和溴在 140 °C 下反应，会给出 74% 的间位产物。我们将在下一节中需要这种反应。



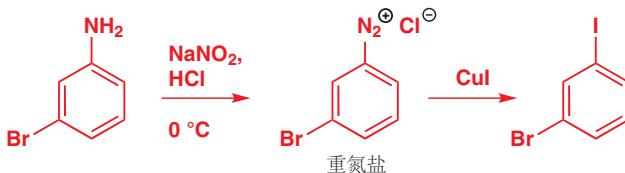
在我们继续前进之前，请思考这种选择性得以工作的原因：由于分子中既有邻对位定位基，又有间位定位基，因此我们可以得到全部的三种异构体。但如果两种取代基都是邻对位定位基——比如氨基和溴——并且我们想得到间位异构体，该怎么办？



上述情境的解决方案，是使用通过还原，由硝基(间位定位基)到氨基(对位定位基)的转化。



由于氨基可以再通过重氮化被取代 (p. 520)，很多其他区域选择性的问题也可以通过用硝基化合物做中间体而解决。例如，您可以用上文的产物，制备如果用其他方法就会很有挑战性的 3-溴代碘苯：

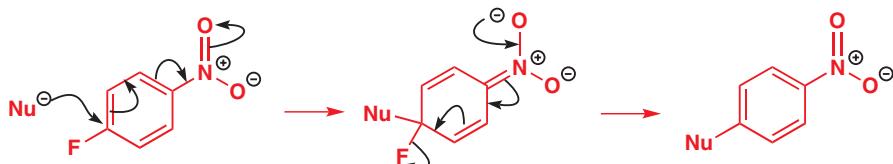


► 重氮盐和它们在芳香化合物合成上的应用，我们在 pp. 495 和 520 讨论过。

## 芳香亲核取代中的区域选择性

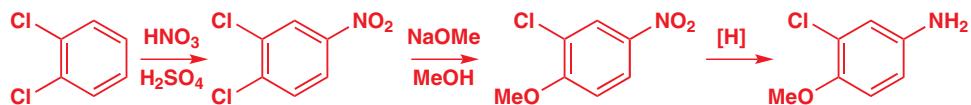
如您在 Chapters 21 和 22 中所学，重氮盐不需要活化即可发生芳香亲核取代反应，但对于其他基团，一般则需要用硝基作为活化基。三种氟代硝基苯都是商业化产品，但只有邻位和对位异构体可以发生亲核取代反应。这使因为，硝基必须能够通过接受负电荷，来稳定加成中间体。

► pp. 514–526 描述了发生芳香亲核取代反应的多种方式。

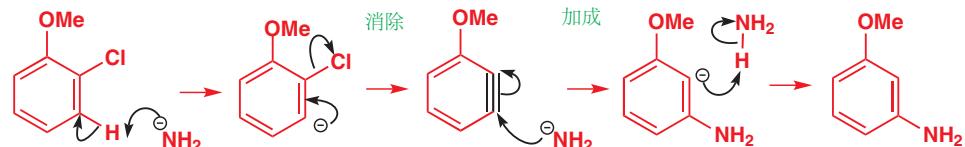


通过亲电取代与亲核取代的仔细结合，能够让我们以精确而可预测的方式，制取芳香化合物。因此，如果我们硝化邻二氯苯，所有的位置都是可能的，但硝基进入的是其中一个 Cl 原子的对位，这是由邻位的空阻导致的。虽然氯很小，但两个相邻的氯之间存在：能将它们与彼此推开的 **buttermessing effect**。在苯环上得到三个相邻的取代基是很难得。现在，再进行芳香亲核取代反应，则只有

硝基对位的 Cl 被取代。我们还可以将硝基还原为对应的胺。

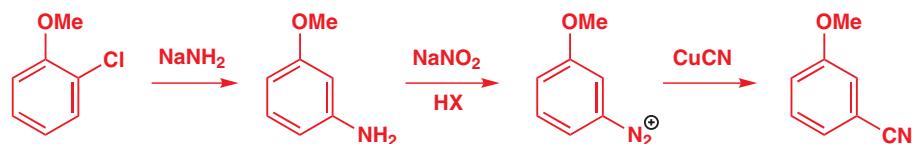


最后一种芳香亲核取代反应的成功方法使用苯炔作为中间体——在 p. 524 中您学习了用苯炔化学制备间氨基苯甲醚的反应，如下所示：



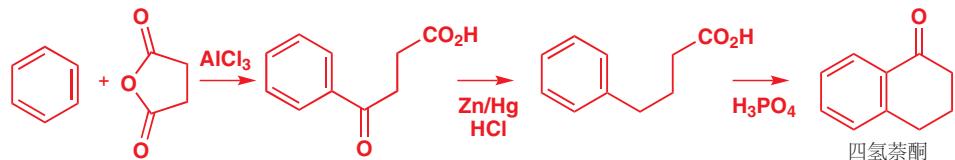
► 这个反应的区域选择性已在 Chapter 22 中阐述过。

于是我们装上了一个氨基；我们可以通过重氮盐将其转化为任何亲核试剂——以氰化亚铜为例：



### 分子内反应的区域选择性

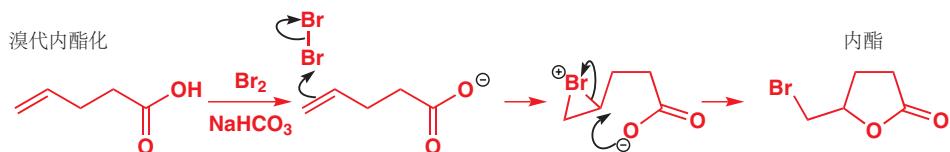
一个狡猾的，得到反常区域选择性的方法是使反应在分子内进行。由苯合成一种被称为四氢萘酮 (tetralone) 的方法也许看起来很困难，因为我们我们必须在苯环上得到邻位关系。但如果我们将 Friedel–Crafts 酰基化反应完成环最后一根键的形成，则没有任何问题。烷基是邻对位定位的，而在 (分子内反应中) 羧基无法到达对位。



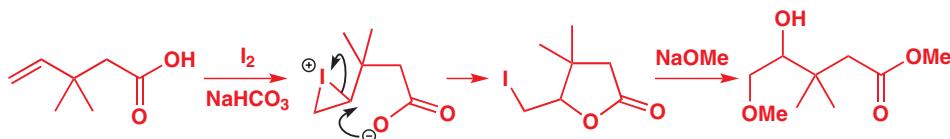
■ 通常需要更强的催化剂 ( $\text{AlCl}_3$ )，但分子内的酰基化不需要它也可以足够快速地进行。

注意第一种 Friedel–Crafts 酰基化反应中环状酸酐的用途。酰化在何处发生并不重要，而由于酮的钝化作用，以及反应中释放的羧基远远没有酸酐亲电，这个反应在酰化后就会停止。随后酮可通过 Clemmensen 方法被还原为  $\text{CH}_2$  基 (见 Chapter 23)，分子内酰基化步骤用多聚磷酸引发。

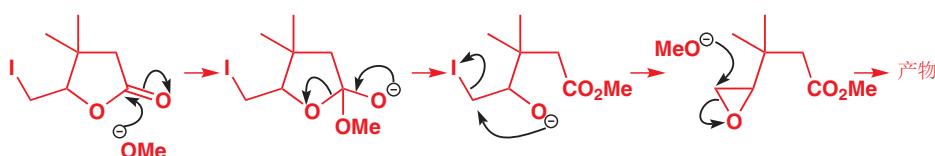
一个更微妙的方法是用一个“拴绳”——先将两种试剂结合在一起，然后再断裂的方法。其中一个例子是卤代内酯化 (halolactonization)。这种思路很简单。卤素，比如溴可以进攻烯烃，所得的溴𬭩离子可以被羧酸阴离子在分子内捕获。这个反应因此选用溴单质和  $\text{NaHCO}_3$ ——一种足够给羧酸去质子的弱碱。如 Chapter 19 中阐释的一致，阴离子进攻溴𬭩离子较多取代的一侧，并形成五元环。



虽然任何卤素也许都可用于这个反应，但其中碘是最万能的，它的反应通常被称作碘代内酯化。所谓的拴绳，是内酯的 C–O 键，可以与烷氧基阴离子反应而断裂。

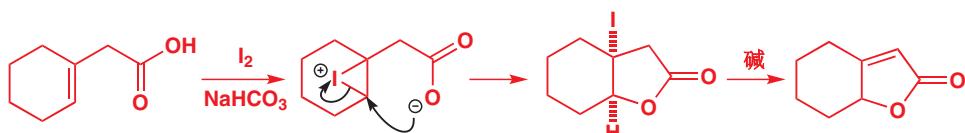


烷氧基阴离子的反应需要一些解释。进攻羰基，断裂内酯，释放一个烷氧基阴离子来形成环氧。第二分子的甲氧基阴离子现在，从较少空阻的一端进攻，使环氧开环（阴离子使环氧开环的选择性，Chapter 19）。



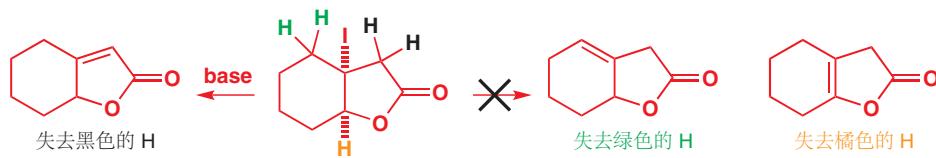
下一个例子中，羧酸阴离子进攻的位点是碘𬭩离子的另一端。进攻叔碳的空阻较大，并且无论如何会给出一个不稳定的四元环。形成的内酯包含在羰基  $\beta$  位的碘原子，因此可以在碱中（吡啶就很有效）通过 E1cB 机理 (Chapter 17) 容易地消除，并给出不饱和内酯。虽然碘代内酯的相对立体化学（非对映构型）由碘𬭩离子开环时的翻转控制，但由于立体化学在消除步骤中消失，它便是无关紧要的了。

我们在 Chapter 32 中利用碘代内酯化来控制立体化学。

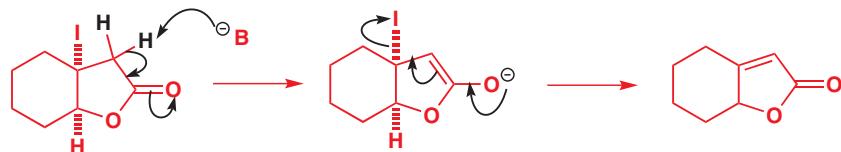


### 消除反应中的区域选择性

这个问题已在 Chapter 17 中讨论过，但在这里我们可以讨论一些更复杂的例子。上一个反应的区域选择性决定了产物中烯烃的位置。所有与碘相连的质子中，只有黑色的一个会被移去：



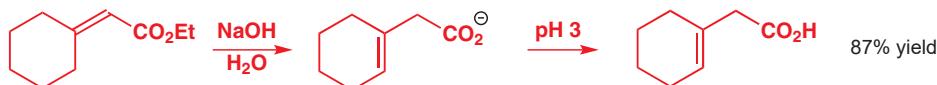
橘色的氢不能通过 E2 移去，因为它与碘处于 cis，而 E2 反应较喜欢的是 trans (反叠式/反式共平面排列)。绿色的氢不被移去，是由于它们比黑色的氢酸性弱。事实上这不是一个 E2 消除，因为黑色氢可以通过烯醇盐的消除而消除，即 E1cB 机理。



但现在却引发了另一个区域选择性的问题：如果消除反应更喜欢在羰基旁边发生，那么碘代内酯化流程的起始原料，即一个不与羧酸共轭的烯烃是如何得到的呢？首先，不符合如上区域选择性的酯可以很容易地用磷酸酯通过 Horner–Wadsworth–Emmons 反应制得。这种 Wittig-方式 的反应已在 Chapter 27 中阐释过。



现在来到了引人注目的区域选择性这里。酯照例在  $\text{NaOH}$  中被水解。酸化至  $\text{pH } 3$ ，游离羧基被释放，双键移入环中。



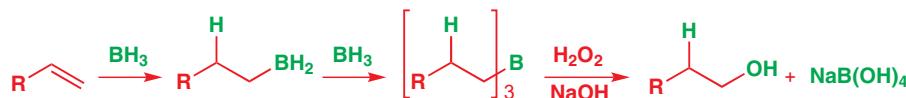
烯烃喜欢羰基共轭；但同样，相较于在环外，它们也喜欢处于六元环内——这个例子中，很有可能是因为除此之外的其他情况，酯基必会与环上的一个碳处于重叠式。与酯基的共轭，会将烯烃从环中拉出（如上一页中的内酯）；但如果是羧基阴离子，则共轭很弱，双键会移入环中。

## 烯烃上的亲电进攻

您在 Chapter 19 中遇到了烯烃上的亲电进攻，我们会简要地回顾它的区域选择性。不对称烯烃与  $\text{HBr}$  的反应，给出两种可能的阳离子中更稳定的一个。如果  $\text{R}$  是烷基或芳基，则指较多取代的阳离子。



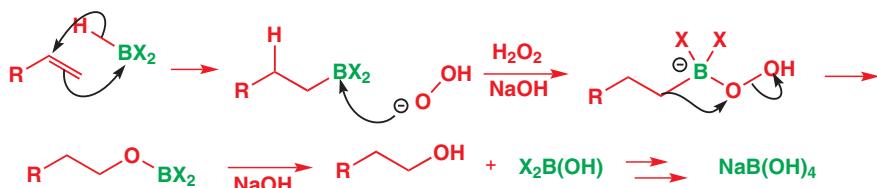
如果您想得到另一种区域异构体，杂原子处在端位，那么您可以使用硼氢化（Chapter 19）或下一节将描述的自由基反应。下面是一个对硼氢化反应的简短回顾。带有至少一根  $\text{B}-\text{H}$  键的硼烷与烯烃反应，给出全部氢原子被烷基取代的烷基硼烷。后续进行的氧化反应将其转化为目标醇。



区域选择性来源于第一步。硼的空  $\text{p}$  轨道与烯烃较亲核的一端成键，氢负转移以得到硼烷。与含碱的  $\text{H}_2\text{O}_2$  反应，导致硼上一个烷基迁移到氧上，以最终转化为醇。

■ 结构中的  $\text{X}$  可以是  $\text{R}$  或  $\text{H}$ 。

Interactive mechanism for hydroboration



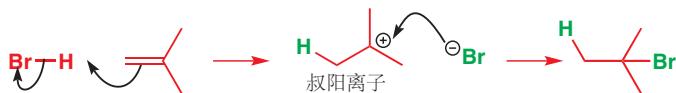
硼烷通常不稳定，但可以很容易地通过  $\text{NaBH}_4$  和  $\text{BF}_3 \cdot \text{OEt}_2$  制备。在由 1-己烯 合成 1-己醇 的过程中，一个水分子被加成到了烯烃上，但与其与酸中的  $\text{H}_2\text{O}$  或  $\text{HBr}$  反应的区域选择性恰恰相反。



## 自由基反应中的区域选择性

到目前为止，我们讨论过的反应大概都是离子型的，但在本短节中，我们需要对我们将在 Chapter 37 中考察的另一类反应给出预告——即自由基 (*radicals*) 的反应。当  $\text{HBr}$  加成到烯烃上时，我们可用箭头表示两个电子的移动，随之形成的两个带电荷的中间体，会在第二步中结合为中性产物。强  $\text{H}-\text{Br}$  键断裂给出一个溴离子和一个稳定的烷基阳离子。这个键发生的是异裂 (*heterolytically adv.*, *heterolysis n.*, *heterolytic adj.*, *heterolyze v.*)——即(电子对)不对称地断裂——烯键同样为异裂。我们可以通过找出最稳定的阴离子、阳离子来预测这些反应的区域选择性，在这个例子中它们是叔烷基阳离子和溴阴离子。

您会在 Chapter 37 中更详细地了解自由基。

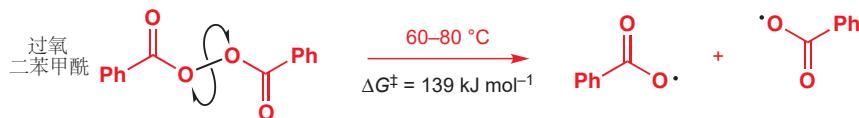


## 自由基加成

如下反应的区域选择性是与之相反的：通过一种自由基参与的不同种机理，形成了一个烷基溴。



在自由基反应中，键发生均裂 (*homolytically adv.*, *homolysis n.*)，一个电子朝一个方向走，另一个电子则朝向另一个方向。所生成的自由基包含奇数个电子，其中一个必然是未成对的。这使它们很活泼，通常不经分离。即使是强键，它们如果是极化的也可以断裂为离子；但自由基的制取则需要弱而对称的键，例如  $\text{O}-\text{O}$ ,  $\text{Br}-\text{Br}$  或  $\text{I}-\text{I}$ 。过氧(二)苯甲酰 (Dibenzoyl peroxide)，这个反应中的  $\text{Ph}(\text{CO}_2)_2$  催化剂，可以轻而易举地像下面这样均裂——单电子移动用“鱼钩”箭头表示，奇数电子用点表示。



现在，我们可用我们刚刚获得的自由基来均裂  $\text{HBr}$  键，这个过程会形成非常亲的  $\text{OH}$  键，因此能够进行。如图开始反应所用的含有一个未成对电子的自由基中间体一样，我们应当以另一个带一个未成对电子的自由基的形成结束反应。此情境中，则为一个溴自由基。



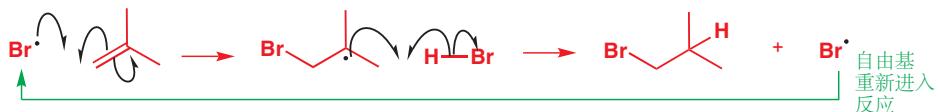
如果我们在刚刚与  $\text{HBr}$  反应所用的的烯烃的存在下做这个反应，溴自由基则会以两种可能的方式

加成到烯烃上。虽然自由基是中性的，但它们是缺电子的 (C 原子缺少一个电子)，并且与阳离子非常像，连有的取代基越多越稳定。因此形成叔自由基而非伯自由基，溴于是就处在伯位置上了。



现在的产物仍是一个自由基，我们的反应也仍然没有结束。它如何变为只有成对电子的分子呢？答案很简单。它会与另一分子的 HBr 反应，并产出更多的溴自由基。现在您已了解到了自由基反应中的某个重要内容：所需的仅是很少量的自由基，更多的自由基又反应在每时每刻，伴随着产物的形成而产出。整个过程是一个自由基链(式)反应 (radical chain reaction)。

Interactive mechanism for radical addition of HBr to alkenes



由于这一点，我们也只需要非常少量的过氧化二苯甲酰，自由基引发剂 (radical initiator)，像很多自由基生成剂一样，它也有潜在的爆炸性。下面是用于制备溴代酸的反应：



### 自由基夺取反应



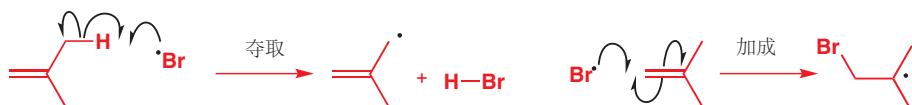
我们在那个序列中偷偷加入了一个新的飞跃。氢原子 (注意：不是质子) 被过氧自由基从 HBr 上移去的反应是一个夺取反应 (abstraction reaction)。如侧边栏所示，溴自由基从我们刚刚用过的同一种烯烃上夺取质子，但得到不同的结构。

当光照射到溴单质时，弱 Br–Br 键会断裂以给出两个溴自由基。加热也可以完成这份工作，但光照则更加干净/彻底。溴是棕色的，这说明它吸收绝大多数波长的可见光。

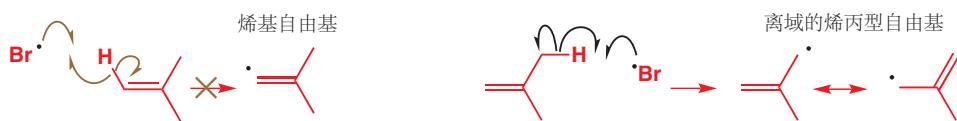
■ 注意，Br–Br 键相比过氧化物中的 O–O 键要更稳定些。



自由基都非常活泼、不稳定，这些溴自由基也许会仅仅重新结合，也许会与其他化合物反应。您已经知道，溴阴离子是 S<sub>N</sub>2 反应中好的亲核试剂，但溴自由基则发生两种很不同的反应：夺取和加成。Br 自由基可能从烯烃上夺取一个氢原子，也可能加成到 π 键上。注意每个反应都生成一个新的碳自由基，第一种情况下还得到 HBr 分子。与离子反应不同的是，自由基反应受键能主导，上述情境中 Br–Br 键弱，而 H–Br 键则强得多 (366 kJ mol<sup>-1</sup>)。

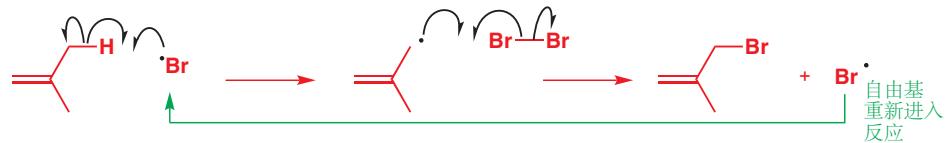


第一个反应引出了另一个重要的区域选择性方面：为什么自由基夺取这个 H 原子，而不是烯烃上的一个？



若移去烯烃 H，则会给出一个定域在  $sp^2$  原子上的碳自由基；而移去甲基 H，则会给出稳定得多的离域烯丙型自由基。另外，这样的 H 原子有六个，而烯烃 H 原子仅有两个。

虽然生成了较稳定的自由基，但反应很明显不会结束于此，烯丙型自由基会从溴分子上采集一个溴原子。注意，烯丙型自由基并不与溴自由基在这一步中反应：自由基非常不稳定，每一时刻自由基的浓度都很小，很少有两个自由基能遇到彼此。

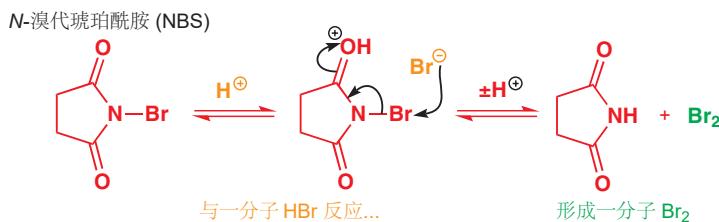


Interactive mechanism for allylic bromination

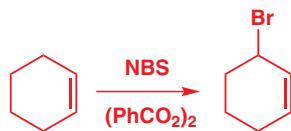
这一步同样产生了新的溴自由基，可用重新开始一系列反应。如同上文 HBr 的加成一样，这个反应是一个自由基链式反应，仅有少量的  $Br_2$  需要断裂为  $Br^\cdot$  来使反应进行。这一点很重要，因为您知道：如果加入过多的  $Br_2$ ，则会以离子型机理发生加成反应，并没有对 H 原子夺取的过程。



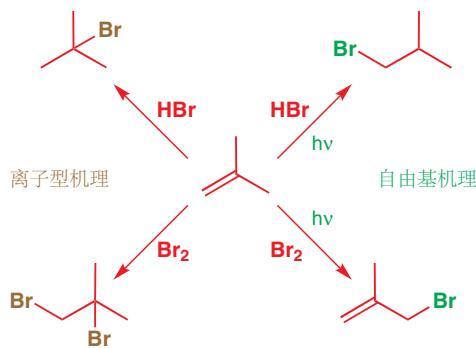
如果我们想要制取二溴代物，我们需要用大量的溴单质；但如果我们想要用自由基过程制备烯丙型溴化物，我们必须充分利用自由基的高活性，使溴单质浓度低。其中一种方法是使用您在 Chapter 19 见到的化合物 NBS (*N*-溴代琥珀酰胺)。NBS 起到了一种闸机的作用，仅当反应生成一分子 HBr 时，释放一分子  $Br_2$  (当然，HBr 是自由基溴代反应的副产物)。



$Br_2$  随着反应进行，缓慢地被释放，它的浓度永远不会累计到足以形成二溴代物。在下面的例子中，过氧化二苯甲酰是引发剂，反应为烯丙型溴代反应 (allylic bromination) 给出有用的环己烯基溴。



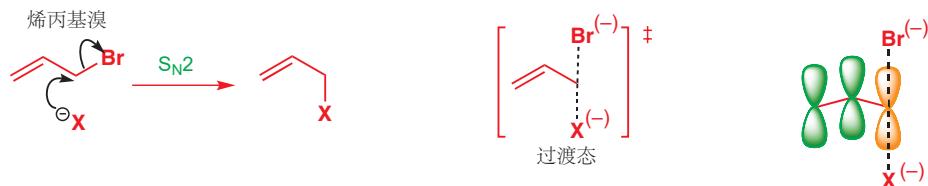
这些自由基反应将在 Chapter 37 中详细得多地描述。对于当下，您仅需要注意，用相同的试剂，它们与离子型反应可以有很不同的区域选择性。



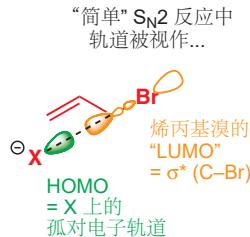
## 烯丙型化合物上的亲核进攻

可通过自由基反应制取的烯丙型化合物表现出很有趣的区域选择性。我们会从您在 Chapter 15 中熟悉的一些取代反应例子开始。那时，我们曾说过，烯丙基溴比丙基溴，或其他饱和烷基卤面对普通 S<sub>N</sub>2 反应的活性要高上 100 倍。

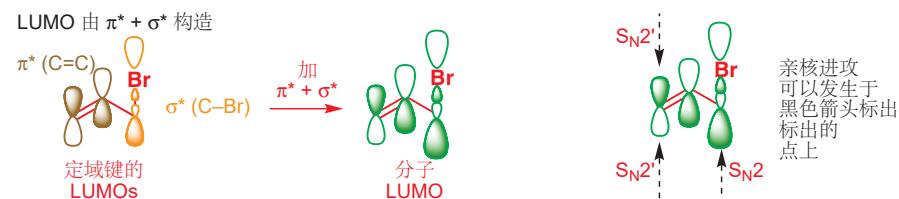
双键通过与被进攻的碳原子的 p 轨道共轭稳定了 S<sub>N</sub>2 过渡态。这个填满的 p 轨道（下图中橘色）在过渡态中与亲核试剂、离去基团同时成半键。任何对过渡态的稳定化作用，都当然会通过降低能垒，加速反应发生。



对于这个反应，有一个可替代的机理，包含对烯烃，而不是饱和碳原子的亲核进攻。这个机理会导向相同的产物，这个机理通常被叫做 S<sub>N</sub>2'（读作“S-N-two-prime S-N-二撇儿”）机理。

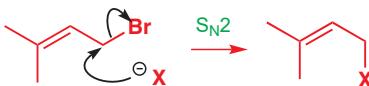


我们可以用一种统一的方式，即通过观察所涉及的前线轨道，来解释这两个反应。亲核试剂必然进攻一个空轨道（LUMO），我们可能觉得仅仅是  $\sigma^*$  (C-Br) 参与了一个简单的 S<sub>N</sub>2 反应。但这却忽略了烯烃。 $\pi^*$  (C=C) 和相邻  $\sigma^*$  (C-Br) 的相互作用会照例产生两个新的轨道，一个更高能，一个更低能。高能轨道， $\pi^* + \sigma^*$ ，会成为 LUMO。为了构造这个轨道，我们必须使所有原子轨道平行排列，并使  $\pi^* + \sigma^*$  之间的联系成为成键相互作用。



如果烯丙型卤被不对称地取代，那么就会产生一个区域选择性的问题。 $S_N2$  和  $S_{N2}'$  的产物是不同的，而一般的结果会是对烯丙型体系较小空阻一端的亲核进攻，无论这意味着  $S_N2$  还是  $S_{N2}'$ 。这种重要的烯丙型溴，被称作异戊烯基(prenyl)溴，通常完全通过  $S_N2$  反应。

异戊烯基溴像这样反应

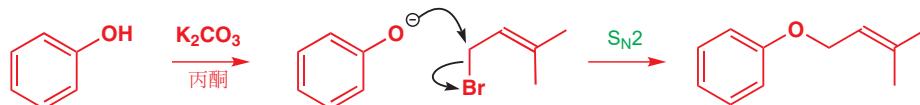


而不像这样



烯丙型体系的两端从空间对比：直接( $S_N2$ )进攻发生于一个伯碳上，而烯丙型( $S_{N2}'$ )进攻发生在一个叔碳上，因此空阻有利于 $S_N2$ 反应。另外，烯烃产物上取代基的数量也意味着 $S_N2$ 产物几乎往往是所偏好的—— $S_N2$ 给出一个三取代的烯烃，而 $S_{N2}'$ 产物则含有较不稳定的单取代烯烃。

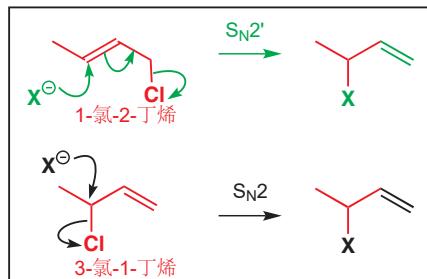
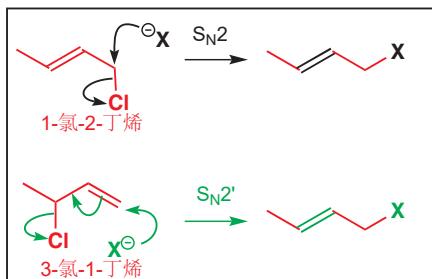
一个重要的例子是异戊烯基溴与苯酚的反应。这个反应可以简单地在丙酮中的 $K_2CO_3$ 下发生，因为苯酚的酸性足够( $pK_a \sim 10$ )被碳酸根大体上地去质子。产物几乎完全由 $S_N2$ 路径形成，产物被用于Claisen重排(Chapter 35)。



如果我们让烯丙基体系的两端更相似，比如一端是伯，一端是仲，那么情况会近乎相等。我们可以考虑丁烯基氯的两种异构体的反应。

目前为止，我们用“烯丙基(allyl)”描述了这些化合物。严格意义上这个词特指除氢外没有任何取代基的化合物 $CH_2=CH-CH_2X$ 。但它也经常被宽松地用于描述在烯烃旁边的碳原子上连有官能团(基本基团)的化合物。我们将用“烯丙型(allylic)”替代如上所述的这种功用，而“烯丙基(allyl)”则仅指未取代版本。

Interactive mechanisms for various nucleophilic substitutions

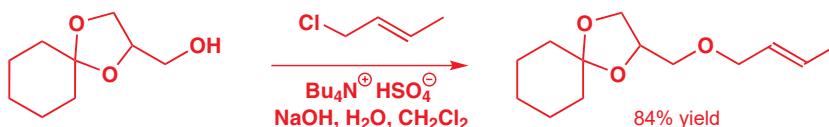


所有路径看起来都是合理的，并且我们会认为在伯碳上进攻得快。左侧框中的反应比右侧框中的更有利。而对于 $S_N2$ 还是 $S_{N2}'$ 机理，并没有特别的偏好——取决于具体情况(空阻)。如果我们使仲丁烯基氯与胺反应，则会完全地得到 $S_{N2}'$ 机理。



如果选用的是伯氯，那么同样，亲核试剂进攻在伯中心上。这次则通过 $S_N2$ 反应，形成带有更多取代的烯烃的更稳定的产物。下面是一个稍微更高级的例子：

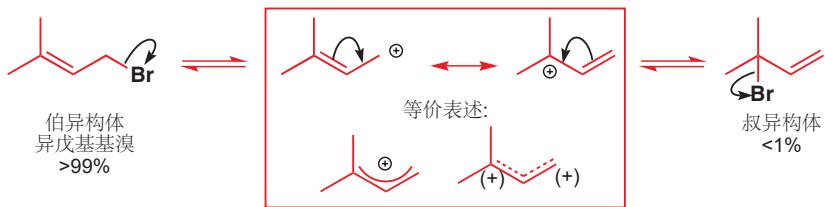
Interactive mechanism for  $S_{N2}'$  nucleophilic substitutions



我们在 p. 341 中解释了相邻双键协助 S<sub>N</sub>2 反应的原因。

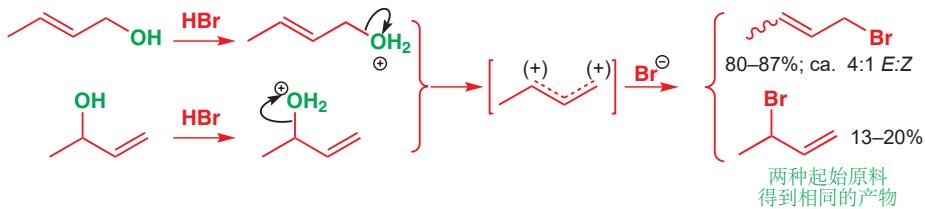
注意，这些反应都发生于烯丙型氯代物上。通常，我们不应当期待一个烷基氯能发生尤其好的 S<sub>N</sub>2 反应，因为氯离子仅仅是一个适中的离去基团；相反，我们应当倾向于选用烷基溴或烷基碘。但烯丙型氯化物却因为烯烃的存在而较活泼。即使是通过简单的 S<sub>N</sub>2 机理，不含重排地发生反应，烯烃也能使分子更加亲电。

您可能会问出一个很好的问题。我们如何知道这些反应，真的以 S<sub>N</sub>2 或 S<sub>N</sub>2' 机理发生，而不是通过稳定的烯丙基阳离子发生 S<sub>N</sub>1 机理的呢？事实上，对于异戊烯基溴的反应，我们不知道！我们怀疑阳离子可能确实作为了反应中间体，因为异戊烯基溴在室温下的溶液中，和其叔烯丙型异构体处在快速的平衡中。

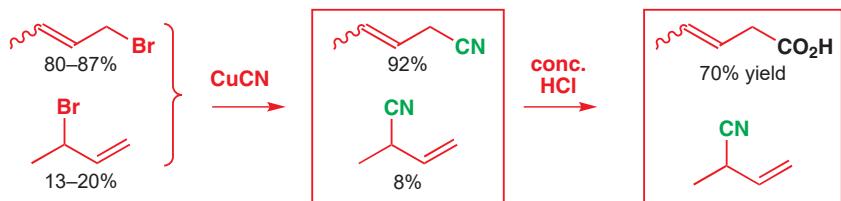


平衡完全偏向于异戊基溴，这是因为其更多取代的双键所致的。在叔烯丙型异构体上的反应，十分倾向于以 S<sub>N</sub>1 机理发生：中间体阳离子既是叔的，又是烯丙型的，平衡告诉我们它已经存在了。即使说，反应是双分子的，那叔溴也不必要通过 S<sub>N</sub>2' 机理发生，因为它通过平衡转化为伯异构体的速率要比 S<sub>N</sub>2 或 S<sub>N</sub>2' 反应发生的速率快。

当离去基团是溴时，甚至是仲体系，我们也考虑它处在快速平衡中。这个时候，两种烯丙型异构体都存在，伯烯丙型异构体（被称作巴豆基溴 crotyl bromide）是一个 E/Z 混合物。通过这两种酸中的任何一种，与 HBr 反应，得到的产物中的两种溴代物比例都是相同的，这暗示两个反应的机理都包含一种一般的中间体。您在 Chapter 15 的开头曾学到，这个反应仅限于能通过 S<sub>N</sub>1 反应的醇。



将溴换作氰离子，即用铜(I) 盐作试剂，会得到腈的混合物，其中较稳定的伯腈占主导，且主导得更明显。产物可以用一种巧妙的方式分离。占主导的伯腈可以成功地在浓 HCl 中水解，但空阻更大的仲腈则并不发生水解。分离两种带有不同官能团的化合物就很简单了：这个情境中，酸可以被碱的水溶液萃取，剩下中性的腈留在有机层中。



再一次，我们并不确信，氰离子的取代反应以 S<sub>N</sub>1 还是 S<sub>N</sub>2' 机理发生，因为试剂会在反应条件下处于平衡。然而，底物是氯代物时，并没有平衡存在，如果我们想用明确的起始原料得到明确的结

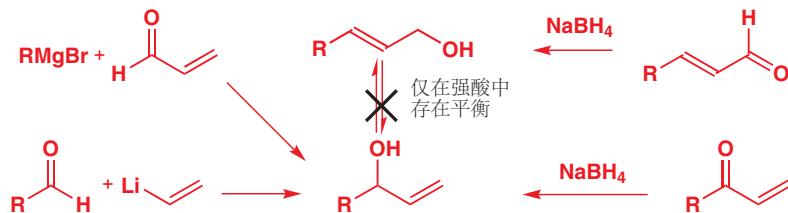
果，那么应当选用的是氯代物。但无论如何，您已看到烯丙型化合物的区域选择性，会取决于空间阻、反应速率，和产物的稳定性（烯烃取代数）。

### 烯丙型氯代物的区域专一性制备

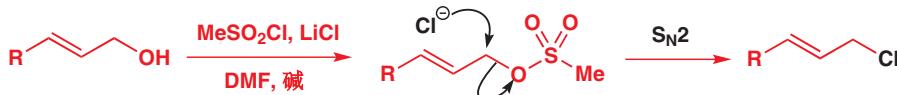
烯丙型氯代物是制备烯丙型化合物好的起始原料，它可以支配双键和离去基团将处于的位置。烯丙型醇，很容易通过格氏试剂或有机锂化合物对烯基醛或烯基酮的直接加成（Chapter 9）或烯基醛、烯基酮的还原（Chapter 23）制备。更重要的是，除非在强酸溶液中，它们并不处于平衡，因此我们预知自己将得到的烯丙型异构体。



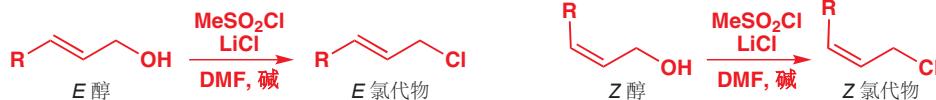
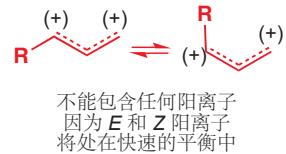
■ 类比立体专一性，我们可以定义区域专一性（*regiospecific*），用于表示产物的区域化学（即官能团的位置）完全取决于起始原料的区域化学。



将伯醇转化为氯代物比仲醇的溶液。我们需要将 OH 转化为一个离去基团，并提供一个充当亲核试剂的氯离子源。一种完成方式是使用甲磺酰氯 ( $\text{MeSO}_2\text{Cl}$ ) 和  $\text{LiCl}$ 。



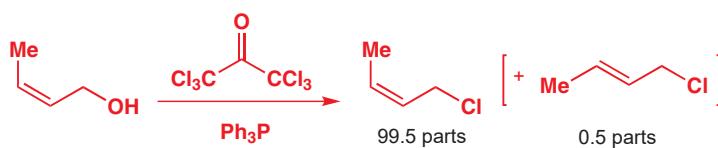
结果看上去并不值得汇报，不过，我们是怎么知道平衡，或者  $S_N1$  反应不发生的呢？嗯，这个反应必然是  $S_N2$ ，因为 *Z*-烯丙型醇反应得到的产物维持了烯烃的构型。如果存在任何形式的平衡，那么 *Z*-烯烃会变为 *E*-烯烃，因为烯丙基阳离子并不能稳定 *E*-、*Z*-几何构型。



不幸的是，这种方法并不能使仲烯丙型醇维持完好，而是会给出烯丙型氯的混合物。



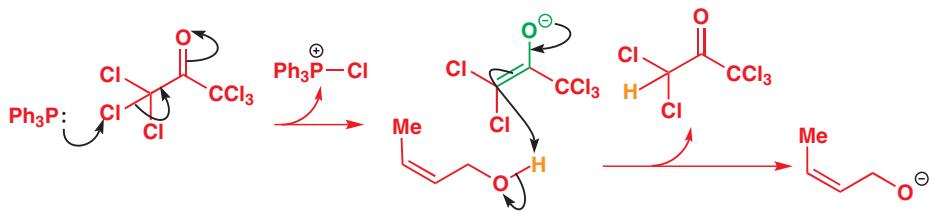
仲烯丙型醇可靠而干净的  $S_N2$  反应仅能提供 Mitsunobu 化学达到。下面是一个 *Z*-烯烃表现良好的例子。其试剂与您上一次遇到的 Mitsunobu-类反应有些许差别：没有用到 DEAD 和羧酸，而是用了六氯丙酮；当然还有三苯基膦。



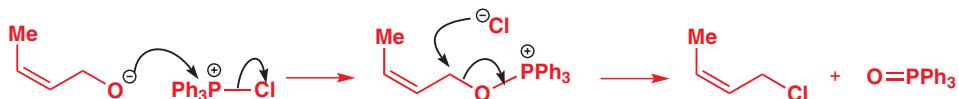
► 对 Mitsunobu 反应的讨论在 Chapter 15, p. 349. Mitsunobu 化学包含一个用于移去 OH 基的磷原子， $\text{PBr}_3$  样式的试剂用于由醇制备烷基溴。

第一件发生的事，是磷上的孤对电子进攻氯代酮中的一个氯原子。这个在氯上的  $S_N2$  反应的离去基团是一个烯丙基盐，是一个可从烯丙基醇的 OH 基上移去质子的碱性物种。

■ 磷在 C–Cl 键上发生了错误方向的取代反应吗？但 P 是软的，因此它不太在意键的极化，只是在意 C–Cl  $\sigma^*$  的能力。不管键的哪段被进攻，能力都是一样的。您可能见到  $\text{PPh}_3$  与  $\text{CBr}_4$  或  $\text{CCl}_4$  发生的相似反应：生成稳定碳阴离子。



现在，烷氧基阴离子可以进攻带正电的磷原子。这个反应由于两点原因是一个好的反应。第一，这是很明显的对电荷的中和；第二，形成非常强的 P–O 键。

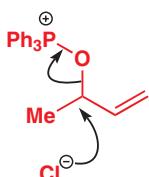


■ 在溴鎓离子和质子化的环氧的反应中有正好相反的情况——“松散的”  $S_N2$  过渡态，和显著的  $S_N1$  特点 (Chapter 17)。

下一步是一个在碳上的真正的  $S_N2$  反应，因为取代了非常好的离去基团。已经很强的 P–O 单键变成了一个更强的 P=O 双键，这可以弥补强 C–O 单键断裂的损失。这步取代反应，毫无疑问没有  $S_N1$  成分 (否则 Z-烯烃会部分地异构化为 E-烯烃)， $S_N2'$  也非常少，大约仅生成 0.5% 的重排产物。 $\text{Ph}_3\text{P}=\text{O}$  的取代反应通常是“最严格的”  $S_N2$  反应。

现在，对于最令人瞩目的结果。即使醇是仲醇，重排产物在热力学上更稳定情况下，也仅很少地形成，而大多数反应则是干净的  $S_N2$ 。

$S_N2$  比  $S_N2'$  有利



重排产物稍有点多，但这是可允许的。直接发生  $S_N2$  的产物占高比例，这表明这个取代反应对于  $S_N2$  比  $S_N2'$  真的更有利。

现在，我们知道如何制备有可预知结构的烯丙基氯了——不管是伯还是仲——现在我们需要探索的是，如何在可预知区域选择性的条件下，用亲核试剂取代氯。到目前为止，对于碳亲核试剂（除去氰离子）我们谈论的很少，因此我们将着重考察烯丙型氯代物的  $S_N2'$  反应中，简单的碳亲核试剂。

### 碳亲核试剂在烯丙型氯代物上的 $S_N2'$ 反应

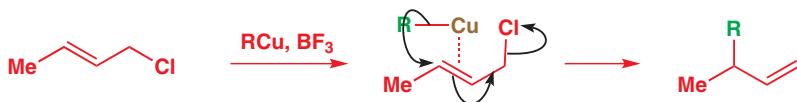
普通的碳亲核试剂，如氰离子、格氏试剂、有机锂化合物，符合我们已经描述过的反应模式。它们的反应模式是给出更稳定的产物，而究竟是  $S_N2$  还是  $S_N2'$  反应则取决于起始原料。如果我们用铜化合物，那么就会有一些倾向性产生——只是一倾向于  $S_N2'$  反应。您可能会回忆起，我们过去常常用铜(I) 来确保对烯基酮的共轭加成 (Chapter 22)，而它在  $S_N2'$  反应中的应用很明显与之相关。简单的烷基铜试剂 ( $\text{RCu}$ ，被称作 Gilman 试剂) 一般倾向于  $S_N2'$  反应，而用与  $\text{BF}_3$  结合的  $\text{RCu}$  则可做得更好。

► 金属–烯烃络合物的性质已在 Chapter 40 中讨论。



铜必然会与烯烃络合，将烷基转移至  $S_N2'$  位置，并随之与氯聚集。如下可能是其机理；通常，绘制有机金属反应的确切机理是困难的。

► 金属-烯烃络合物的性质已在 Chapter 40 中讨论。



仲烯丙基异构体也几乎完全地给出经重排的产物。这也许不太令人惊讶，因为主要产物恰恰也是较稳定的异构体。这意味着，仅仅通过选择正确的异构体（或者我们应当说是错误的异构体，因为反应过程中包含一个烯丙型重排），我们就可以以高产率得到任何产物。

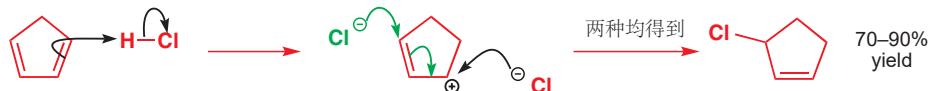


所有结果中最引人注目的一个，当属异戊烯基氯的反应，它也以好产率给出重排产物。这大约是当这个化合物能伯中心上完成  $S_N2$  反应的情况下，却在叔中心上通过  $S_N2'$  反应被进攻的唯一方法。

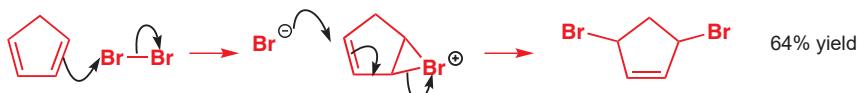


## 共轭烯烃上的亲电进攻

另一种制备烯丙型氯代物的方式，是用 HCl 处理二烯。亲电试剂对共轭二烯的进攻比对孤立烯烃的容易。Chapter 19 中有关于这个问题的讨论，所提出的主要观点是：进攻最亲核的碳原子，最初反应产生一个烯丙型阳离子。下面是 HCl 对环戊二烯加成的一个简单例子。



虽然在最初的质子化步骤中，有区域选择性的问题，但烯丙型阳离子是对称的，因此在任何一端被氯离子进攻都得到相同的产物。然而，如果亲电试剂是卤素而不是氢卤酸，那么中间体阳离子就不再是对称的，反应也因此是区域选择性的了。发生的变化如下：

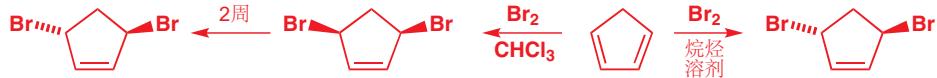


另一种方式是直接进攻溴𬭩离子中间体（图在下一页），我们认为这个过程会发生在烯丙型位点（黑色箭头），而不是普通仲位点（黑色）。这种 1,2-二溴代物 产物并没有被观察到，这是由于虽然它可以进行，但 1,2-产物可以通过溴交换 (bromide shift) 重排为所观察到的 1,4-二溴代物。

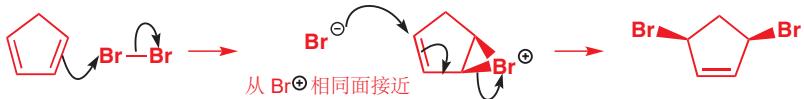
► “溴交换” 指的是您在 p. 576 遇到的烯丙型溴代物可逆的异构化过程。



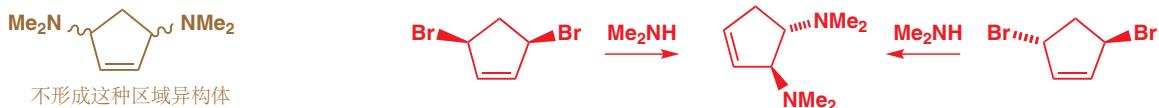
这个反应的最终产物事实上可能是下面两种产物中的任意一种，因为两个溴原子既可以是顺式也可以是反式。在  $-20\text{ }^{\circ}\text{C}$  下的氯仿中溴代，给出的主要的是液态的顺式二溴代物，转化为反式异构体的过程持续而缓慢地发生；而在碳氢骨架溶剂中的反应，则直接给出结晶的反式异构体。



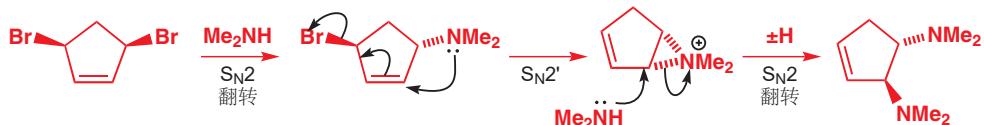
这说明，顺式二溴代物是动力学产物，而反式化合物则是更稳定的热力学产物；它是通过可逆的溴离子的失去，和溴𬭩离子的重新形成的过程得到的。



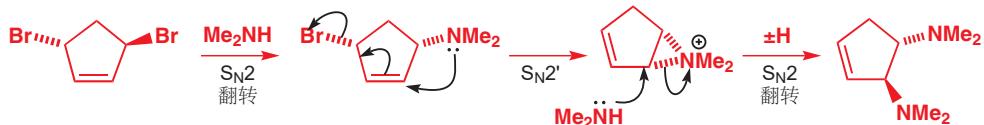
二溴代物若发生亲核取代，则也会引发类似问题。二甲胺与顺式或反式的二溴代物反应，都给出反式的二胺异构体。着眼于区域化学——这不是您所料到的。唯一的解释，是一个  $\text{S}_{\text{N}}2$  取代和一个  $\text{S}_{\text{N}}2'$  取代。



但对于立体化学呢？由顺式异构体出发，会发生伴随构型翻转的  $\text{S}_{\text{N}}2$  取代，然后也许会有分子内的  $\text{S}_{\text{N}}2'$  取代紧跟其后，最后则是另一个在烯丙型中心上伴随反转的  $\text{S}_{\text{N}}2$  取代。



反式异构体的反应几乎是完全相同的：两种流程中都有相同的三元环中间体，因此产物终归是相同的。



如果亲核试剂与亲电试不同，我们就可以得到更多的一点关于反应过程的信息。当用溴在甲醇溶剂中处理丁二烯时，以 15:1 比例生成两种加合物，还随同一些二溴代物。甲醇是一个弱的亲核试剂，主要在烯丙型位点进攻溴𬭩离子（如下黑色）；仅有很少量的产物，又甲醇进攻烯丙型体系的远端得到。注意，没有对溴𬭩离子另一端的进攻（绿色虚线箭头）。



## 共轭加成

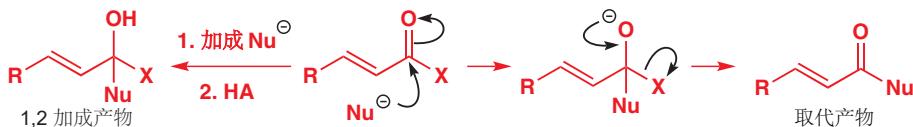
在 Chapter 22 中，我们将相当多的篇幅献予了对共轭加成，以及对为什么有些反应通过对羰基的直接甲醇发生，而有些反应则共轭加成  $\alpha,\beta$ -不饱和羰基化合物的原因的讨论。我们将简要地回顾这些反应的区域选择性方面。

一个共轭的  $\alpha,\beta$ -不饱和  
羰基化合物



$R = \text{烷基, 芳基}$   
 $X = \text{H, R, Cl, OH, OR, NR}_2$

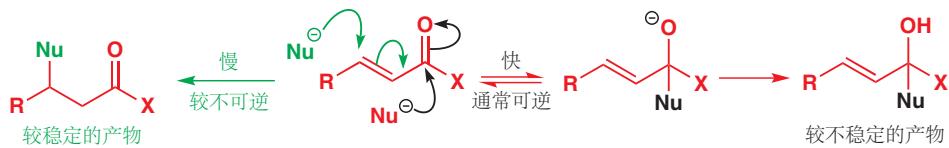
直接 (或 1,2) 加成，意味着亲核试剂直接进攻羰基。形成一个加成化合物；如果  $X^-$  是一个离去基团，或者质子化后可以给出醇，则可能随后失去。



共轭 (或 1,4) 加成则意味着，亲核试剂进攻离羰基最远的烯烃端。电子穿越共轭体系，进入羰基，形成烯醇阴离子，通常会被质子化以给出酮。



两种路径的第一点区别是，直接加成得到的产物保持了烯烃，但失去了羰基；而共轭加成的产物保持了羰基，失去了烯烃。因为  $C=O$   $\pi$  键比  $C=C$   $\pi$  键强，**共轭加成给出的是热力学产物**。但因为羰基比烯烃远端更加亲电，尤其是对于带电的、硬的亲核试剂，**动力学产物由直接加成给出**。因此由于 1,2 加成是可逆的，低温和短反应时间有利于直接加成，高温和长反应时间有利于共轭加成。



第二点区别取决于  $\alpha,\beta$ -不饱和羰基化合物 亲电性的强弱。越亲电的，例如酸酐和酰氯倾向于使直接加成有利；而较不亲电的，例如酮或酯倾向于使共轭加成有利。



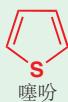
亲核试剂的选择也与之类似：越亲核的物种，例如  $\text{MeLi}$  或格氏试剂，尤其当它们的反应不可逆时，倾向于直接加成；而较不亲电的物种，例如胺、硫醇倾向于共轭加成，这些亲核试剂可逆地加成到  $\text{C}=\text{O}$  基上，为直接加成产物转化回起始原料，再进行共轭加成提供机会。



## 实践中的区域选择性

我们将用一个例子说明区域选择性的几个方面，并介绍接下来两章的主题。糖精(saccharin)是第一种合成甜味剂，新的甜味剂，例如 BASF 化合物噻吩糖精(thiophenesaccharin)比它的需求量大得多。其钠盐是活性物质，而中性化合物可以经由较简单的噻吩中间体制备。

■ 噻吩(Thiophene)是如下含硫芳香化合物的名称。在 Chapter 29 中有更多关于它的内容。

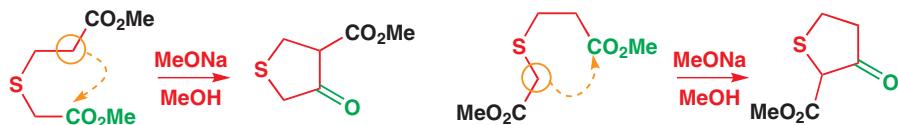


合成开始于一种硫醇对不饱和酯的共轭加成。硫醇很明显是亲核试剂，区域选择性选择共轭加成，而不是在两种酯基中任何一个上的直接加成。

■ 噻吩可以进攻它自己的酯基（一种直接加成），并导致聚合，但这并未发生。



下一步中，二酯被用碱处理，然后发生一个您将在 Chapter 26 中学习的羧基缩合反应。此时有一个真正的区域选择性问题：烯醇盐可以在任何一个酯基旁生成（如橘色所示），随后会作为亲核试剂进攻另一个酯基。这两种酯基间的区分很小，我们所需的仅是第一种，这是通过小心的实验条件控制的，不过到头来产率只有 50%；由于产物可经过重结晶，所有方法中最实用的一个，分离，此过程的产率在大规模生产上是可以接受的。



像这样的反应——烯醇盐对羧基亲电试剂的进攻——是下两章的主体，我们将在那里详实地研究这类反应的细节。

## 延伸阅读

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邻位锂化: P. Wyatt and S. Warren, *Organic Synthesis: Strategy and Control*, Wiley, Chichester, 2007. 和 J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, 2002.

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Wyatt and S. Warren, *Organic Synthesis: Strategy and Control*, Wiley, Chichester, 2007. 非共轭化合物的合成: C. W. Whitehead, J. J. Traverso, F. J. Marshall, and D. E. Morrison, *J. Org. Chem.*, 1961, **26**, 2809.

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加有缓冲碱的(芳基)环氧化, 以避免酸性下产物的重排: M. Imuta and H. Ziffer, *J. Org. Chem.*, 1979, **44**, 1351. 双烯的单环氧化和双环氧化: M. A. Hashem, E. Manteuffel, and P. Weyerstahl, *Chem. Ber.*, 1985, **118**, 1267.

双烯区域选择性的溴代反应: A. T. Blomquist and W. G. Mayes, *J. Org. Chem.*, 1945, **10**, 134. 烯丙型溴代物上区域选择性的亲核取代反应: A. C. Cope, L. L. Estes, J. R. Emery, and A. C. Haven, *J. Am. Chem. Soc.*, 1951, **73**, 1199. V. H. Heasley and P. H. Chamberlain, *J. Org. Chem.*, 1970, **35**, 539. 但请忽略理论部分, 尤其是三个“different”中间体。

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 25

## 烯醇盐的烷基化

### 联系

#### 基础

- 烯醇和烯醇盐 ch20
- 对烯烃的亲电加成 ch19
- 亲核取代反应 ch15
- 共轭加成 ch22

#### 目标

- 如何用作为亲核试剂的羰基化合物构筑新的 C–C 键
- 如何防止羰基化合物与自身反应

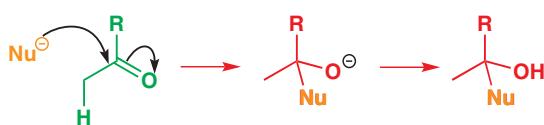
#### 展望

- 通过与亲核的烯醇盐与亲电的羰基化合物反应构筑 C–C 键 ch26
- 逆合成分析 ch28

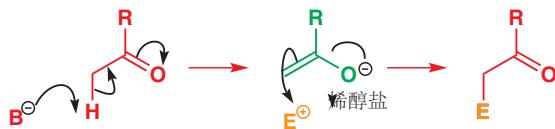
### 羰基表现出不同的反应性

在较早的几章中，我们讨论了羰基会表现出的两种不同类型的反应性。我们首先讨论了包含在羰基上亲核进攻的反应，并在 Chapter 9 中告诉过您，这是构筑新 C–C 键的最好方法。本章中我们还将构建新的 C–C 键，但使用的确实羰基化合物上的亲电进攻：换句话说，羰基化合物在反应中做亲核试剂。我们在 Chapter 20 中已经介绍了羰基的亲核形式——烯醇和烯醇盐，那时所遇到的都是碳与基于其他元素的亲电试剂的反应，经过精心谋划，也可以得到基于碳的亲电试剂。本章的大部分内容都在关注这个短语，“精心谋划 (thoughtfully devised)”。

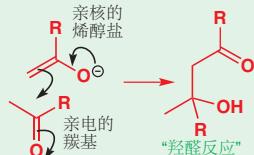
#### 羰基化合物做亲电试剂



#### 烯醇盐做亲核试剂



■ 下一章中，我们将讨论如何促进或控制羰基化合物与其本身发生反应（缩合），即羟醛反应。



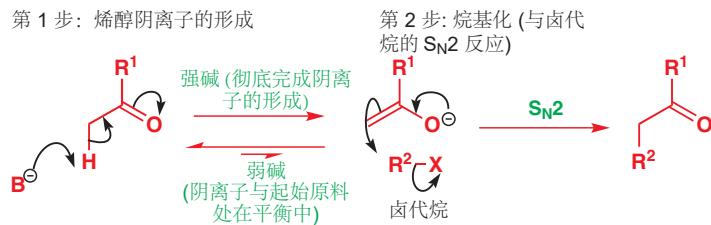
我们需要谋划，以确保羰基化合物表现出正确的反应性种类。特别的，如果我们打算让其称为亲核试剂，那我们就必须控制羰基化合物不作为亲电试剂。如果它这样做了，那么它可能与自身反应，生成二聚体——甚至是聚合物——而不是进攻我们需要的亲电试剂。本章会考虑避免在羰基 C=O 键上发生我们不期望发生的亲核进攻的方式。

幸运的是，在过去的四十年中，烯醇盐与碳亲核试剂反应这一领域已经涌入了很多的想法。这意味着这些问题都有很多绝妙的解决方案：本章的任务就是帮助您理解可以用哪些解决方案，以及什么时候去用它们，以设计出有用的反应。

### 一件会影响所有烷基化反应的因素

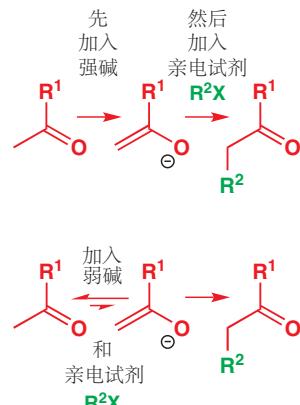
本章中的烷基化反应分为两步。第一步是一个稳定阴离子的生成——通常（但不是往往）是烯醇阴离子——通过碱性下的去质子化形成。第二部是一个取代反应：亲核的阴离子进攻亲电的卤代

烷。所有我们在 Chapter 15 讨论过的，控制 S<sub>N</sub>1 和 S<sub>N</sub>2 反应的方法，在这里都是适用的。



在每种情况下，我们都要从以下两种中选择一种碱。

- 强碱 (其共轭酸的 pK<sub>a</sub> 比羰基化合物小) 可以用做彻底地为起始原料去质子。亲电试剂在下一步加入，而在亲电试剂加入之前，起始物就完全转化为了阴离子。
- 或者，在亲电试剂的存在下加入弱碱。弱碱不能彻底地为起始原料去质子，因为它的共轭酸比羰基化合物的 pK<sub>a</sub> 大：只生成少量的阴离子，但这少量的阴离子会与亲电试剂反应，烷基化将其消耗掉后再继续形成更多的阴离子。



第二种实行起来更简单 (将起始原料、碱、亲电试剂混合就可以了)，但只有当碱和亲电试剂可兼容，并不会发生反应时才可行。对于第一种操作要求更高的方法，亲电试剂和碱并不会遇到彼此，因此不需要考虑兼容性的戊酮。我们将从一些不那么亲电的化合物说起，这是为了避免它们自己与自己的亲核形式反应，即不发生羟醛反应。

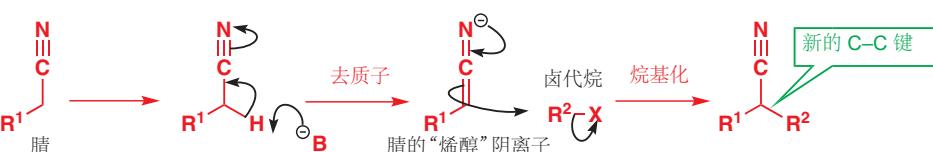
## 腈和硝基烷可以烷基化

由羰基的亲电性引发的问题可以通过用其他不那么亲电，但又能稳定邻位的阴离子的官能团替代 C=O 得以避免。我们将考虑两个例子，它们都是您在 Chapter 20 遇到过的。

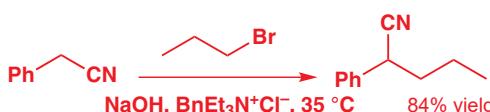
► 脂也有亲电性，您在 Chapter 10 遇到过脂的水解和加成反应。

### 腈 (nitriles) 的烷基化

氨基 (nitrile group) 在一些反应性中表现出羰基的性质，并且远不如羰基容易被亲核试剂进攻 (N 的电负性低于 O)。脂在强碱下去质子形成的阴离子不会与其他分子的脂反应，但却会很有效地与卤代烷反应。这种阴离子纤细的、直线型的结构使其成为 S<sub>N</sub>2 反应很好的亲核试剂。



脂不必为了烷基化彻底地去质子：用氢氧化钠，使之形成少量的阴离子就足够了。在下面的例子中，一种脂与溴丙烷反应得到 2-苯基戊腈。

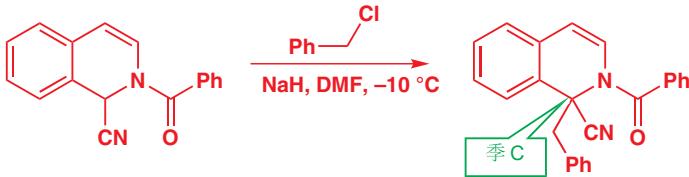


### 相转移催化剂 (Phase transfer catalyst)

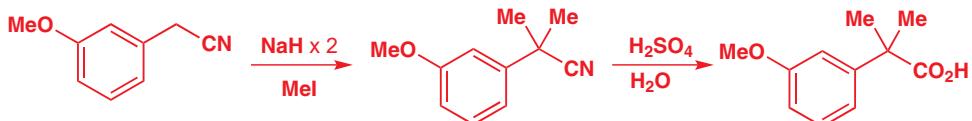
这个反应在两相的混合体系 (水 + 不互溶的有机溶剂) 中进行，这是为了避免溴丙烷与氢氧根反应得到丙醇。氢氧根处在水溶液层，而其他的试剂处在有机层。我们需要用到氯化季铵 (氯化三乙基丁基铵 BnEt<sub>3</sub>N<sup>+</sup>Cl<sup>-</sup>) 做相转移催化剂，它使足够脂去质子的氢氧根进入有机层。

被腈稳定的阴离子非常亲核，以至于拥挤的季中心位点（形成阴离子后没有其他 H 原子）都可以与卤代烷相当好地反应。在这个例子中，用强碱氢氧化钠使带支链的腈彻底地去质子，并用氯化苄做亲电试剂。苄基亲电试剂极好的反应性弥补了离去基团较差的离去性。在 DMF 中，阴离子的反应性尤其强，因为它不会被溶剂化（您在 Chapter 12, p. 255 看到的，DMF 只溶剂化  $\text{Na}^+$  阳离子）。

■ 还记得在 Chapter 6 中关于氢负离子 ( $\text{H}^-$ ) 缺乏亲核性的论述吗？这就是一个例子，即使在有亲电试剂的存在下，氢负离子也仅做碱：这是一个并不需要分两步进行的反应，因为亲电试剂不会与任何其他的化合物反应。



氯化钠与亲电试剂是兼容的，这意味着如果我们加入两当量的碱，那么烷基化也可以再一次发生。这个二甲酸用于一种潜在的药物的合成，可以通过腈的两次甲基化得到。



■ 第二个和第四个结构中的“•”代表直线型碳原子，如果不额外点出来，就可能会忽略。

### 多烷基化

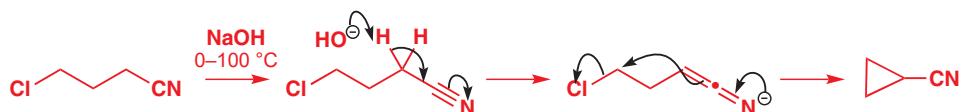
多烷基化并不总是我们需要的，而且双烷基化产物也会成为我们打算单烷基化的副产物之一。这种问题会在第一次烷基化的产物仍然有可去的质子时产生。很明显，这在存在的碱过量时才会真正成为问题，而我们通常可以只加入一当量的碱来避免。



如果反应中心连有两个氰基，那么离域阴离子就会非常稳定，这样即使是一个弱碱性的、中性的胺（三乙胺）都足以作为起始原料去质子。下面的例子也发生了双烷基化，而且以 100% 产率：注意亲电试剂擅长  $S_N2$ ，而且非质子极性溶剂 DMSO（和 DMF 一样）不能溶剂化“烯醇”阴离子，这使其更加活泼。



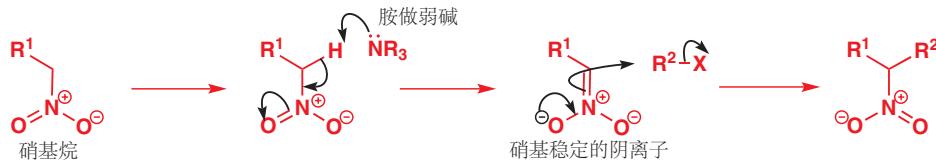
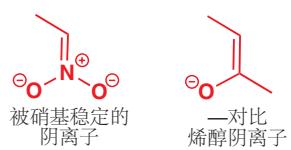
如果亲电试剂和腈在同一个分子中，而且它们之间的间距得当，那么它们就会发生分子内的烷基化，随之环化 (cyclization) 以成环。下面展示了环丙烷的一种制备方法，使用氢氧化钠做碱，氯离子做离去基团。对于分子内烷基化，碱和亲电试剂必然要共存，但相比分子间  $S_N2$  取代，环化是非常快的，因此并不构成  $\text{Cl}^-$  被  $\text{HO}^-$  取代的问题。



### 硝基烷 (nitroalkanes) 的烷基化

硝基强吸电子的性质，使其邻位的去质子可以在甚至碱性很弱的条件下发生。 $\text{MeNO}_2$  的  $pK_a$  为 10，大约与酚相同。硝基邻位质子的酸性事实上相当于与两个羰基相连的碳上质子的酸性；您

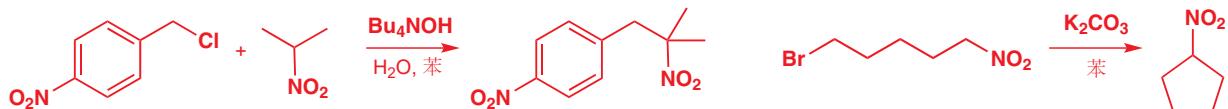
可以把硝基的吸电子能力想象为羰基的两倍。被硝基稳定的阴离子（“nitronate 阴离子”）与碳亲电试剂反应，可以产出很宽范围的含氮产物。右侧的对比图展示了这种阴离子与烯醇阴离子的密切相关性，它的烷基化反应也与后文将描述的烯醇的烷基化高度相似。



令人惊讶的是，市面上能买到的硝基烷是很少的，不过，有了硝基甲烷、硝基乙烷和 2-硝基丙烷做原料，剩下的硝基烷都很可以很容易地制得。例如，硝基丙烷在丁基锂作用下去质子，并随后于叔丁基碘反应，以好的产率给出 3-硝基庚烷。这个反应是要分两步进行的：BuLi 与卤代烷并不兼容！



氢氧根做碱时，硝基烷的烷基化可以一步完成：相转移条件（见 p. 585）使  $\text{HO}^-$  和亲电试剂分离，避免醇的生成。下面左边的反应尽管在产物包含季碳的情况下也能反应，而右侧的反应得到环状硝基烷：现在别无选择：碱和亲电试剂必须在反应混合体系中共存，因此必须使用一个较弱的碱，例如碳酸钾——氢氧根和胺都不是好的选择，因为它们会与卤代烷发生取代反应。



## 烷基化亲电试剂的选择

烯醇盐的烷基化是  $S_N2$  反应（极性溶剂，带电的亲核试剂），因此烷基化若想成功，亲电试剂需要是有  $S_N2$ -反应性的：伯卤代烷和苄卤都是其中最好的烯醇化试剂；多支链的卤代烃倾向于发生我们不想看到的 E2 消除反应，因为它们的阴离子是具有碱性的。结果是，叔卤代烷对于烯醇盐的卤代是无用的；本章中还会讨论这个问题的解决办法。

→ 控制取代反应的因素已在 Chapter 15 详细介绍过，消除反应的内容在 Chapter 17 中。

甲基	烯丙基	苄基	伯烷基化物	仲烷基化物	叔烷基化物
$\text{H}_3\text{C}-\text{X}$					

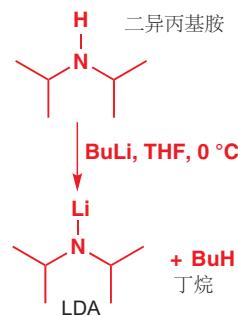
非常地烷基化      很好地烷基化      缓慢烷基化      不发生烷基化

## 羰基化合物的烯醇锂

羰基化合物存在自缩合的问题（即烯醇盐与未烯醇化的羰基反应），但如果根本没有未烯醇化的羰基化合物，就理所当然避免了这一问题。一种方法是使用很强的碱 ( $\text{pK}_a$  至少比羰基化合物的  $\text{pK}_a$

► LDA 的描述位于 p. 465.

提醒: 如何制备 LDA



■ 烯醇是烯烃的一种，而且也许会包含两种可能的几何异构体。烯醇几何结构的重要性会在 Chapter 33 中讨论，它们并不是当前我们需要关心的。更重要的是不对称酮去质子时区域选择性的问题。我们将在本章中讨论这一方面。

Interactive mechanism for lithium enolate formation

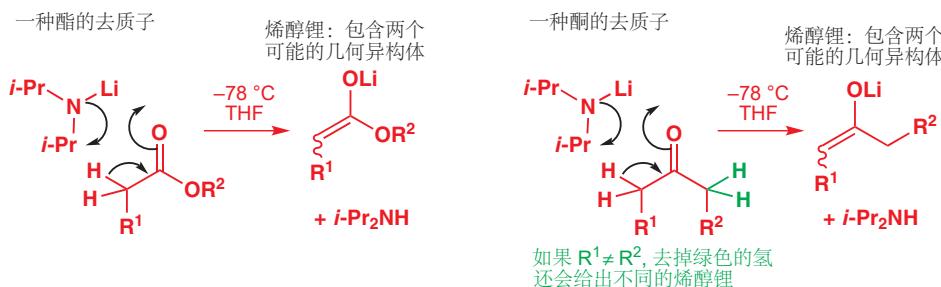
### LDA 的变种

LDA 在 1970s 成为常用试剂，并且您会遇到其它的变体，例如由丁基锂和 2,2,6,6-四甲基哌啶获得的四甲基哌啶锂 (lithium tetramethylpiperidide, LTMP)，和六甲基二硅基胺获得的六甲基二硅基胺基锂 (lithium hexamethyldisilazide, LHMDS)，都具有更大的空阻，因此有更小的亲核性。



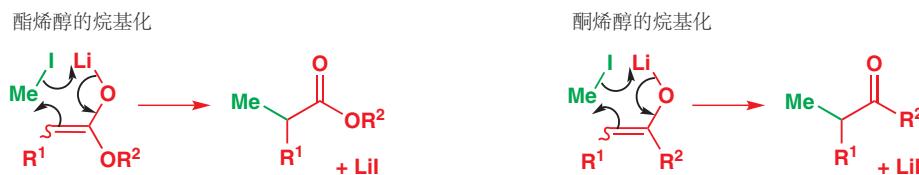
高 3 或 4 个数量级) 确保全部的起始羰基都被转化为了对应的烯醇。并且这也需要所得的烯醇足够稳定，可以存活到烷基化完成。如同您在 Chapter 20 中看到的一样，烯醇锂是很稳定的，它是对于烷基化反应最好的烯醇等价物试剂。

制备烯醇锂最好的碱通常是 LDA，由二异丙基胺 ( $i\text{-Pr}_2\text{NH}$ ) 和  $\text{BuLi}$  制备。LDA 几乎会为所有的酮和酯去质子，并迅速地、彻底地得到相应的烯醇锂，甚至在低温 (大约  $-78^\circ\text{C}$ , 某些活性物种存活的必要条件) 下也是不可逆的。去质子通过一个环状的机理发生，下面以酮和酯为例做出了说明。碱性的氮原子用做去质子，与此同时锂转移，形成氧阴离子。



### 烯醇锂的烷基化

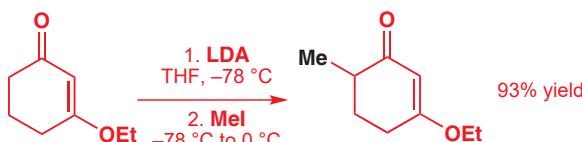
这些烯醇锂与卤代烷的反应是化学上最重要的形成 C–C 键的反应之一。非环状、环状的酮，非环状、环状的酯 (内酯) 都可以通过烯醇锂反应。一般的机理如下所示。



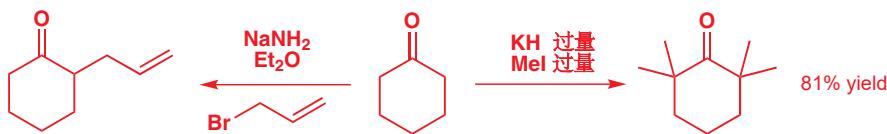
酮烯醇的反应 (涉及烯醇盐生成) 的典型实验条件是低温 ( $-78^\circ\text{C}$ )，在 THF 中进行。强碱 LDA 用于避免羰基化合物的自缩合，但在烯醇生成时，仍常常有机会发生自缩合。越低的温度，自缩合的缩率越慢，因此也有越少的副产物。当烯醇的生成完成后，再加入亲电试剂 (仍在  $-78^\circ\text{C}$  下：烯醇锂在高温下可能不稳定)，然后，通常允许反应混合物升至室温，以加速  $\text{S}_{\text{N}}2$  烷基化的速率。

### 酮的烷基化

以上顺序原封不动地也用于甲基化下面的酮，LDA 做碱，然后碘甲烷做亲电试剂。



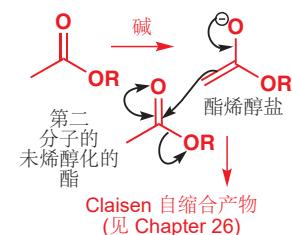
低温下的稳定性使烯醇锂通常作为我们的首选，但烯醇钠和烯醇钾也同样可以用强碱攫取质子获得。碱金属越大，金属阳离子与烯醇阴离子间的分离就越明显，这使其更易反应，也更不稳定。典型的 Na 和 K 的强碱包括氯化物 (NaH, KH)，由胺衍生的氨基化物 (NaNH<sub>2</sub>, KNH<sub>2</sub>) 或六甲基二硅基氨基化物 (NaHMDS, KHMDS)。烯醇盐的不稳定性意味着它们的制备和反应通常在同一步，因此碱和亲电试剂需要兼容。下面是两个环己酮烷基化的例子：烯醇钾的高反应性，在过量氯化钾与碘甲烷作用下有效的四甲基化上得以体现。



## 酯的烷基化

在 Chapter 26 中您会遇到一个酯和其自己的烯醇盐的反应：Claisen 缩合反应。这个反应会成为在渴望 酯烯醇锂 烷基化时，一个非常恼人的副反应，只有当酯被完全地转化为其烯醇盐时，Claisen 缩合便会慢下来，这一问题才可得到避免。阻止它发生的一个好方法是在 LDA 的溶液中加入酯（而不是在酯中加入 LDA），这样就永远不会有过量的酯会与烯醇盐反应了。另一个成功的策略是使 R 基团尽可能地大，以阻止羰基的进攻。叔丁基酯的价值被淋漓尽致地体现了，也同样因为它们容易制得，但要注意，它们在酸的水溶液中，即使是温和的条件也会水解 (p. 556)。在这个例子中，叔丁基醋酸酯产生烯醇锂，并在反应混合物温度上升至室温时与丁基碘反应。

### 要避免的酯的 Claisen 自缩合



## 羧酸的烷基化

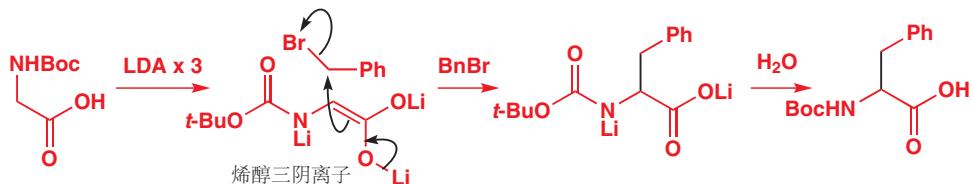
羧酸的烯醇锂可以通过加入两当量的碱制得：一份用于生成羧酸阴离子，另一份用于生成烯醇盐。去掉第一个质子所用的碱不必要是强碱，但因为第二次的去质子需要如 LDA 的强碱，通常来说，生成双阴离子 (dianion) 方便的做法是加入两当量的 LDA。对于羧酸，即使是 BuLi 都可以偶尔使用，因为中间体羧酸锂要比醛或酮的亲电性小得多。



下一个酸烯醇的烷基化反应有关一个被氨基甲酸酯保护的甘氨酸。如您在 Chapter 23 所见，氨基甲酸酯保护在碱性条件下稳定。三个酸性质子都被 LDA 夺去，但烷基化仅发生在其中一个碳原子上——最后一个质子被去除的位点。发生烷基化反应，会使最后一个负电荷消失，仅剩下更稳定的两个电荷，因此如果分子有机会发生烷基化，它们就会如此做，来得到更稳定的阴离子。双阴离

■ 为什么 BuLi 不会像您在 Chapter 10 中看到的那样进攻羰基以形成酮？据推测，并不是由于羧酸不活泼导致的，而是由于芳环酸化了苯基质子，并使平衡偏向去质子过程。其他例子中，即使是羧酸，LDA 也应成为您用碱的首选。

► 在 Chapter 23 中我们考察过双阴离子的反应性：最后引入的负电荷是最活泼的。



- 酮、酯和羧酸的烷基化最好使用其烯醇锂完成。

### 为什么烯醇盐在碳上烷基化？

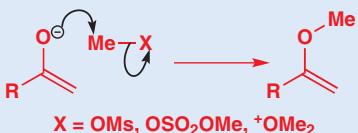
烯醇有两个亲核位点：碳原子和氧原子，在 p. 453 我们提到：

- 碳有更大的 HOMO 系数，是更软的亲核位点。
- 氧带有最多的负电荷，是更硬的亲核位点在 Chapter 20 中您看到硬亲核试剂倾向于在氧上反应——例如，这就是烯醇硅醚可以被制备的原因。一些带有非常好的离去基团的亲电试剂同样倾向于在氧上反应，但像卤代烷这样较软的亲电试剂在碳上反应，您会在本章中看到这类亲电试剂。

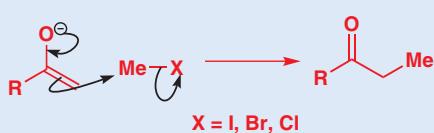
通常来说：

- 硬亲电试剂，尤其是烷基硫酸酯或磺酸酯(甲磺酸酯, 对甲苯磺酸酯)倾向于在氧上反应。
- 软亲电试剂，尤其是卤代烷 ( $I > Br > Cl$ )，在碳上反应。
- 非质子极性溶剂 (DMSO, DMF) 通过将烯醇阴离子与其反荷离子分开(增强键的极性，并增加在 O 上的电荷)以促进 O-烷基化；而醚类溶剂 (THF, DME) 促进 C-烷基化。
- 碱金属越大 ( $Cs > K > Na > Li$ )，离子对就越分离(极性更强的键)，这使在氧上反应更加困难。

硬亲电试剂在 O 上反应



软亲电试剂在 C 上反应



### 醛的烷基化：避免 LDA

醛十分亲电，这使得即使是用 LDA 在  $-78^{\circ}C$  下处理，去质子的速率仍然很慢，不足以超过生成的烯醇锂与混合物中剩余的还未去质子的醛反应。而且强亲电性也会造成碱直接加成，这也是个问题。

与醛烯醇盐的生成竞争的反应



- 请避免使用醛的烯醇锂。

## 特别的烯醇等价物用于烷基化醛和酮

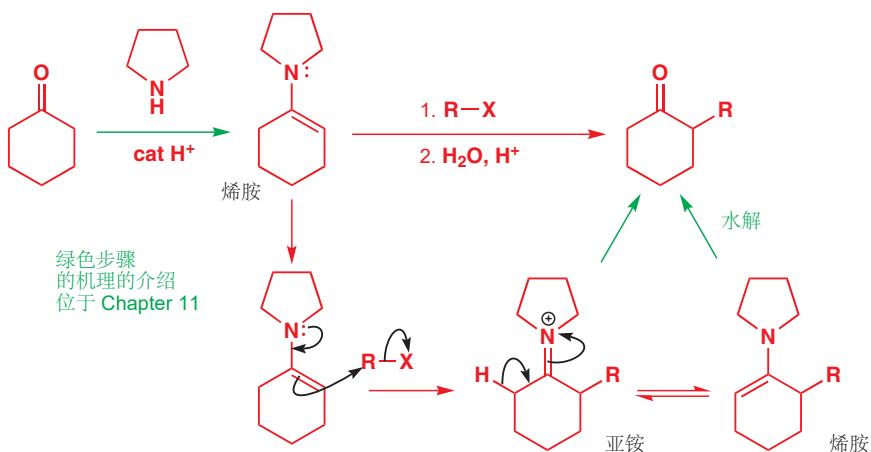
这些副反应意味着醛烯醇通常不是很好的反应中间体。相反，有很多醛烯醇等价物可以保证醛在烯醇化和烷基化步骤中全部以武装模式（masked form, 指烯醇式）出现。

- 烯胺 (enamines)
- 烯醇硅醚 (silyl enol ethers)
- 烯胺盐 (aza-enolates, 氮杂烯醇盐)

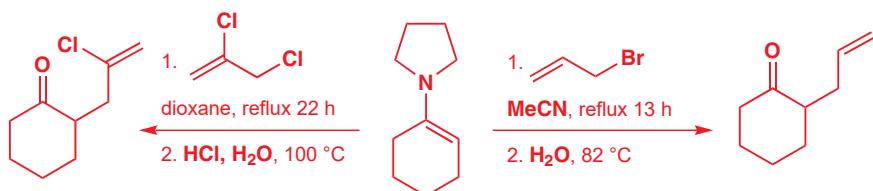
您在 Chapter 20 中简短地见到过这些烯醇等价物，而在此我们会将它们用于醛的烷基化上。这三种特别的烯醇等价物都不仅在醛上有价值，也可以很好地应用于酮；对于每种烯醇等价物的介绍，我们都将给出这两种类型的羰基化合物的例子。

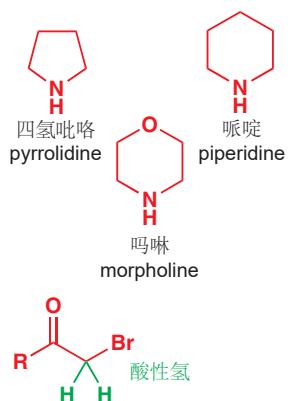
### 烯胺通过活泼的亲电试剂烷基化

醛或酮与仲胺反应可以形成烯胺。这一步骤的机理在 Chapter 11 已经提及。下方所展示的机理是它（环己烷与四氢吡咯衍生的）与烷基化试剂，形成新的 碳–碳 键的步骤。第一步的产物不是一个羰基化合物：是一个亚铵离子（iminium ion）或去除质子后得到的烯胺。然后酸性下温和地水解，可使其转化为对应的烷基化的羰基化合物。



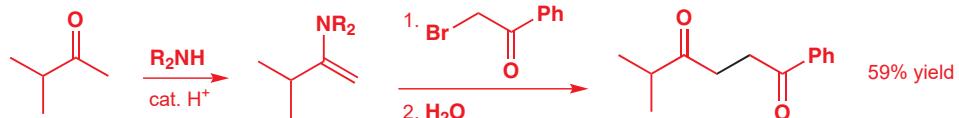
整个过程仍是由羰基化合物到羰基化合物，等同于烯醇盐的烷基化，但不需要强碱或烯醇盐的参与，也因此没有我们担心的自缩合发生。下面是两个用烯胺完成的环己酮的烷基化。注意这种方法需要相对高的温度，和较长的反应时间：烯胺是中性亲核试剂中反应性最强的，但和烯醇阴离子相比，仍然不能望其项背。





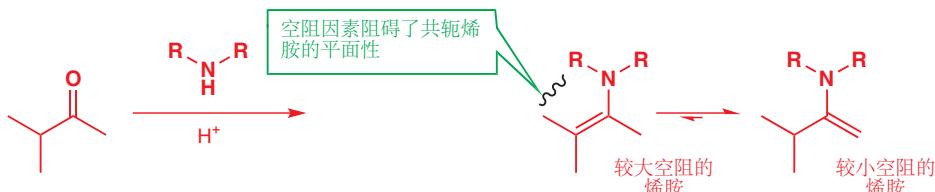
用于烯胺生成的二级胺，虽然不会在产物中体现，但对它的选择并不是完全是任意的。可以使用简单的二烷基胺，但环状胺，例如四氢吡咯、哌啶、吗啉是更为流行的，环状结构使起始胺与得到的烯胺都更加亲核（环状胺中的两个烷基被“扎在后面 tied back”，不再能阻碍胺）。这些胺的高沸点也允许我们在烯胺生成时加热。

由于羰基的活化作用， $\alpha$ -溴代羰基化合物是  $S_N2$  反应极好的亲电试剂（Chapter 15）。然而卤素和羰基之间的质子相比于那些仅连着羰基的质子，显著地具有酸性，这导致烯醇阴离子可能不做亲核试剂，只做碱。而烯胺的碱性很弱，亲核性却很好，对于与  $\alpha$ -溴代羰基化合物的反应是一个很好的选择。

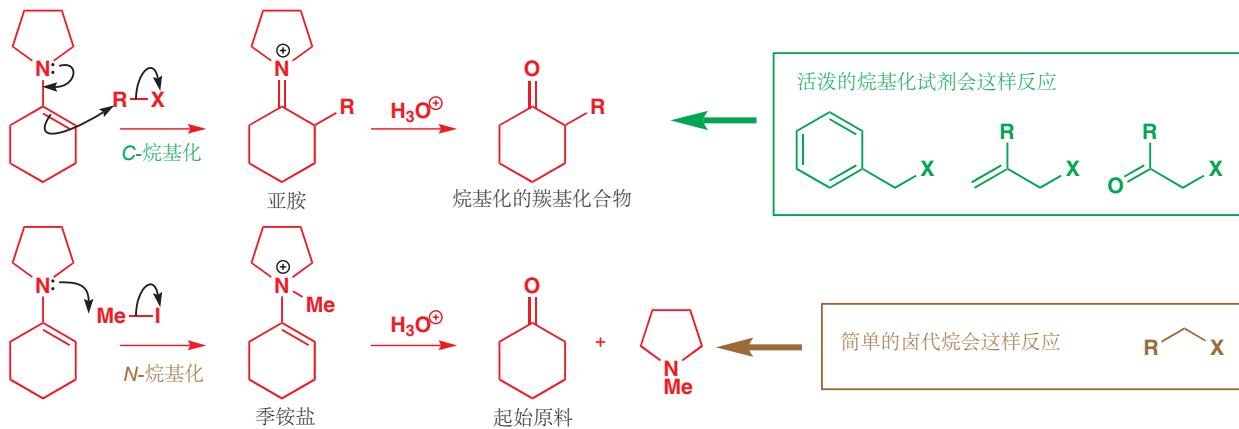


■ 烯醇倾向于多取代，烯醇阴离子倾向于少取代，回忆一下我们在 p. 464 讨论的内容。

这里的起始酮是不对称的，因此有两种可能的烯胺。然而，典型的情况是仅生成少取代的烯胺。这一结果可以被解释为热力学控制：烯胺的生成是可逆的，因此较少空阻的烯胺占主导地位。对于多取代的烯胺，空阻会使烯胺失去平面性，并因此使之不稳定；另一方面，少取代的烯胺就相当稳定了。



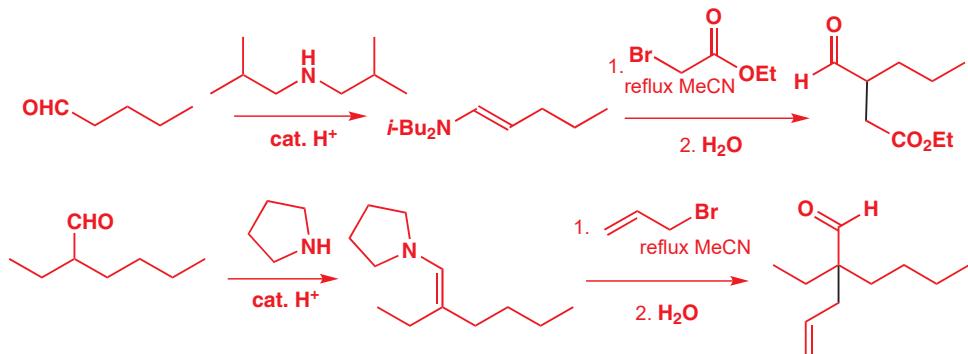
然而，烯胺面临的一个主要问题是：在氮上发生反应。反应性较弱的烷基化试剂——简单的卤代烷，例如碘甲烷——在 N 上反应的比例显著地比在 C 上大。产物是一个季铵盐，会水解为起始产物并导致低产率。



● 与烯胺配合最好的活泼烷基化试剂：

- 烯丙基卤
- 苄卤
- $\alpha$ -卤代羰基化合物

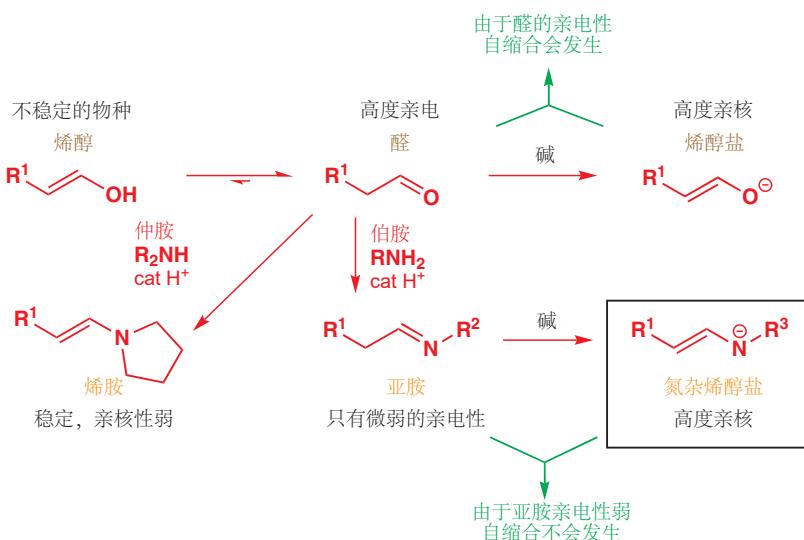
也就是说，烯胺是醛烯醇化问题的一个很好的解决方案。醛很容易形成烯胺（醛高亲电性的一个好处），并且烯胺也不受亲核试剂进攻（包括最重要的，受烯胺本身进攻）的影响。下面两个醛烷基化的例子都使用了烯胺的方法。它们所用的都得是高  $S_N2$ -反应性的亲电试剂，这是烯胺存在的最主要的局限性。



### 烯胺盐与更广范围的 $S_N2$ -反应性亲电试剂反应

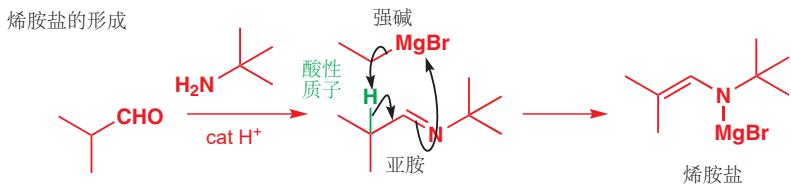
烯胺是烯醇的氮杂类似物，亚胺是醛和酮对应的氮杂类似物，用烯胺的方法解决了醛和酮高度亲电的问题，但由于烯胺的亲核性不够，又产生了其他问题。横向的思考会让您想到，用烯醇盐（烯醇阴离子）的氮杂类似物，烯胺盐来作为亲核试剂。用 LDA 或其他强碱处理亚胺可以使之形成烯胺盐。

在碱性和中性溶液中，亚胺仍比醛有更弱的亲电性：它们可以与有机锂反应，但对于其他较弱的亲核试剂却无动于衷（可以使其质子化的酸性溶液会令其更加亲电）。因此，不需要担心自缩合。

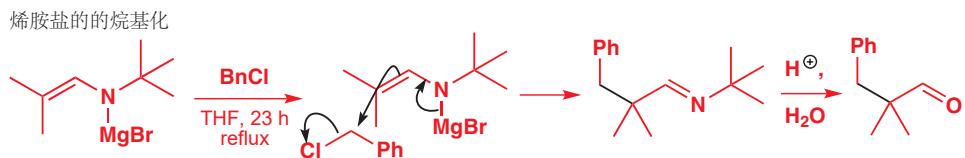


■ 注意，烯胺盐由伯胺与醛酮生成的亚胺去质子得到，而烯胺由仲胺与醛酮生成的亚胺去质子得到。

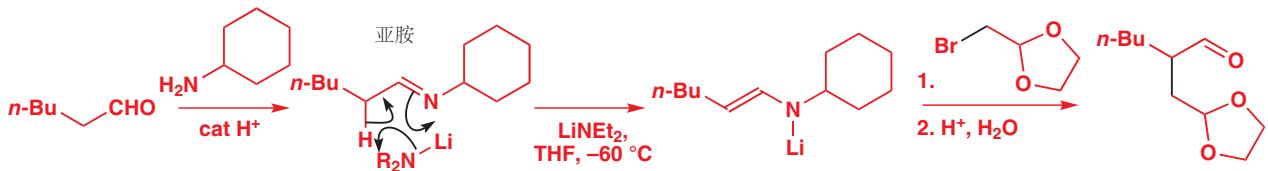
整个顺序包括由醛生成待烷基化的亚胺——通常用大空阻的伯胺，例如叔丁基胺或环己基胺，这也能抑制对亚胺碳的亲核进攻。亚胺通常不经分离，直接用 LDA 或格式试剂去质子（它们不会加成到亚胺上，而是会去质子生成烯胺盐）。



所得的烯胺盐像酮的烯醇盐一样与  $S_N2$ -反应性 烷基化试剂——此处是苄氯反应——生成新的碳–碳 键并重新得到亚胺。烷基化的亚胺通常经温和的、酸性的后处理 (work-up) 水解得到烷基化的醛。



下一个例子使用锂碱 (二乙基氨基锂) 制备烯胺盐，所添加的烷基带有一个缩醛。亚胺在酸性下水解时，对缩醛没有产生任何影响，这也印证了亚胺水解的容易性。所得的产物是一个单保护的二醛，用其他方法是难以制得的。



烯胺盐的烷基化非常成功，不仅是醛烷基化的基本方案，而且也是酮烷基化时一个实用的选项。环己酮是简单的酮中亲电性最强的，也会面临我们不希望见到的副反应。由环己酮和环己胺得到的亚胺可以用 LDA 去质子，得到烯胺盐。在这个例子中，用碘甲基锡烷 (iodomethylstannane) 做烷基化试剂，经过水解最后得到含锡的酮。



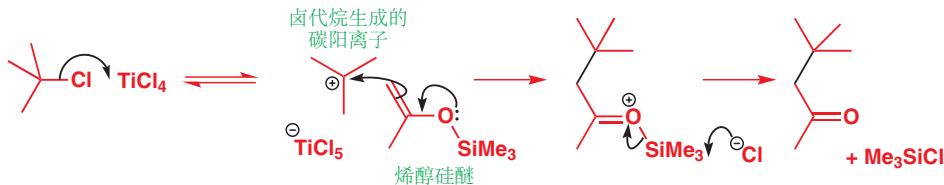
### ● 醛的烷基化

烯胺盐是醛与大多数亲电试剂发生烷基化时最好的通用解决方案。对于高  $S_N2$ -反应性的烷基化试剂，可以选用烯胺；对于高  $S_N1$ -反应性的烷基化试剂，可以选用烯醇硅醚。

## 烯醇硅醚可以在 Lewis 酸存在下用 $S_N1$ -反应性亲电试剂烷基化

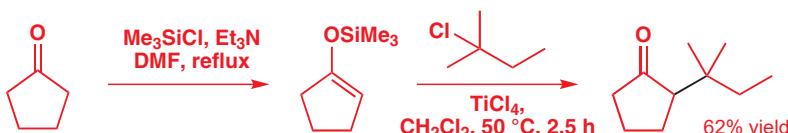
烯胺盐的强亲核性意味着它们能与很广泛的亲电试剂反应，它们的碱性也较强，与烯醇锂类似，这意味着它们不能与叔烷基卤等  $S_N1$ -反应性亲电试剂反应。这一问题的解决方案是使用烯醇硅醚，它们的反应性较弱，因此需要一个强有力的亲电试剂来引发反应。碳阳离子就符合上述要求，并且它们可随饱和碳原子上卤素或其他离去基团的离去，而在反应混合物中(*in situ*)生成。

您在 Chapter 20, p. 466 遇到过烯醇硅醚。



$TiCl_4$  在此处做 Lewis 酸 (见 p. 180 关于 Lewis 酸的更多讨论)，接受来自 Cl 原子的一对电子。在 Chapter 15 有用相关的方法定量地得到碳阳离子的例子。

对于烯醇硅醚最好的烷基化试剂是叔烷基卤：它们在 Lewis 酸，例如  $TiCl_4$  或  $SnCl_4$  的存在下生成稳定的碳阳离子。更幸运的是，叔烷基卤对于烯醇锂或烯胺锂是不适合的，因为得到的会是消除产物，而不会发生烷基化：烯醇硅醚正好是与之互补(complementary)的选择。下面是一个例子：环戊酮与 2-氯-2-甲基丁烷 发生的烷基化反应。酮在三乙胺和三甲基硅基氯的作用下转化为烯醇三甲基硅醚：我们在 p. 466 (Chapter 20) 讨论过这一步。干燥二氯甲烷中的四氯化钛用于促进碳阳离子的生成(也是在促进烷基化)。



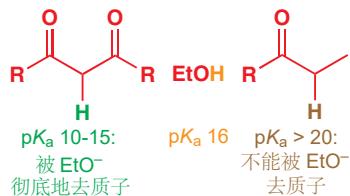
### ● 总结：用于醛和酮的特别的烯醇等价物：

- 烯醇锂可用于  $S_N2$ -反应性亲电试剂，但不能用于醛。
- 醛或酮的烯胺盐可用于相同的  $S_N2$ -反应性亲电试剂，相比烯醇锂可用于醛。
- 醛或酮的烯胺可用于烯丙基、苄基或  $\alpha$ -卤代羰基化合物亲电试剂。
- 醛和酮的烯醇硅醚可以用于  $S_N1$ -反应性亲电试剂，例如烯丙基、苄基或叔丁基卤。

## β-二羰基化合物的烷基化

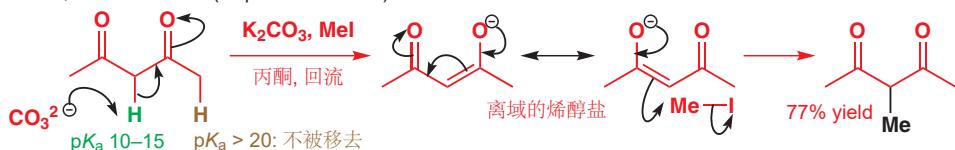
如果一个碳上同时存在两个，甚至三个吸电子基团，就会使余下的质子具有十足的酸性 ( $pK_a$  10–15)，进而温和的碱都可以将其完全转化为烯醇盐形式。烷氧基阴离子的碱性 (ROH 的  $pK_a$  = ca. 16) 不足以彻底地夺去简单羰基化合物的质子 ( $pK_a$  20–25)，但却很容易生成有多于一个吸电子基稳定的阴离子。具有上述性质的最重要的一类化合物是 1,3-二羰基 1,3-dicarbonyl (或 β-二羰基 β-dicarbonyl) 化合物。

所生成的阴离子能很有效地烷基化。甚至用碳酸钾都能烷基化这种二酮，继而与碘甲烷高产率地反应。碳酸根是很差的亲核试剂，因此碱和亲电试剂可以在同一步中添加。



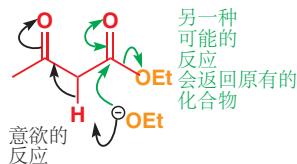
被两个以下的吸电子基团稳定的烯醇盐可以通过烷氧基阴离子生成: COR,  $CO_2R$ ,  $CN$ ,  $CONR_2$ ,  $SO_2R$ ,  $(RO)_2P=O$ 。

一种 1,3-二羰基化合物 (或  $\beta$ -二羰基化合物) 的烷基化



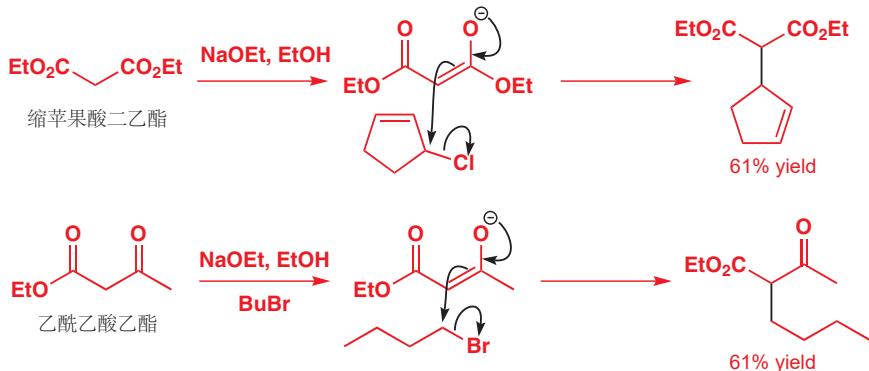
有两种  $\beta$ -二羰基化合物 在重要性上最引人注目——缩苹果酸二乙酯 (或二甲酯) 和乙酰乙酸乙酯 (化工上简称“三乙”). 您应当确保记住它们的结构和俗称。

您在 Chapter 20 见到过相关的稳定烯醇。



这两种碱的反应中，碱的选择是很重要的：亲核加成可以在酯羰基上发生，这会导致酯交换 transesterification (烷氧基阴离子加成)，水解 (氢氧根加成) 的发生，或是酰胺的形成 (氨基阴离子进攻). 最好的选择是用与酯相同的烷氧基阴离子 (缩苹果酸二乙酯中用乙氧基，缩苹果酸二甲酯中用甲氧基). 烷氧基阴离子的碱性足够去除两个羰基间的质子，但也会在  $\text{C}=\text{O}$  上取代，不过这并不会构成完整的反应).

在下面的第一个例子中，亲电试剂是烯丙基的环戊烯基氯，碱是乙醇中乙醇钠——可以通过将一当量的钠加入干燥的乙醇真方便地制得。相同的碱用于第二个烷基化，乙酰乙酸乙酯与正丁基溴的反应。



各种各样的吸电子基团可以任意组合，大多数都能得到很好的结果。下面是一个酯基与氰基合作稳定阴离子的例子。氰基稳定阴离子的能力比不上羰基，因此这个烯醇盐的生成还需要在非质子溶剂 (DMF) 中完成，所用的碱是强碱氢氧化钠。伯烷基对甲苯磺酸酸酯用作亲电试剂。

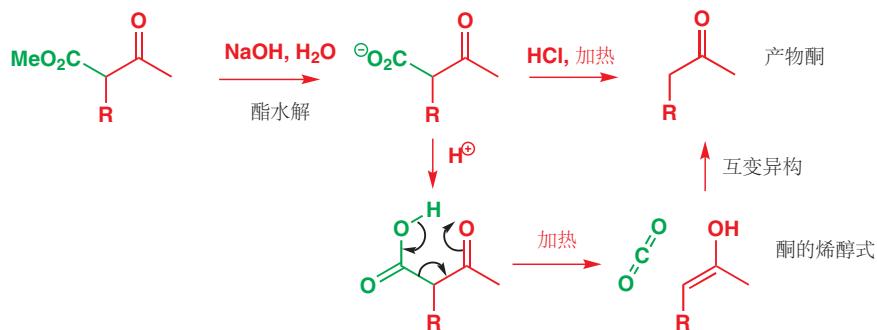
如果您需要回忆对甲苯磺酸离去基的内容，请返回至 p. 349.



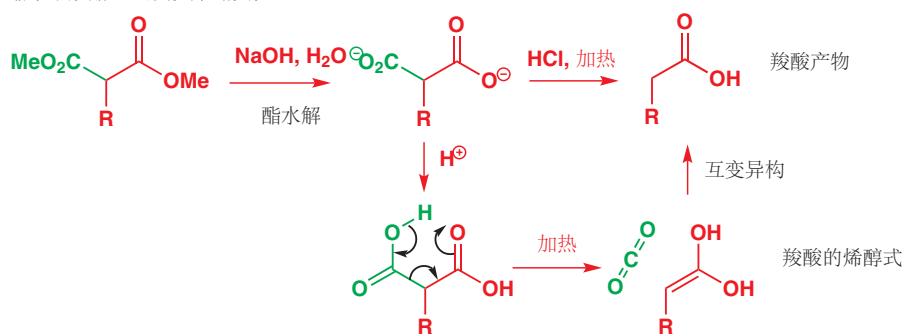
这些双重稳定的阴离子能很好地发生烷基化，因此也常用二羰基化合物发生烷基化，后面的阶段中再移去其一。这是由于加热时带有  $\beta$ -羰基的羧酸会脱羧 decarboxylate (失去二氧化碳). 机理如下所示。这个例子中的二羰基化合物先发生烷基化，然后在碱性下水解掉不想要的酯，最后酸化并

加热，经过一个六元环过渡态脱羧：连接羧基的键断裂，同时质子转移到羰基上，释放一分子二氧化碳。最初得到的产物是一个羰基化合物的烯醇式，它会迅速互变为更稳定的酮式——现在只有一个羰基了。使用这种方法，可以由  $\beta$ -酮酯得到酮，由缩苹果酸酯得到简单的羧酸（两个酯基都水解为羧基，其中一个羧基通过脱羧失去）。因为脱羧产物为烯醇，脱羧只可在第二个羰基处于羧基的  $\beta$  位时发生。

乙酰乙酸酯通过脱羧得到酮

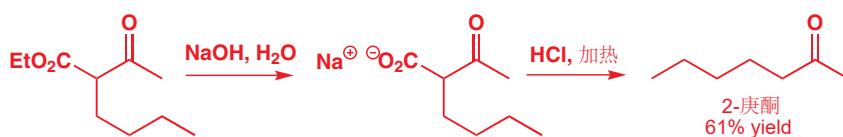


缩苹果酸酯通过脱羧得到羧酸

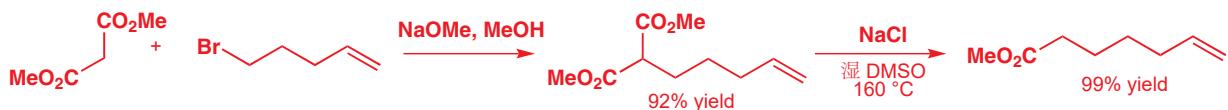


在 p. 596 有乙酰乙酸乙酯与正丁基溴烷基化的例子，此过程的目的是经过进一步的脱羧得到 2-庚酮。脱羧需要的条件是加热，这是为了增加熵项 ( $\Delta S^\ddagger$ ) 在活化能中侧重的比例（脱羧过程由一个分子生成两个分子），以从体系中赶走  $\text{CO}_2$ 。

我们在 Chapter 12 中已经讨论了温度在驱动反应上扮演的角色。



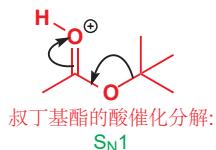
酯远比羧酸容易脱羧，下面是一个能在不水解另一个酯基的条件下去除其中一个酯基的实用程序。缩苹果酸酯在非质子极性溶剂——通常是 DMSO——中加热，在氯化钠和少量水的存在下。不需要酸或碱，除了需要的高温，其他条件都还算温和。下面的图示展示了缩苹果酸二甲酯的烷基化（注意缩苹果酸二甲酯需要用  $\text{NaOMe}$  做碱）和其中一个甲酯基的去除。



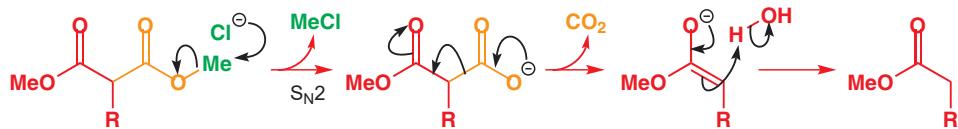
■ 叔丁基酯的水解也是通过 O–烷基键断裂而分解的经典机理之一，我们在 p. 556 曾向您介绍过。叔丁基导致机理必然为 S<sub>N</sub>1。

酯脱羧的机理在所有酯分解反应中是相当不寻常的。所断裂的键并不是 MeO–CO 键，而是 O–烷基键：反应是 Cl<sup>-</sup> 对羧基酯的 S<sub>N</sub>2 取代。

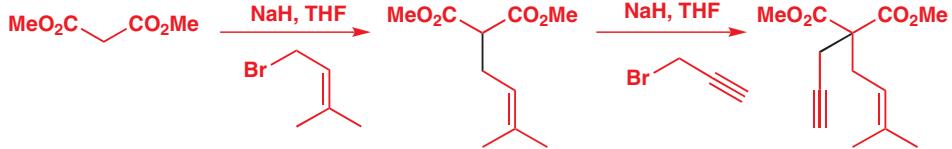
酯裂解的几种机理



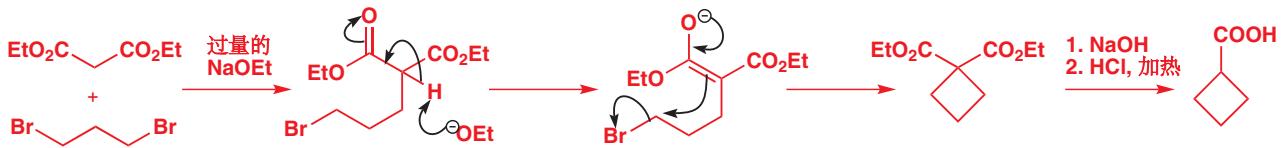
氯离子是很弱的亲核试剂，在 DMSO 中它不能溶剂化，进而反应性可被增加。并且，一旦羧酸酯被取代，高温就会驱动（熵驱动）不可逆的脱羧发生。另一个副产物，MeCl，也作为气体离去。这类“脱羧”过程（事实上是 CO<sub>2</sub>Me 基的失去，而不是 CO<sub>2</sub> 的失去），被称作 **Krapcho 脱羧** (**Krapcho decarboxylation**)。由于经历 S<sub>N</sub>2 步骤，这一过程在 **甲酯**中最容易进行。



我们仅考察了二羰基化合物的单烷基化，但两个羰基之间应有两个酸性质子，因此双烷基化通常也是可能的。过量的碱和卤代烷的存在下，会发生第二次烷基化。更加实用的是，每一步中加入一当量的碱，并分别加入两种卤代烷，可以给出两次引入的烷基不同的双烷基化产物。

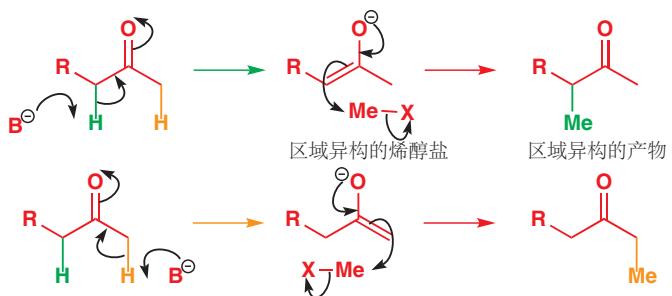


对于二卤代烷，还可以通过双烷基化成环：这是制备环烷羧酸 (cycloalkanecarboxylic acids) 的一种重要方法。甚至，通常难以形成的 (见 Chapter 31) 四元环也可以通过这种方法制备。



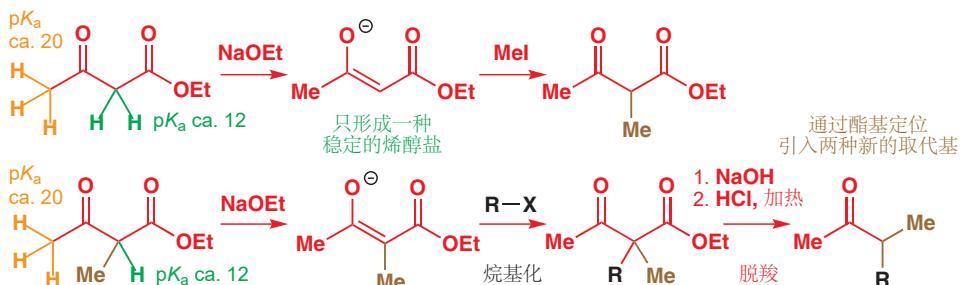
## 酮的烷基化引发区域选择性问题

酮在羰基的两侧都有可烯醇化的质子，因此它们是独一无二的。除非酮是对称的，或者酮在一侧的邻位没有质子，那么它都将有两种可能的烯醇盐，和两种可能发生得烷基化位置，这会导致区域异构的产物。我们需要能够控制烯醇盐生成的区域。如果我们想让酮的烷基化变得有用，那么必须做到的是控制其中一种烯醇盐的生成。



### 热力学控制的烯醇盐形成

如果酮一侧的质子比另一侧的质子显著地更具酸性，那么很明显，烯醇盐的生成是选择性的。这是您在乙酰乙酸乙酯的例子中已经见到过的：它是一个酮，但在较弱的碱（共轭酸的  $pK_a < 18$ ）下，仅在一侧烯醇化，因为该侧的质子被第二个吸电子基团酸化了。如果引入两个新的取代基，那么正如您看到的，它们都会加入到相同的碳原子上。这是热力学控制的一个例子：只有两种烯醇盐中更稳定的一个才能形成。



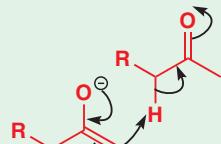
这一原则也可以拓展到两种烯醇盐稳定性差异不大的酮上。因为烯醇和烯醇盐都是烯烃，那么它们携带的取代基越多，也就越稳定。因此，原则上，如果是热力学控制，那么即使是烷基的存在都会导致烯醇形成的选择性。形成更稳定烯醇盐的条件是热力学控制，即两种烯醇盐间需要存在平衡，也就是质子转移的机理。如果有可用的质子源——可以是过量的酮——那么两种烯醇盐间的平衡就会建立。并且，平衡混合物的组成，很大程度地取决于酮本身，对于 2-苯基环己酮，平衡会保证只有一种烯醇盐生成。所用的碱是氢化钾：强碱，而且较小（对于移去较大空阻的质子没有困难），可在允许烯醇盐建立平衡的条件下使用。

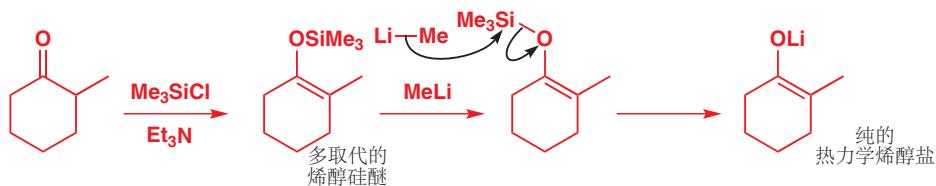
取代基对烯烃稳定性的影  
响见 p. 394. 多取代的烯醇更  
加稳定的事实在 Chapter 20,  
p. 464 中曾经给出。



通过烯醇硅醚在硅上的取代（Chapter 20），多取代的烯醇锂（烯醇锂盐）也可以得以生成。这个反应的价值现在已经变得清晰了，因为不对称酮制备烯醇硅醚的条件 ( $Me_3SiCl$ ,  $Et_3N$ ) 通常得到两种烯醇醚中多取代的一个。因为烯醇硅醚（不像烯醇盐）无法提纯，平衡会建立，得到的便是区域选择性的产物。

■ 平衡的机理很简单，就是一分子的酮（所谓的质子源）被一分子的烯醇盐去质子：

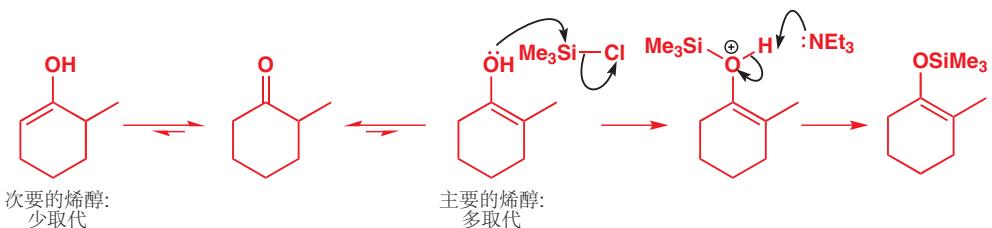




对于烯醇硅醚的生成中热力学区域选择性的一个合理解释，与我们在 p. 464 讨论过的酮的酸促溴代的区域选择性解释有关。三乙胺的碱性很弱 ( $\text{Et}_3\text{NH}^+$  的  $\text{pK}_a$  大约为 10)，不足以使起始的羰基化合物 ( $\text{pK}_a$  ca. 20) 去质子，因此反应的第一阶段应是 氧–硅相互作用。然后去质子才能通过一个阳离子过渡态发生，而在甲基一侧去质子通过的是相比另一侧稳定得多的过渡态：如同甲基稳定阳离子一样，甲基同样稳定部分阳离子 (partial cations)。



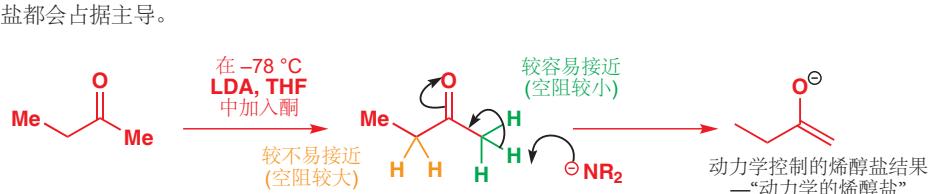
另一种理解是，这个反应经历烯醇： $\text{Si}-\text{O}$  键很强，中性的烯醇也可以在氧上与  $\text{Me}_3\text{SiCl}$  反应。烯醇的形成有多取代选择性，而烯醇作为中间体也主导整个过程的区域选择性，继而得到多取代的烯醇硅醚。



► 在 Chapters 12, 23, 和 24, pp. 264, 546, 和 581 中，讨论了所谓的动力学和热力学控制。

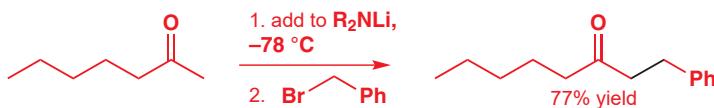
想要理解为什么越少取代的 C 原子上的 C–H 键酸性越强，那就想想共轭碱的碱性： $\text{MeLi}$  的碱性比  $t\text{-BuLi}$  弱，它们共轭酸的酸性应是相反的。

混合物中酮的量一定要比碱少，否则就会有酮和烯醇盐的质子交换平衡，选择性就不再是动力学控制了。对于 LDA 控制的动力学过程，必须确保是将酮加入 LDA 完成，而不是反过来，以便在整个反应中都有过量的 LDA 存在。

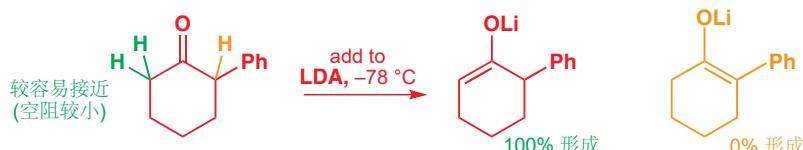


这些因素统统都在确保烯醇盐在少取代的一侧生成——尽管如此，由于少取代的烯醇盐并不是热力学稳定的，我们都需要确保没有之前所讲过的平衡建立。这意味着反应需要在低温下进行，经典的条件是  $-78^\circ\text{C}$ ，来确保反应在短时间内完成；还需要过量的强碱的加入，不可逆地去质子，来确保没有剩下任何酮可以作为质子源。我们由此得到的烯醇盐是在动力学控制下，形成得最快的一个——被称作“动力学烯醇盐”——它不一定是最稳定的一个。

通常来说，上述影响足以选择性地、动力学地为甲基酮去质子，即选择 Me 而舍弃烷基：



相同的方法在 2-取代环己酮 上也应用良好：形成较少取代的烯醇盐。甚至是对于我们刚才提到的，在多取代的一侧有强烈热力学偏好的 2-苯基环己酮，都可以形成少取代烯醇盐。



2-甲基环己酮可以通过此方法，用 LDA 和溴苯选择性地烷基化。



### ● 由酮生成烯醇盐的区域选择性

热力学的烯醇盐：

- 较多取代
- 较稳定
- 过量酮，高温，较长时间反应所得

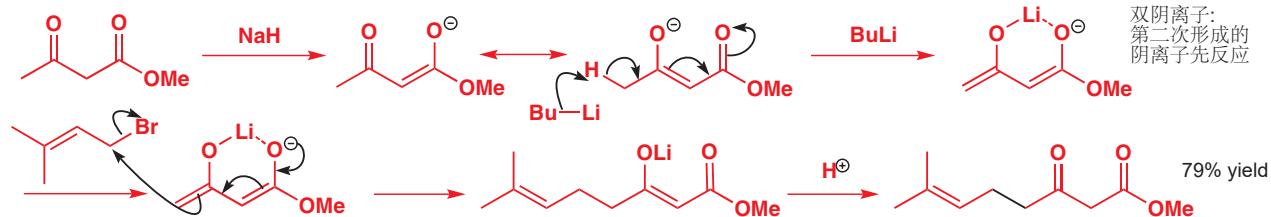
动力学的烯醇盐：

- 较少取代
- 较不稳定
- 强的、大位阻碱 (e.g. LDA)，低温，较短时间反应所得

### 乙酰乙酸甲酯烷基化中双阴离子引起的不寻常的区域选择性

在 Chapter 23 中，我们引入了一个观点，双阴离子或三阴离子中最后引入的一个负电荷都是最活泼的。乙酰乙酸甲酯通常在中心碳原子上烷基化，因为那是最稳定的烯醇盐生成的位置。但乙酰乙酸甲酯双阴离子——用非常强的碱（通常是丁基锂）处理通常的烯醇盐，以移去第二个质子——会首先在最不稳定的一个负电荷上反应：也就是甲基上。反应后再质子化较稳定的烯醇盐，得到产物。由于烯醇盐阴离子中间体不具亲电性，因此丁基锂可以用作此反应的碱。

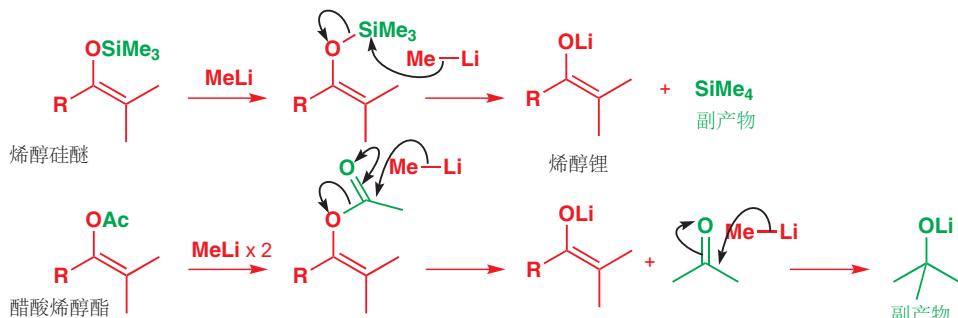
→ 在 p. 547 讨论了双阴离子。



### 烯基酮为区域选择性问题提供了解决方案

烯醇盐，可以通过用烷基锂处理醋酸烯醇酯或烯醇硅醚，选择性地得到。它们都是  $\text{RLi}$  取代烯

醇盐的反应：一个是  $S_N2(Si)$ ，另一个是对  $C=O$  的进攻。在没有质子源的条件下，所得的烯醇盐产物的区域化学与其稳定前体的相同，形成单一的烯醇盐区域异构体。



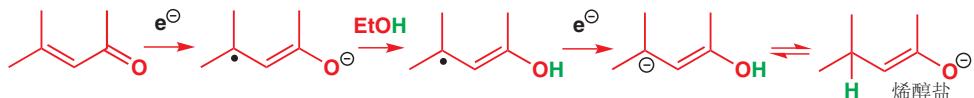
但有一个问题：烯醇醚和烯醇酯的生成本身也往往要求一个区域选择性的烯醇化过程！尽管如此，仍有会使之有用的情况：一个情况是我们需要多取代的烯醇锂（其他方法很难区域选择性地制得），另一个情况是我们可以通过不涉及去质子的方法形成烯醇硅醚——这就是我们现在要讨论的内容。

### 烯基酮通过溶解金属还原区域选择性地给出烯醇盐

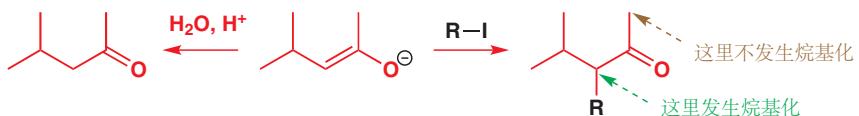


在 Chapter 23 中您曾遇到 Birch 还原：用溶解金属（例如液氨中的 K, Na, 或 Li）还原芳环和炔。与这些反应相类似，烯基酮与液氨中的锂可发生溶解金属还原（dissolving metal reduction）——还原烯基酮中的  $C=C$ ，而  $C=O$  键原封不动。需要醇做质子源，总体上，逐步添加了两个电子和两个质子，在双键上获得了一分子氢的加成。

下面的机理已在 p. 543 中描述过：单个电子的迁移得到自由基阴离子，自由基阴离子再被醇质子化生成自由基。第二个质子的迁移形成阴离子，并可以通过互变异构转化为烯醇盐。



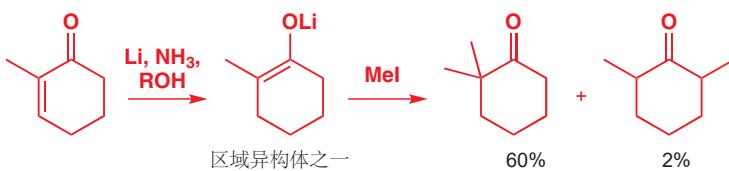
这个烯醇盐不会继续被还原，并可以通过后处理的质子化转化为酮。更有成效的操作是加入卤代烷：烯醇盐的双键仅在原先烯基酮的一侧形成，因此烷基化是区域选择性的。



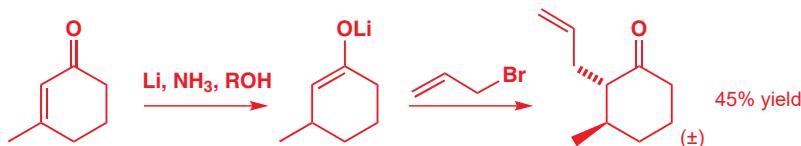
■ 甲基环己酮的两种烯醇，在热力学控制下选择性比例仅为 4:1。



下面的例子所得到的产物是甲基环己酮的区域选择性甲基化产物。仅形成了 2% 的次要区域异构体。



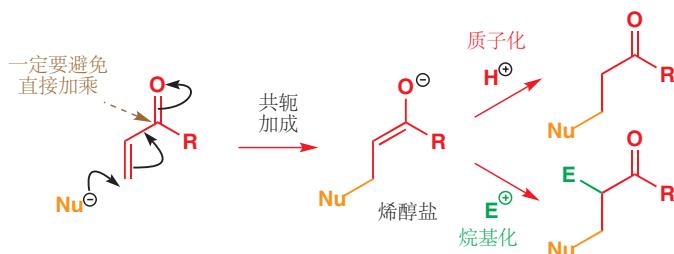
电子的迁移不受空阻的影响，因此烯烃的取代会不构成问题。在下一个例子中，烯醇盐与烯丙基溴反应，得到产物的单一非对映体（烷基溴会从甲基的对侧进攻）。自然，仅有一种区域异构体很好地生成。



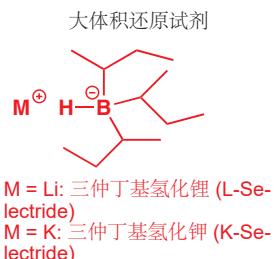
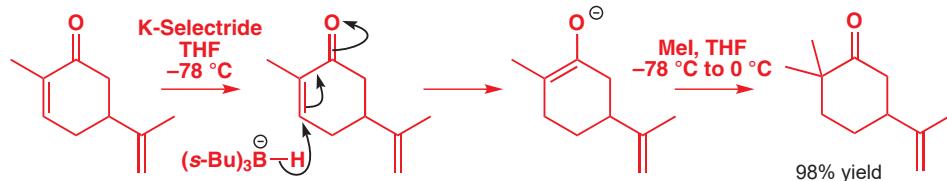
我们在 Chapters 32 和 33 更加详细地讨论单一非对映体立体选择性地生成的问题。

### 烯基酮的共轭加成区域选择性地给出烯醇盐

我们在 Chapter 22 中讨论了烯基酮的共轭加成 (conjugate addition)，这一反应首先给出的产物是烯醇盐，当时我们没有过多地涉及细节，因为烯醇盐通常会在后处理中直接质子化。但我们可以利用所生成的烯醇盐，在妥当的条件下做一件更有成效的事情。

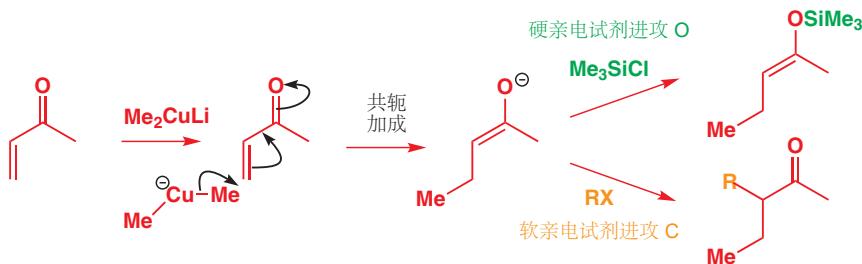


对于共轭加成的步骤，如果我们只想形成像普通的酮的烷基化那样最简单的产物，则  $\text{Nu}=\text{H}$ ，由此我们还面临一个加成的区域选择性的问题：我们需要亲核的氢负等价物走共轭加成的路线。通常选用的是非常大的氢化物试剂，例如三仲丁基硼氢化锂或钾 lithium 或 potassium tri(sec-butyl)-borohydride (通常分别以其商品名 L- 或 K-Selectride 称呼)。在下面的例子中，K-Selectride 将烯基酮还原为烯醇盐，然后再被碘甲烷烷基化，得到单一的区域异构体。



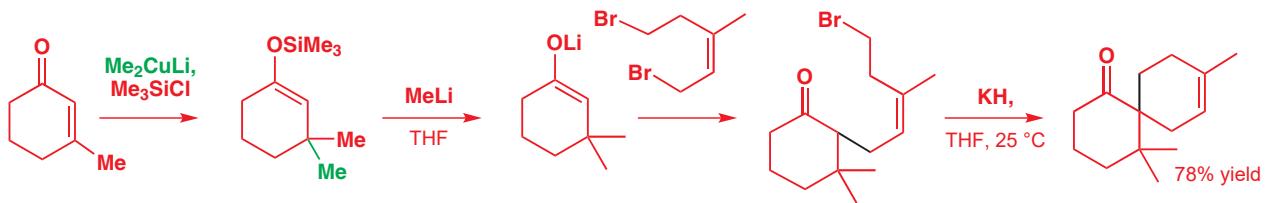
这个反应也说明了共轭双键和孤立双键的区别。

用有机铜试剂替代，可以共轭加成一个新的烷基，如果所得的烯醇盐再被烷基化的话，那么整个过程就在一步操作中形成了两个新的 C–C 键 (这是一个串联反应 tandem reaction: 一个 C–C 键紧随着另一个形成)。在 Chapter 22 中我们解释了，最好的有机铜锂的加成在  $\text{Me}_3\text{SiCl}$  的存在下进行：反应产物为烯醇硅醚，并且是区域选择性的 (“烯醇” 双键往往都在烯基酮原先的位置上)。



烯醇硅醚直接用于和卤代烃反应烷基化的反应性不高，可以将其转化为烯醇锂。这类反应是天然产物， $\alpha$ -花柏烯 ( $\alpha$ -chamigrene) 的合成中关键的一步。 $\text{Me}_2\text{CuLi}$  发生共轭加成，得到烯醇盐，烯醇盐会被三甲基硅基氯捕获。甲基锂在 Si 上发生取代，将所得的烯醇硅醚转化为烯醇锂。这种天然产物含有一个螺 (spiro) 六元环，附着在烯醇盐的一侧，这是通过二溴代物参与的烷基化 (在 p. 598 有这类例子) 形成的。第一次取代发生在更活泼的烯丙基溴上。而第二次取代的发生还需要第二次烯醇化，两侧烯醇化没有区别，但两种情况所形成的产物分别是六元环和八元环，在热力学条件下六元环形成得更快。

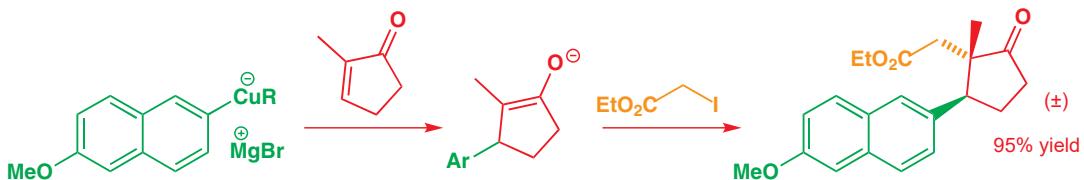
不同大小环形成的难易将在 Chapter 31 中讨论。



在这些串联的 加成–烷基化 反应当中，最重要的是环戊烯酮 (cyclopentenone) 的反应。对于环戊烯酮本身，通常所得的是反式对映体，因为烷基化试剂会进攻烯醇盐空阻较小的一侧。

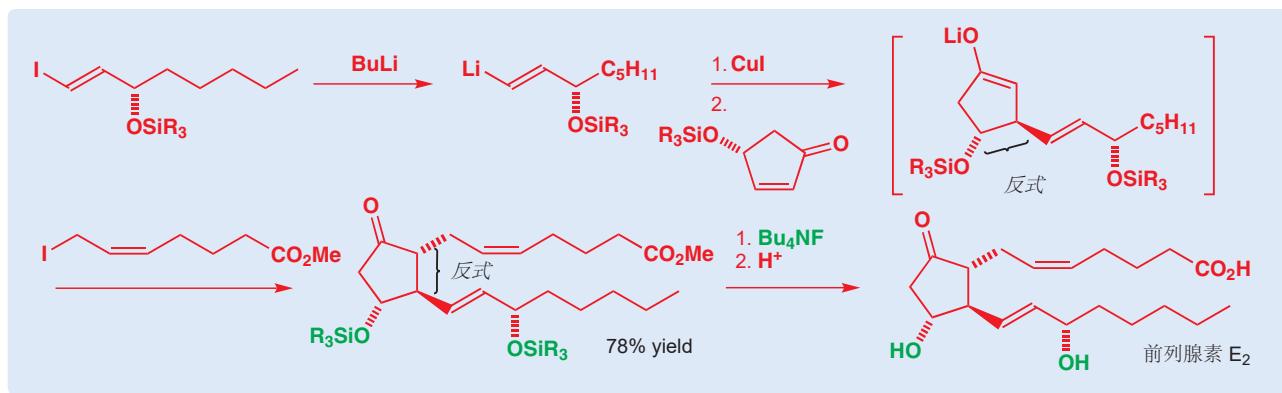


这种选择性在下一个例子中显而易见，虽然看起来很复杂，但实际上就是烷基铜试剂的加成，和紧跟着的与碘代酯发生的烷基化 (与大体积的 Ar 基反式)。



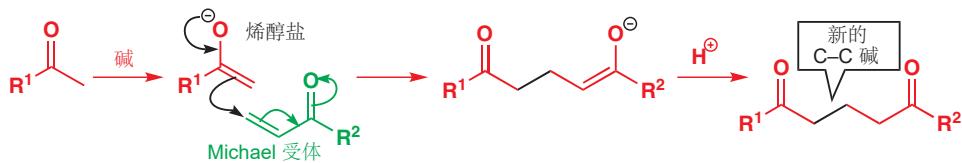
### 前列腺素 E<sub>2</sub> (prostaglandin E<sub>2</sub>) 的合成

将 共轭加成+烷基化 的实力体现得最好的例子，是由日本的 Ryoji Noyoridin 完成的，重要的生物分子前列腺素 E<sub>2</sub> 的简短合成。有机铜试剂和烷基化试剂分别包含了带有经保护的全部官能团的两个链。在它们相组装的关键的一步中，也得到了所需的反式立体化学，并在去除硅醚和酯保护基前，达到了 78% 的产率。有机金属亲核试剂通过 卤素–金属 交换反应 (Chapter 9) 由乙烯基碘制备。随后在碘化铜的存在下，将乙烯基锂加入环戊烯酮，并共轭加成给出中间体烯醇盐。因为起始的烯基酮已经含有一个立体中心，这一步是立体选择性的：进攻空阻最小的区域 (烯醇醚的对侧) 并给出反式产物。所得的烯醇盐再用带有端酯基的烯丙基碘烷基化：再次得到反式产物。尤其重要的是，要避免烯醇盐平衡的存在，以防止两分子的烯醇盐交换质子，通过不可逆的 E1cB 消除，消去硅氧基。用 TBAF (Chapter 23) 脱去硅醚保护基即可得到产物。

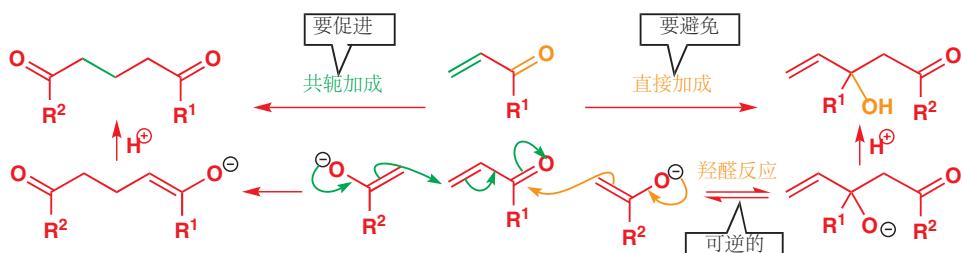


## 使用 Michael 受体做亲电试剂

如您已经看到的， $\alpha,\beta$ -不饱和羰基化合物是区域定位的（regio-defined）烯醇盐等价物极好的来源。它们也同样是与烯醇盐反应很有效的亲电试剂。在本节中，我们将考虑烯醇盐对这些化合物的共轭加成，这也是形成 C–C 键很好的方法。



和其他共轭加成一样，防止亲核试剂（此处是烯醇盐）直接进攻  $C=O$  基也很重要。支配最终产物的因素与我们在 Chapter 22 中论述的一致。热力学控制导向共轭加成，动力学控制导向直接加成，因此共轭加成成功的关键是确保对羰基的直接加成是可逆的。这样共轭加成才能被允许加入到竞争当中，于是，最终单一地形成更加稳定的产物（共轭加成失去的是较弱的  $C=C \pi$  键而不是较强的  $C=O \pi$  键）。



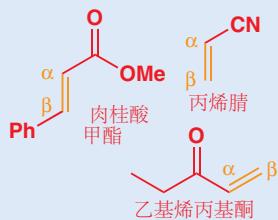
使直接加成可逆的其中一种重要方法，是令起始烯醇盐更稳定，这样直接加成产物就更倾向于转换回稳定的阴离子。我们可以通过添加吸电子基团，例如  $CO_2Et$  解决这一问题。另外，添加新基团后直接加成的产物还比共轭加成的产物有更大的空阻（并因此更不稳定）。



$\alpha,\beta$ -不饱和亲电试剂中的羰基还有一个特点，那就是较亲电的羰基给出更多的直接加成产物，较不亲电的羰基（酯、酰胺）给出更多的共轭加成产物。想要在醛和酮上共轭加成，需要仔细选择烯醇

回忆 Chapter 22: Michael 受体 (Michael acceptor) 指的是一类可以进行共轭加成的化合物——例如  $\alpha,\beta$  不饱和羰基化合物、腈。很多 Michael 受体都是有毒、致癌的化合物，处理时需要小心。

一些 Michael 受体...



► 烯醇盐对一个  $C=O$  基的直接进攻——称作羟醛反应 (aldol reaction)——也是我们在下一章的一个主题。

Interactive mechanism for conjugate addition of enolates



等价物，而酯和胺中羰基的亲电性远远小于醛、酮，因此是共轭加成很好的底物。

- 共轭加成是热力学控制的；直接加成是动力学控制的。

稳定的烯醇盐促进共轭加成，通过：

- 使直接加成（羟醛反应）更加可逆；
- 使直接加成的产物（羟醛）空阻更大。

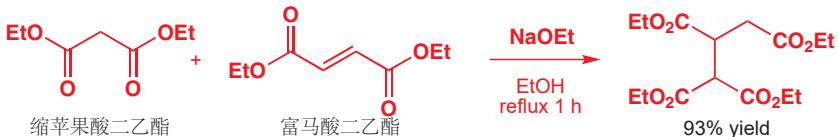
反应性较弱的 Michael 受体促进共轭加成，通过：

- 使直接加成（羟醛反应）更加可逆；
- 羰基亲电性较弱。

### 1,3-二羰基化合物发生共轭加成

$\beta$ -二酯  $\beta$ -Diesters (缩苹果酸酯及其取代衍生物，见 p. 595) 的共轭加成包含三种有价值的特征：

- 它们形成能干净地进行共轭加成的稳定烯醇阴离子；
- 如果需要，其中一个酯基可以通过水解和脱羧去除；
- 剩下的酸或酯在转化为其他官能团上是理想的。

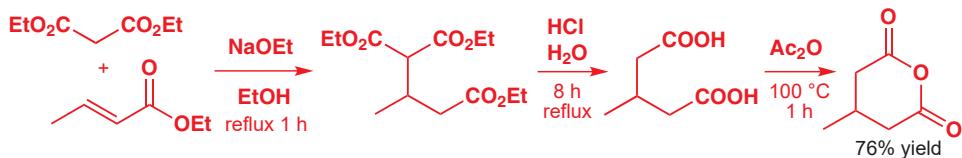


► 水解、脱羧及碱的选择  
详见 p. 597 上的讨论。

缩苹果酸二乙酯在共轭加成反应中加入到富马酸二乙酯上，这一反应通过干燥乙醇中的乙醇钠促进，并给出一个四酯 (tetraester)。富马酸二乙酯是一个极好的 Michael 受体，因为两个酯基都从烯烃上吸电子。机理包含缩苹果酸的去质子，共轭加成，以及烯醇阴离子被溶剂乙醇重新质子化。在这个反应中，两个酯基用于稳定烯醇（缩苹果酸酯中的），而另两个酯基用于促进共轭加成（富马酸酯中的）。



缩苹果酸酯的价值在用巴豆酸乙酯 (ethyl crotonate) 合成环状酸酐的过程中得以体现，过程包含共轭加成、水解、脱羧，以及乙酸酐作用下的脱水。这套路径可适用的范围很广，仅仅通过选择合适的不饱和酯就可以制备一系列酸酐。



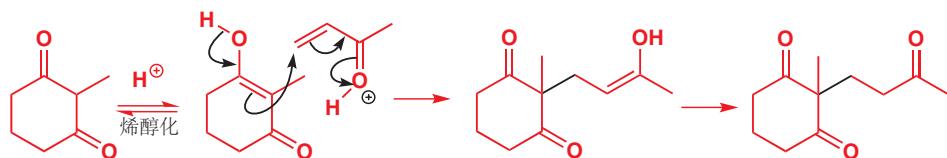
如果亲核试剂在反应条件下能够被充分地烯醇化，那么烯醇本身（酸性）都可以去进攻不饱和羰基化合物。烯醇是中性的、软的亲核试剂，因此倾向于共轭进攻。 $1,3$ -二酮可以很大程度地烯醇化

(Chapter 20), 并且在酸性条件下会很充分地进行共轭加成。在下面的例子中, 甲基烯丙基酮 methyl vinyl ketone (也称丁烯酮 butenone) 和环状的  $\beta$ -二酮乙酸的促进下生成季中心。



► 产物中的烯酮是甾族合成的重要中间体, 您会在 Chapter 26, p. 652 中见到。

机理包含酸催化下, 环状的  $\beta$ -二酮由酮式转化为烯醇式, 继而能够进攻质子化的烯基酮。详细的机理和烯醇盐进攻的非常类似; 唯一的差异是所有的反应物都被质子化了。产物是三酮的烯醇式, 迅速互变异构化为更稳定的酮式。



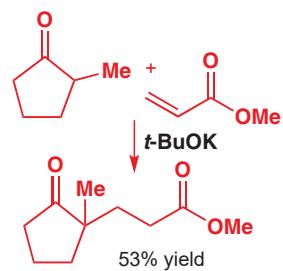
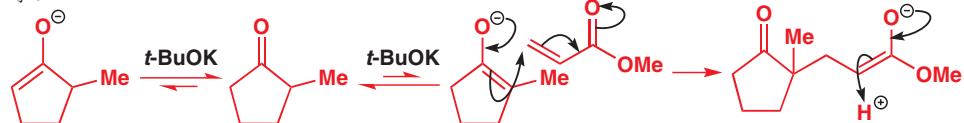
热力学控制下, 即使是羰基碳非常亲电的化合物, 例如 enals 都能成功地进行共轭加成。正如您在下一章会看到的, 羟醛反应 (直接对 C=O 键加成) 在这里必然是可行的, 但是它是可逆的, 于是 1,4-加成最终胜出了。丙烯醛在非常温和的条件下, 和五元环二酮结合, 给出定量产率的产物。



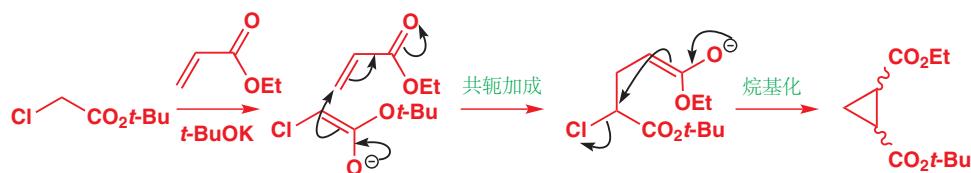
### 烯醇碱金属盐 (尤其是 Na, K) 可以发生共轭加成

用两个阴离子稳定基来推动共轭加成, 当然是可行的, 但这并不是必须的。对比直接加成产物 (羟醛) 和共轭加成产物, 羟醛的稳定性更差, 而共轭加成产物与碱金属阳离子更容易解离。这种现象在用烯醇锂时不能观察到, 因为锂与氧成的键较强, 可以用来稳定羟醛产物; 而如果用钠碱或钾碱, 则可以倾向于共轭加成。理想的碱是叔丁醇钾, 因为它的空阻较大, 不会进攻酯, 但却有足够的一定程度上为酮去质子的碱性。

有两种可能的烯醇盐, 但在热力学条件下, 只有最稳定的烯醇盐导向产物, 产物含有一个季碳原子。

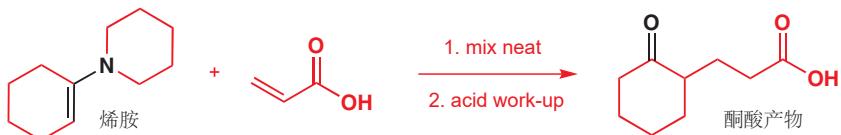


如果烯醇盐带有离去基团, 共轭加成所生成的烯醇盐就可以发生烷基化, 于是我们获得了一个制备环丙烷很好的方法。

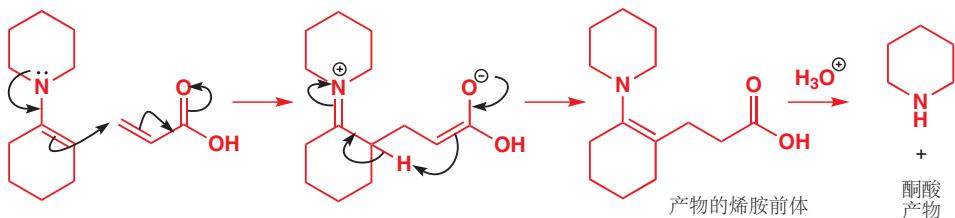


### 烯胺是用于共轭加成的方便的稳定烯醇等价物

如果您不想添加第二个阴离子保护基，更可靠的共轭加成方法是使用相对较不活泼的烯醇等价物。在 p. 591 中我们应用了烯胺，尤其是那些来源于环状仲胺的烯胺，对于烷基化反应都是实用的。这些中性的物种是软的亲核试剂，对于共轭加成是完美的，另外它们又比烯醇反应性强，且可以提前被定量地制备。烯胺较强的反应性使得，只需要将试剂混合并加热，有时需要无溶剂 (neat) 条件，即可反应。酸性催化剂也可以用于催化低温下的反应。



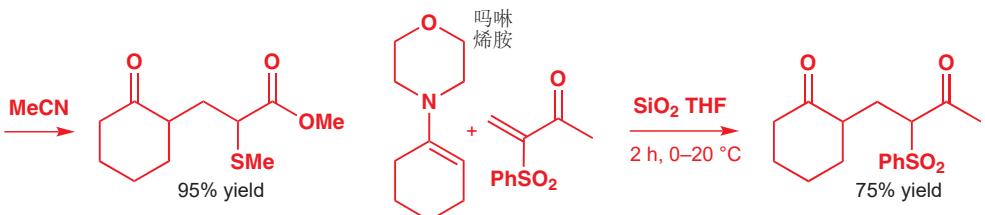
其机理相当地像烯醇的加成。区别在于，以氮替代氧后的烯胺的亲核性更强。反应的产物仍是个烯胺，可以通过温和酸性下的水解转化为羰基。这一过程通常在后处理中完成，并不需要实质上的额外步骤。胺以其盐酸盐的形式被洗去，分离过程是很直接的。共轭加成后所得的是烯醇盐-亚铵例子(enolate-iminium ion)，随即发生快速的质子交换转化为更稳定的羰基-烯胺(carbonyl-enamine)互变体；既可以画作分子内过程，又可以画作外部碱和质子源参与的过程。所得的烯胺直到后处理前都是稳定的，酸的水溶液的加入完成了反应。水解通过亚铵离子的中间体发生，呈现第二个羰基，并释放仲胺。



► 在 Chapter 41 中我们将讨论手性胺在推动不对称的相关反应时催化作用的体现。



如下两个例子中，烯胺由环己酮与四氢吡咯(吡咯烷)或吗啉产生，它很好产率地加入到一个带有额外吸电子基团的  $\alpha,\beta$ -不饱和羰基化合物中，吸电子基团分别为甲硫基(methylthio) 和苯磺酰基(phenylsulfonyl)。



► 烯醇硅醚的介绍参见 Chapter 20, Lewis 酸的描述参见 p. 466。您在 p. 604 看到过一个卤代烷做亲电试剂的类似反应。

### 烯醇硅醚的共轭加成给出产物的烯醇硅醚形式

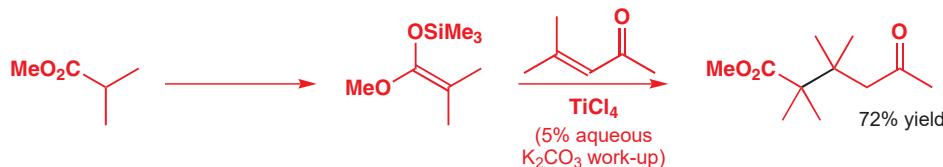
在醛、酮和羧酸衍生物的共轭加成中，烯醇硅醚是替代烯胺的最好选择。无论是使其自发反应，还是用 Lewis 酸 ( $TiCl_4$ ) 催化低温反应，稳定的中性亲核试剂都可与 Michael 受体可以很好地作用。如果需要 1,5-二羰基化合物，那么可以用酸或碱的水溶液后处理，以断裂产物中的硅-氧键。



由苯乙酮 ( $\text{PhCOMe}$ ) 衍生得到的烯醇硅醚，在四氯化钛的推动下与双取代的烯基酮反应，纵使共轭加成会形成一个季碳原子，这个反应仍然十分迅速，并以好产率给出二酮产物。这是这类非常强大的共轭加成反应 (烯醇硅醚参与的) 的一个典型例子。

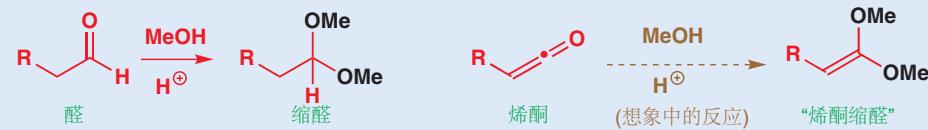


甚至，用烯醇硅醚形成一个连接两个季中心的新 C–C 键也是可能的。硅烯酮缩醛 Silyl ketene acetals (酯的烯醇硅醚) 比普通的烯醇硅醚更加亲核，在这个例子中，硅烯酮缩醛在 Lewis 酸 (TiCl<sub>4</sub>) 催化下，共轭加成到一个不饱和酮上。

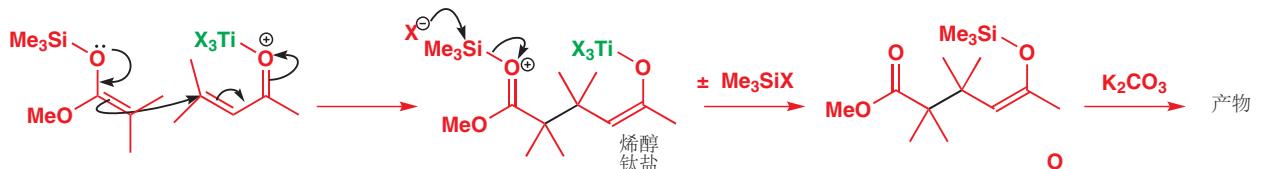


### 烯酮缩醛

由于酯的烯醇醚有两个等价的 OR 基处在同一根双键的同一段，因此它们被称作“烯酮缩醛 (ketene acetals)”，或是在这里特指的“硅烯酮缩醛”。这个描述是合理的，您可以想象烯酮 (ketene) 的羰基像醛中的羰基一样形成缩醛 (acetal)；虽然事实上烯酮缩醛并不是那样得到的。

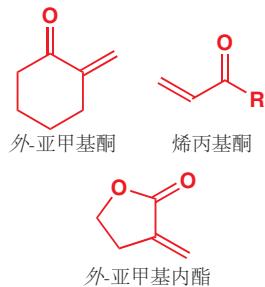


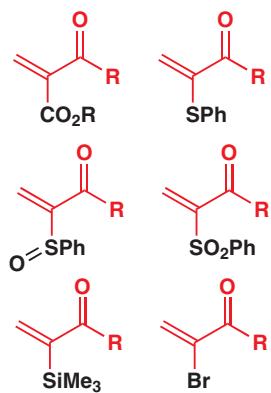
在这些反应在，亲电试剂先于  $\text{TiCl}_4$  Lewis 酸配位，生成一个活化的烯基酮等待硅基亲核试剂的进攻。三甲基硅醚何时经历分子内转移，从其原来的地方移动到产物中它位于的地方是我们不得而知的。很多时候，从 Lewis 酸中释放出来的阴离子 ( $\text{Cl}^-$ ,  $\text{RO}^-$ ,  $\text{Br}^-$ ) 都是对于硅很好的亲核试剂，因此我们可以合理地假设先形成了游离的三甲基硅基物种 ( $\text{Me}_3\text{SiX}$ )，用于随后捕获烯醇钛盐。



### 种种可接受烯醇(盐)亲核进攻的烯烃

最简单的，也是最好的 Michael 受体是带有暴露的不饱和  $\beta$  碳原子的  $\alpha,\beta$ -不饱和羰基化合物，例如外-亚甲基酮、内酯 (*exo*-methylene ketones, lactones) 以及乙烯基酮。然而，它们极高的反应性也使它们难以处理 (它们很容易聚合)，而在下一章中 (p. 621) 您会遇到让它们在反应混合物中 (*in situ*) 避免这些问题的方法。

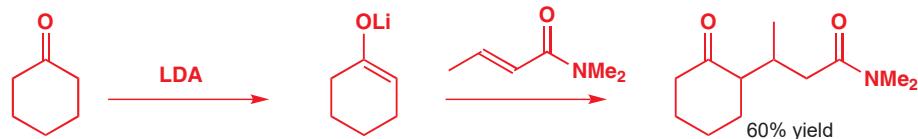




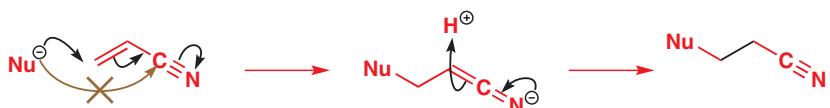
► 本章的开始就阐述了氰基对烯醇盐烷基化的选择性活化作用。

说服一个顽固的烯醇盐去共轭加成，而不是直接加成的技巧之一是在其  $\alpha$  位加上一个吸电子基团。侧边栏展示了几种用于这一用途的试剂。每种中额外添加的基团 ( $\text{CO}_2\text{Et}$ ,  $\text{SPh}$ ,  $\text{SOPh}$ ,  $\text{SO}_2\text{Ph}$ ,  $\text{SiMe}_3$ , 和  $\text{Br}$ ) 都可以在共轭加成完成后被去除。

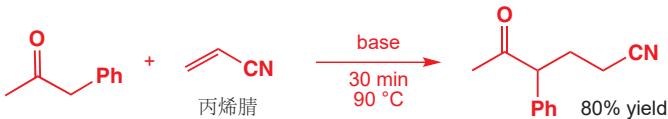
不饱和酯是很好的 Michael 受体，因为它们并不非常亲电。不饱和酰胺相比之下就更遑论亲电性了（叔胺，没有酸性的 NH 质子的条件下），与烯醇锂反应会更多地给出共轭加成产物。



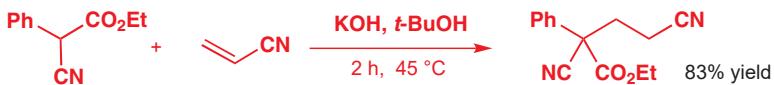
**氰基**相比于它羰基的兄弟，面对亲核试剂的直接进攻反应性并不高，但它却是可以稳定邻位负电荷的。因此，与腈共轭的烯烃面对亲核进攻是被活化了的，而且它还无需面临与直接进攻相竞争的麻烦。



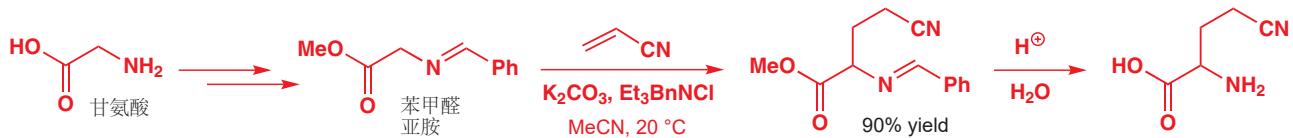
碱性下，甲基苄基酮生成它烯醇盐中更稳定的一个，随后顺利且快速地共轭加成到丙烯腈。丙烯腈是对于烯醇盐，最好的 Michael 受体之一。



氰基同样可以作为亲核试剂中的阴离子稳定基。与酯基共同作用，使得烯醇化的质子酸性很强，仅用氢氧化钾做碱即可去除。



最简单的氨基酸，甘氨酸，会使合成其他更复杂的氨基酸的理想起始原料，但它生成烯醇或烯醇盐的过程不容易。将其转化为其苯甲醛亚胺的甲酯，于是就引入了两个帮助稳定烯醇盐的吸电子基，继而对丙烯腈的加成就是可能的了。所用的碱是固态的碳酸钾。烷基化产物经简单的水解，即可转化为扩展后的氨基酸。

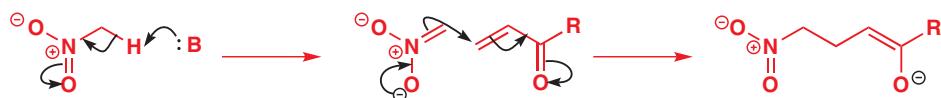


您在 p. 606 中看到了富马酸二酯中的两个酯基是如何促进共轭加成的，但如果 Michael 受体的两端是两个不同的基团呢？那么您需要比较它们吸电子能力的强弱。有一个情形是很清楚的。硝基的吸电子能力价值两个羰基 (p. 586) 因此下面的例子中共轭加成发生在硝基的  $\beta$  位。



### 硝基烷烃是共轭加成极好的亲核试剂

本章到目前为止，您已经看到了很多高度稳定的阴离子，例如  $\beta$ -二羰基化合物衍生的烯醇阴离子，是尤其好的亲核加成试剂，因为它们的稳定性有利于将不理想的直接  $C=O$  加成产物（羟醛）转化回反应物，也促进了这个反应催化版本中的质子转移。硝基是很强大的吸电子基团，仅一个就与两个羰基在  $pK_a$  方面等价 (p. 586)。因此如果  $\beta$ -二羰基混合物是共轭加成很好的亲核试剂，那么您会希望硝基烷烃也能以相同的方式参与共轭加成。好消息是它们确实如此，而且作用得很好。第一阶段是碱催化的共轭加成。

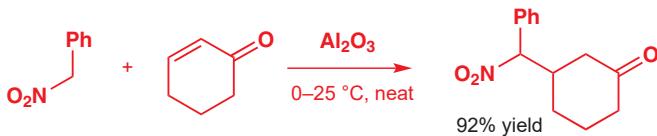


■ 在机理中，如果需要用到硝基，往往将其充分地画出来。

产物烯醇盐比硝基化合物阴离子的碱性更强，因此它会从另一分子的硝基化合物中夺去质子，自己变为产物，也为下一轮的反应提供另一分子的阴离子。



硝基的酸化效果（对质子）十分显著，因此它们的反应选用了很温和的碱来催化。这样做可以选择性地去除硝基旁边的质子，并避免羰基化合物的副反应发生。温和的碱常见的例子包括胺、季铵碱和氟化物。甚至是碱性氧化铝 basic alumina（一种通常惰性的粉末）都足以在室温下，催化这个几乎定量的，苄基硝基烷与环己烯酮的加成反应！



硝基化合物的阴离子很容易通过与  $\alpha,\beta$ -不饱和单、双酯的加成形成季中心。选用了很温和的碱性条件，为了确保通过酸性，将硝基的质子与产物中挨着酯基的质子区分开来。

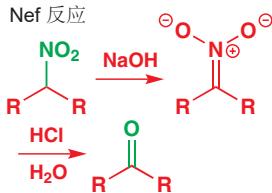
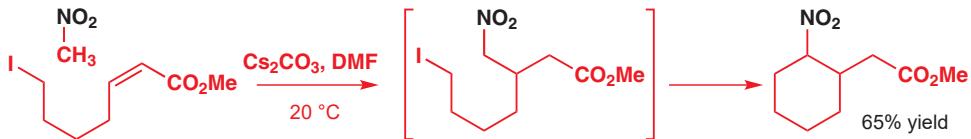


■ 如您会在 Chapter 26 中见到的，可烯醇化的酯、酮和醛在强碱的存在下，都很容易遭受与自己发生的缩合反应。

硝基化合物共轭加成的有效性，使其成为能与其他反应结合着，在一锅中形成多根键的理想方法。下一个例子将共轭加成与分子内共轭加成结合，制得了一个六元环。两步使用的碱都是

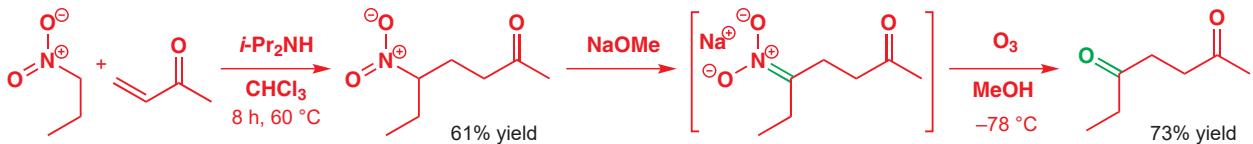
铯是易用的金属中最具电正性的：  
电负性 = 0.79.

$\text{Cs}_2\text{CO}_3$  较大的铯阳离子形成完全离子化的化合物，碳酸根离子不能与之结合，因此它的碱性得到了最大程度的运用。共轭加成产物又在其硝基旁形成第二个阴离子，继而发生对碘的，分子内的  $\text{S}_{\text{N}}2$  取代形成六元环。



有关臭氧解 (Ozonolysis) 反应的描述在 Chapter 19.

在共轭加成后，硝基可以转化为其他有用的基团。将其还原可以给出伯胺，将其水解可以呈现出酮。这种水解反应被称为 **Nef 反应 (Nef reaction)**，先通过例如氢氧化钠的碱，使之形成硝基稳定的阴离子，然后在加入硫酸水解来实现。这些条件对很多底物 (和产物) 都是相当苛刻的，因此以及开发出了更为温和的方法。其一是用硝基“烯醇盐”与臭氧在低温下发生的臭氧解反应替代酸处理。硝基丙烷在碱催化下顺利地共轭加成到甲基乙烯基酮上，给出硝基酮。然后用乙醇钠将其转化为盐，并通过臭氧化将  $\text{C}=\text{N}$  键断裂，并连接到臭氧上。产物为 1,4-二酮，在此阶段分离，整个流程中没有羟醛副反应发生。

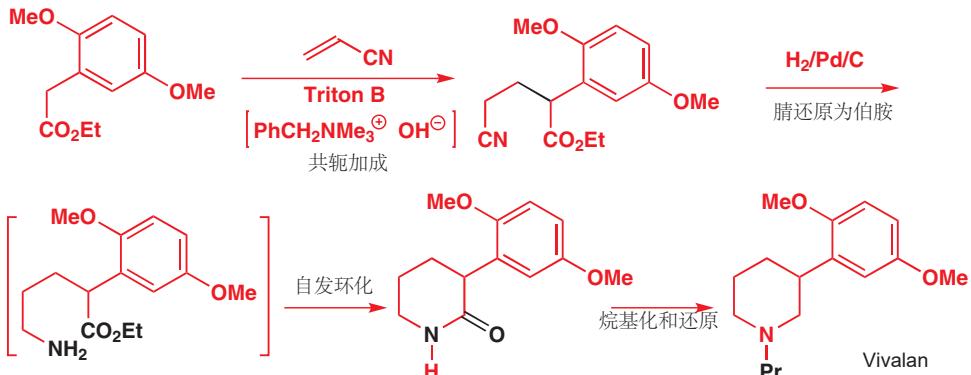


这是一种很好的合成 1,4-二酮 的通用方法，而其他方法却很难制备，烯基酮很容易被安置上额外的取代基——这是共轭加成的一个特定。

### 一种作用于脑化学的药物的合成

我们将以一个药物分子简单的商业化合成作为本章的结尾——该分子为 **vivalan**——是一种“多巴胺拮抗剂 (dopaminergic antagonist)”。它用到了四种您见过的反应：烯醇盐对丙烯腈的共轭加成， $\text{CN}^-$  还原为伯胺，烷基化，和酰胺的环化生成——这个反应自发发生。

此处的共轭加成用了三甲基苄基氢氧化铵 (benzyltrimethylammonium hydroxide) 做碱，此物种以 Triton B 为商品名出售，用于将氢氧根溶解在有机溶剂中。



### 小结

我们以及考虑了烯醇盐及其等价物与卤代烷和亲电的烯烃的反应。在下一章中，我们将转向考虑从前总是故意要采取措施避免的反应。我们将考虑同样的几类烯醇盐等价物与羰基化合物本身的反

应。

### ● 烯醇盐烷基化的方法总结

特别的烯醇盐等价物	注意
用于酯的烷基化	
<ul style="list-style-type: none"> <li>LDA → 烯醇锂</li> <li>用缩苹果酸二乙酯、二甲酯并脱羧</li> </ul>	得到酸 (NaOH; HCl) 或酯 (NaCl, DMSO)
用于醛的烷基化	
<ul style="list-style-type: none"> <li>用烯胺</li> <li>用烯醇硅醚</li> <li>用烯胺盐阴离子</li> </ul>	与活泼烷基化试剂 与 $S_N1$ -反应性 烷基化试剂 与 $S_N2$ -反应性 烷基化试剂
用于对称酮的烷基化	
<ul style="list-style-type: none"> <li>LDA → 烯醇锂</li> <li>用乙酰乙酸酯并脱羧</li> <li>用烯胺</li> <li>用烯醇硅醚</li> <li>用烯胺盐阴离子</li> </ul>	与丙酮发生烷基化等价 与活泼亲电试剂 与 $S_N1$ -反应性 烷基化试剂 与 $S_N2$ -反应性 烷基化试剂
用于不对称酮在多取代侧的烷基化	
<ul style="list-style-type: none"> <li><math>Me_3SiCl, Et_3N \rightarrow</math> 烯醇硅醚</li> <li><math>Me_3SiCl, Et_3N \rightarrow</math> 烯醇硅醚 → 烯醇锂和 MeLi</li> <li>烷基化乙酰乙酸酯两次并脱羧</li> <li>用烯基酮的加成或还原 给出特定的烯醇锂或烯醇硅醚</li> </ul>	与 $S_N1$ -反应性 烷基化试剂 与 $S_N2$ -反应性 烷基化试剂 乙酰乙酸乙酯连续两次烷基化
用于不对称酮在少取代侧的烷基化	
<ul style="list-style-type: none"> <li>LDA → 热力学的烯醇锂</li> <li>LDA 然后 <math>Me_3SiCl \rightarrow</math> 烯醇硅醚</li> <li>用烷基化的乙酰乙酸酯的双阴离子并脱羧</li> <li>用烯胺</li> </ul>	与 $S_N2$ -反应性 亲电试剂 与 $S_N1$ -反应性 亲电试剂 乙酰乙酸乙酯连续两次烷基化 与活泼亲电试剂

## 延伸阅读

P. Wyatt and S. Warren, *Organic Synthesis: Strategy and Control*, Wiley, Chichester, 2007, chapter 10. 此领域的先驱者所写的一篇早期文章: H.O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, 1971, 36, 2361. 特定的烯醇盐的形成与烷基化的一个很好的例子:

D. Caine, S. T. Chao, and H. A. Smith, *Org. Synth.*, 1977, 56, 52. F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry B, Reactions and Synthesis*, 5th edn, Springer 2007, chapter 1.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 26

## 烯醇盐和羰基化合物的反应： 羟醛反应和 Claisen 反应

### 联系

#### 基础

- 羰基化合物与氰离子、硼氢化物和亚硫酸氢盐反应 ch6
- 羰基化合物与有机金属亲核试剂反应 ch9
- 羰基化合物参与亲核取代反应 ch10 & ch11
- 烯醇和烯醇盐如何与杂原子亲电试剂，例如  $\text{Br}_2$  和  $\text{NO}^+$  反应 ch20
- 烯醇盐和它的等价物如何与烷基化试剂反应 ch25

#### 目标

- 羰基化合物既作为亲核试剂，又作为亲电试剂的反应
- 如何通过羟醛反应，制取羟基-羰基化合物（羟醛）或烯基酮
- 如何确保您在羟醛反应中得到了想要的产物
- 用醛、酮和酯的烯醇盐完成羟醛反应的可用的不同方法
- 如何用甲醛做亲电试剂
- 如何预测分子内羟醛反应的结果
- 酯如何与烯醇盐反应：Claisen 缩合
- 如何酰基化酯和酮的烯醇盐
- 如何得到获得 C-酰基化 而避免 O-酰基化
- 如何用分子内酰基化制备环状酮
- 酰基化反应中的烯胺
- 模拟自然界中的酰基化

#### 展望

- 逆合成 ch28
- 芳杂环的合成 ch29 & ch30
- 不对称合成 ch41
- 生物有机化学 ch42

### 引入

上一章我们谈论了烯醇和烯醇盐与卤代烃、 $\alpha,\beta$ -不饱和羰基化合物等烷基化试剂的反应。我们强调了，避免在羰基上发生亲核进攻是多么重要。

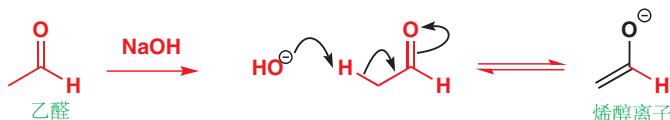
烯醇盐的烷基化



本章的设置也特意选择了烯醇和烯醇盐亲核进攻的反应，前半部分的羟醛反应 (aldol reaction) 是对醛或酮的进攻，而后半部分的内容是对酰基化试剂的进攻。

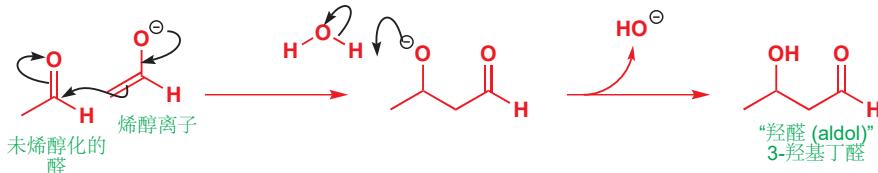
## 羟醛反应

最简单的可烯醇化的醛是乙醛 (ethanal, acetaldehyde,  $\text{CH}_3\text{CHO}$ )。如果我们在其中加入少量的碱，比如说  $\text{NaOH}$ ，会发生什么呢？一部分的乙醛会形成烯醇离子。



仅生成了很少量的具亲核性的烯醇离子：如我们在 Chapter 25 指出的，氢氧根的碱性不足以将醛全部烯醇化。每个形成了的烯醇离子都被其他没有烯醇化的醛分子所包围着，这些醛分子都还含有具亲电性的羰基。烯醇离子会进攻这些醛中的一个的羰基，并生成烷氧基离子，继而再被第一步所生成的水质子化。

$\text{pK}_a \text{ H}_2\text{O} = 15.7$ ;  
 $\text{pK}_a \text{ MeCHO} \sim 20$



产物是一个带有羟基 (*ol*) 的醛 (aldehyde)，因此我们将其俗称作羟醛 (aldol)。羟醛这一名称之所指包含烯醇 (或烯醇盐) 与羰基化合物反应 (羟醛反应 aldol reaction) 得到的一整类化合物。注意碱催化剂 (氢氧根离子) 在最后一步重新生成，因此它确实是催化剂。

这个反应十分重要，因为在亲核的烯醇盐进攻亲电的醛时，形成了 碳–碳 键，如图是羟醛反应最关键的一步，描黑的键即为新形成的 碳–碳 键。

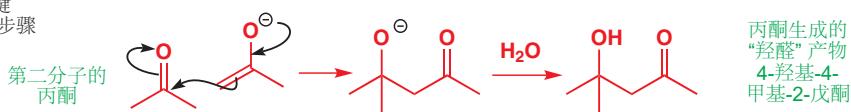


这个反应在酮上也能很好地发生。有一个很适合在开篇提的很好的例子，就是丙酮，它会给出一个重要的产物，而且它本身是对称的酮，这使得我们不需要被在哪边烯醇化所困惑。每一步都与醛的羟醛反应完全相同，其产物也是一个羟基-羰基化合物，是一个羟基-酮。

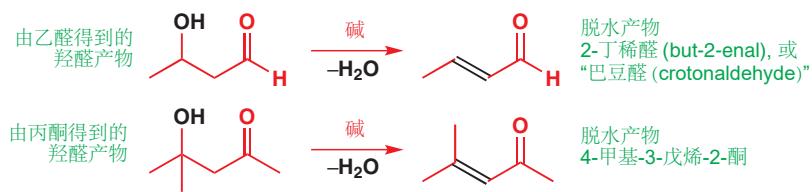
烯醇化的步骤



碳–碳键形成的步骤

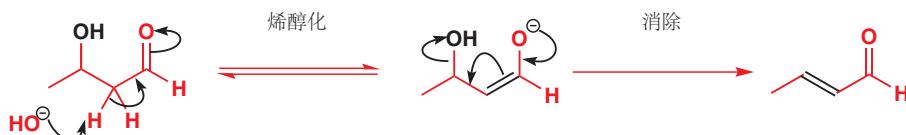


乙醛的反应在滴入一滴稀氢氧化钠后就可以很好地进行，而丙酮反应的最佳条件是使用不溶的氢氧化钡， $\text{Ba}(\text{OH})_2$ 。它们都要求保持碱的低浓度。如果没有这种预防措施，从反应体系中分离出来的就不再是羟醛产物了。有了更多的碱，羟醛产物就会相当容易地脱水 (dehydrate)，发生后续反应，并得到共轭的不饱和羰基化合物。



见 p. 399 关于 E1cB 机理的讨论。

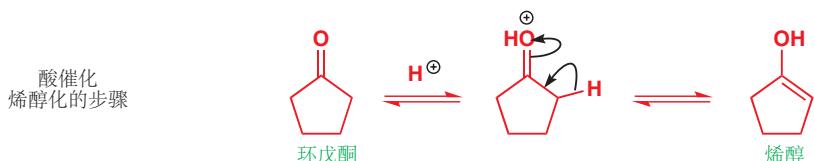
羟醛产物的脱水过程是您在 Chapter 17 已经遇到过的消除反应，当时讨论过其可能的机理。通常的机理不允许您在碱溶液中消去水，因为氢氧根是差的离去基团。此处的消除受羰基的帮助：它们是 E1cB 反应，烯醇化允许随后  $\text{OH}^-$  的离去。



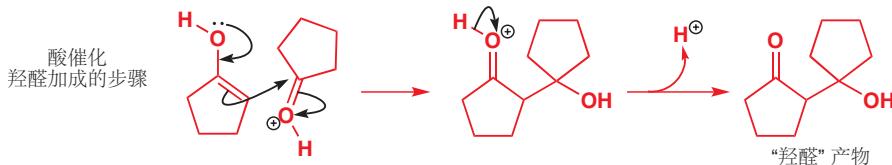
您当然不需要分别记住所有的条件所对应的结果：如果您需要做一个简单的羟醛反应，您可以查阅 1968 年 *Organic Reactions* 中的大量综述。

在下面的例子中，您会发现碱催化的羟醛反应有时给出烯醇，而有时却给出消除产物。这种选择部分地取决于条件——条件越强硬（强碱，高温，长时间反应），则更容易发生消除——也部分地取决于试剂的结构。

消除在酸催化的羟醛反应中甚至更容易，这一过程通常给出不饱和产物，而不是羟醛。在下面的对称的环状酮参与的简单例子中，不论碱性还是酸性都能高产率地得到烯基酮、烯基醛。我们会使用酸催化反应来说明机理。首先是我们在 Chapter 20 中讨论过的，酸催化烯醇化。

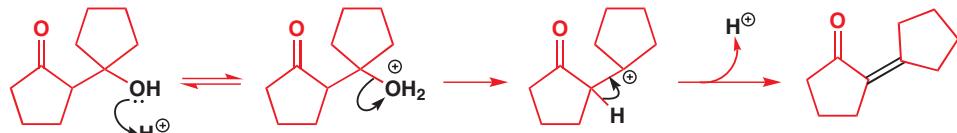


然后羟醛反应发生了。烯醇比烯醇盐的亲核性较弱，反应的发生是因为另一个亲电的羰基化合物已经被质子化了：此反应在酸催化下进行。酸催化的羟醛反应如下进行。



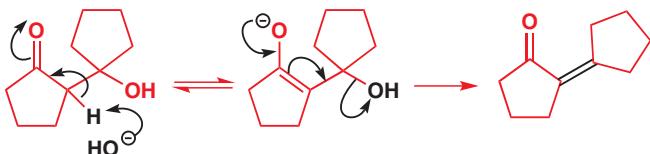
所生成的羟醛是一个叔醛，因而在酸性下会很乐意通过 E1 机理消除，即使没有羰基的参与消除也很容易，而羰基的作用只是确保最终生成的是唯一的、稳定的、共轭的烯基酮。同样要注意，脱水过程的酸也是真正的催化剂，因为它在最后一步重新出现。

酸催化脱水的步骤 (E1 消除)



在实践中，这些中间体都不需要被检测或者分离出来——只要简单地用酸处理酮，即可以很好的产率得到烯基酮。碱催化的反应也通过羟醛-E1cB 消除机理得到相同的产物。

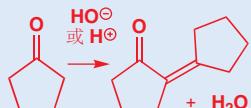
碱催化脱水的步骤 (E1cB 机理)



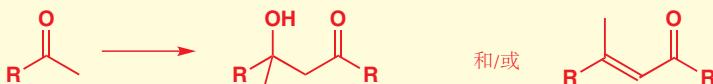
### 羟醛缩合 (Aldol condensations)

术语“缩合 (condensation)”所描述的就是这类反应。缩合指的是两个分子结合的反应，还要伴随着一个小分子的离去——通常是水。在这个情形中，两个酮伴随着水的失去而结合。这个反应被称作羟醛缩合，化学家可能这样描述：“两分子的环戊酮缩合 (condense) 并给出一个共轭的烯基酮。”并且您还会发现不论最后是否脱水，人们都会用“缩合”来形容羟醛反应。这种差别已经不再重要。

#### 环戊酮的缩合



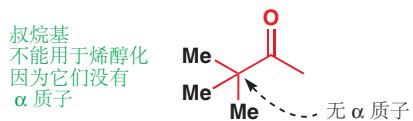
- 碱催化的羟醛反应可能得到羟醛产物，也可能通过 E1cB 机理脱水，得到烯基酮或烯基醛。
- 酸催化的羟醛反应可能得到羟醛产物，但通常得到的是通过 E1 机理脱水后的烯基酮或烯基醛。



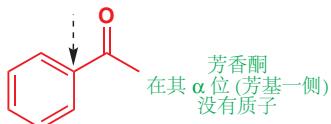
### 不对称酮上的羟醛反应

如果酮在一侧被阻塞，不能烯醇化——换句话说就是没有质子——那么仅会有一种可能的羟醛反应。这种情况发生于带叔烷基或芳香取代基的酮。例如叔丁基甲基酮 (3,3-二甲基丁-2-酮)，在各种各样的碱中都能 60–70% 产率地发生羟醛反应。叔丁基的一侧不能烯醇化，因此烯醇化必定发生于甲基的一侧。

#### 只能以一种方式烯醇化的酮

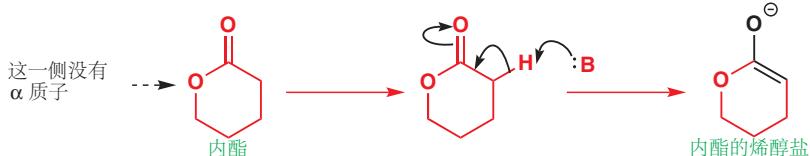


#### 芳环上的三角型碳 无质子



另一个由其有趣的，被阻塞的羰基化合物是内酯 (lactone, 环酯 cyclic ester)。开链酯 (Open-chain esters) 并不发生羟醛反应：它们倾向于发生本章的后半部分所要讨论的反应。但内酯有些方面很像酮 (IR 中它们 C=O 基的伸缩频率相似，而且不同于酯，它们不能与 NaBH4 反应)，并会在碱催化剂下给出不饱和羰基化合物。由于酯基氧原子的阻塞，烯醇化的位置是非常清晰的。

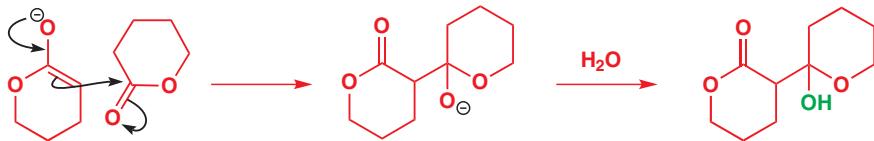
#### 内酯生成的烯醇



■ 本图中的 B 代表 碱 (base)。

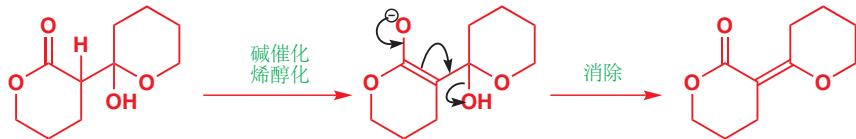
烯醇盐随后进攻另一未烯醇化的内酯分子的羰基，与醛和酮的反应一样。

### 内酯的羟醛反应



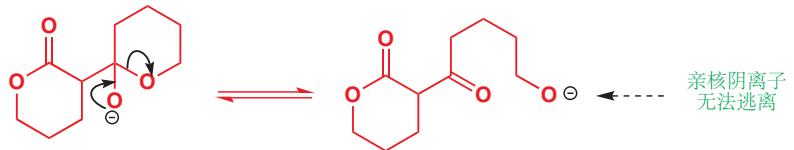
最后一步是我们熟悉的脱水。由于这个反应在碱中进行，于是我们最好用经历羟醛产物的烯醇化的 E1cB 机理表示。

### 脱水的步骤



您可能会对一件事感到意外，那就是为什么羟醛中间体不发生分解呢。羟醛中间体还可以被描述为羰基上的亲核取代 (Chapter 10) 的四面体中间体。那么为什么它不以四面体中间体的常规方式分解呢？

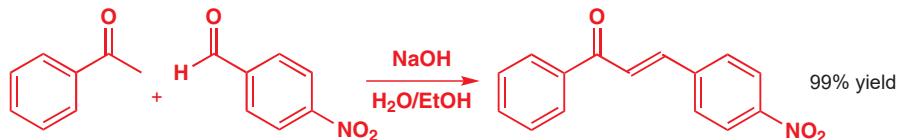
### 内酯的羟醛反应中的四面体中间体可能的断裂方式



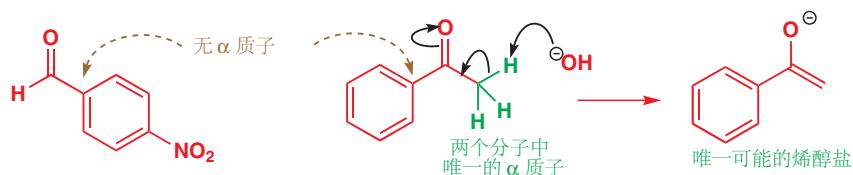
最好的离去基团是烷氧基阴离子，而产物也很有道理。但接下来会怎么样？唯能接下去的步骤就是重新进攻回来。因为内酯是一个环状的酯，离去基团无法逃离——它仍然附着在分子上。这个反应是可逆的，但脱水却是不可逆的，进而也是有效的，因为脱水得到的是一个稳定的共轭产物。通常，无环酯与之不同：它们的烷氧基离去基团可以离去，其结果正是本章后面会遇到的另一类反应。

## 交叉缩合

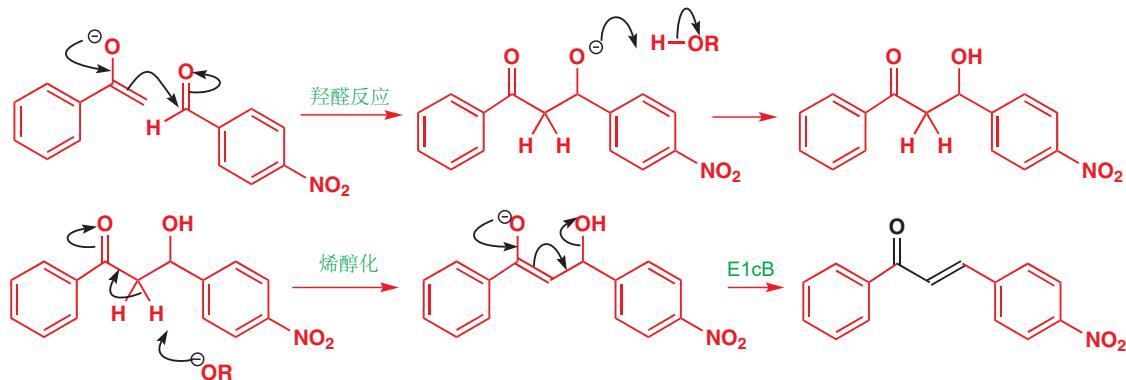
到目前为止，我们只考虑过“自缩合 (self-condensations)”——简单羰基化合物的二聚反应。这只是已知的羟醛反应，很小的一部分。而发生于两种不同的羰基化合物之间的反应，一种以其烯醇式做亲核试剂，而另一种做亲电试剂，被称为**交叉缩合** (cross-condensations)。它们比其自缩合更加有趣，但是想弄清楚它们也需要更多的思考。我们会以一个运行良好的例子开始。酮 PhCOMe 与 4-硝基苯甲醛在乙醇水溶液中，NaOH 催化下给出定量产率的烯基酮。



第一步一定是 NaOH 做碱下烯醇阴离子的形成。两个羰基化合物都是不对称的，但即使这样仍然只有一个位点有  $\alpha$  质子，继而可以烯醇化，这个位点就是酮上的甲基，而醛上根本没有  $\alpha$  质子。



从产物的角度推断，烯醇盐进攻醛，并得到羟醛，然后再经 E1cB 机理脱水。

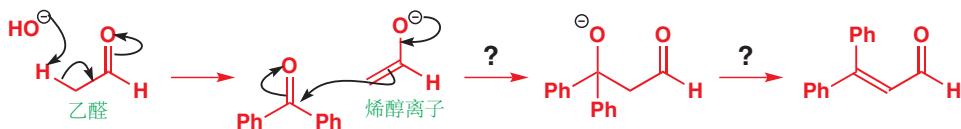


但在进攻时，烯醇盐却会面对选择，它还可以进攻另一分子未烯醇化的酮。但它没有，这是因为酮没有醛活泼 (Chapter 6)。在上述情形中，醛上还有吸电子的硝基取代基，这使其活性进一步增强。烯醇盐选择更加亲电的试剂——即醛。

在其他情形中，平衡有可能倾向于自缩合。您也许认为乙醛和二苯甲酮 ( $\text{Ph}_2\text{C}=\text{O}$ ) 的交叉缩合能很好地发生。



无论如何，仅有醛可以烯醇化，得到的烯醇盐去以进攻酮。



但事实并非如此。酮的空阻很大，而且非常共轭。它相比于普通的酮亲电性较差，而普通的酮又比醛亲电性差。因此在做选择时，烯醇盐舍弃了酮，而进攻另一分子 (未烯醇化的) 乙醛；并且在每一次选择时都是如此。本章开头论述的反应发生了，而酮仅作为一个旁观者。

### ● 成功的交叉羟醛反应

这类交叉羟醛反应若想成功，必须具备以下两个条件：

- 仅有一个组分可以烯醇化。
- 另一个组分必须不能烯醇化，而且要比能烯醇化的组分的亲电性强。

所有人都会记得第一个条件，但却很容易忘掉第二个。

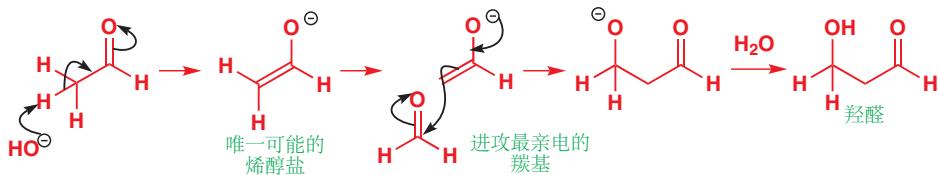
### Mannich 反应

乍一看，甲醛 ( $\text{CH}_2=\text{O}$ ) 像是混合的羟醛反应中理想的亲电组分。它不能烯醇化。(通常我们关心醛中的  $\alpha$  氢原子，而甲醛中根本没有  $\alpha$  碳原子。) 并且甲醛还是醛中独占鳌头的一个。醛比酮亲电性好的原因是因为一个氢原子替代了一个烷基，而甲醛中有两个这样的氢原子。

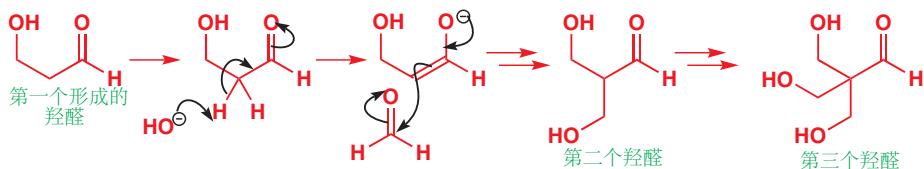
### 甲醛

纯净的甲醛不可获得，因为在纯净状态中它会形成三聚体或四聚体。可以获得的是其水溶液，即常用于保存生物标本的“福尔马林 (formalin)”——含 37% 的甲醛，大部分以水合物  $\text{CH}_2(\text{OH})_2$  的形式存在；见 Chapter 6。纯净而干燥的聚合物“多聚甲醛 (paraform aldehyde)”也可获得，我们在 Chapter 9 中介绍过。这两种试剂在羟醛反应中都不很实用。其水溶液可用在我们将简短描述的 Mannich 反应中。短暂存在的甲醛单体可以制得，也可用烯醇锂将其捕获，但这是很复杂的实验。

乙醛与甲醛的交叉羟醛反应

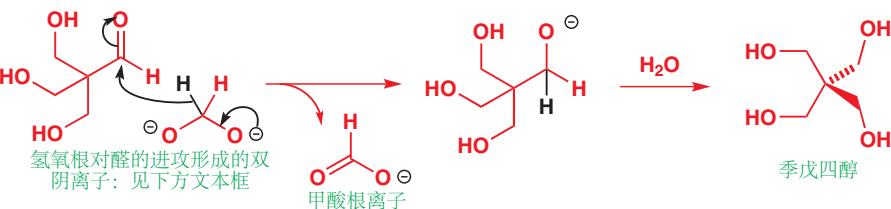


这个羟醛可以顺利地生成，但它并不是反应的最终产物。在像甲醛这样强的亲电性的试剂的作用下，第二个、第三个羟醛迅速地接踵而至。



这还没有完。第四分子的甲醛会与氢氧根离子结合，然后还原第三个羟醛。这个还原过程被称作 Cannizzaro 反应 (康尼查罗反应, Cannizzaro reaction)，在下方的文字框中有关于它的描述。最终产物是一个高度对称的“季戊四醇 (pentaerythritol)”， $\text{C}(\text{CH}_2\text{OH})_4$ ，同一个碳原子上四面体型排列着四个  $\text{CH}_2\text{OH}$  基。整个反应消耗了四分子的甲醛，可以以高产率 (典型的是 NaOH 参与的反应，产率为 80%；而用  $\text{MgO}$  可以达到 90%) 得到产物。

通过 Cannizzaro 反应还原

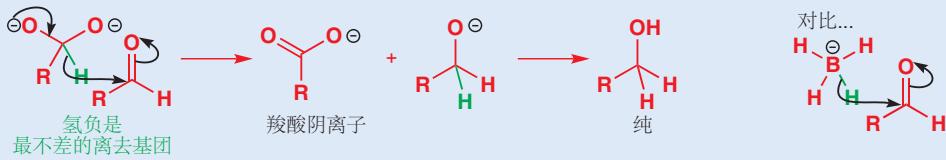


### Cannizzaro 反应

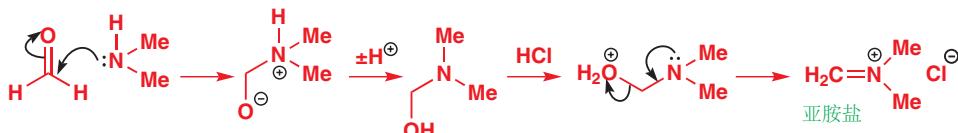
如您所知，醛在水中通常至少部分地水合。水合受碱催化，我们可以将碱中水合的步骤如下表示。水合产物是一个单阴离子，但如果碱性足够强 (或浓度足够高)，只要醛不会被质子化，至少会有一部分以双阴离子存在。



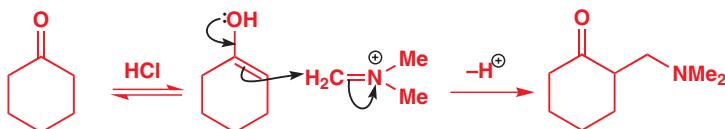
双阴离子十分不稳定，能使其稳定性大大提高的一种方法是像四面体中间体一样表现。那么谁是最好的离去基团？从  $O^{2-}$ 、 $R^-$  和  $H^-$  中选择，正是  $H^-$ （虽然勉强）需要离开。氢负离子不稳定，当然不能释放进溶液中，但如果手边就有一个合适的亲电试剂（例如另一分子醛），它就可以以下类似于硼氢化还原的机理，迁移到亲电中心上。



机理的开始是由胺和甲醛形成亚胺盐。胺是亲核试剂，进攻两个可用的羰基化合物中更亲电的一个，当然就是甲醛。在这步加成中，不需要酸的催化，但酸催化剂给加成产物去质子，并给出亚胺盐。在一般的 Mannich 反应中，这只是一个中间体，但由于它十分稳定，相应的碘化物也以 Eschenmoser 盐 (Eschenmoser's salt) 出售，并直接在 Mannich 反应中使用。

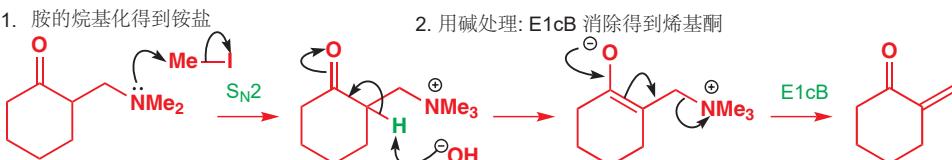


亲电的盐现在可以加成到酮的烯醇（现在处于酸性）上了，并给出反应的产物，一种有时被称作 **Mannich 碱** (Mannich base) 的胺。



通过这个反应，您可以将一分子的甲醛——也仅有一分子——加到羰基化合物上。您也许，当然有理由反对这并不是羟醛产物——事实上，如果您想要羟醛产物，Mannich 反应对您的帮助并不会很大。尽管如此，这仍是一种很重要的反应。首先，它是制备氨基酮最简单的方法，很多药物分子都属于氨基酮。

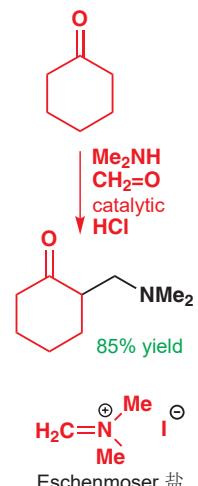
其次，Mannich 产物可以转化为烯基酮。制备烯基酮最可靠的方式，是用  $MeI$  烷基化 Mannich 反应的胺产物得到铵盐，然后用碱处理。烯醇阴离子的生成导向 E1cB 反应，这与羟醛的脱水相当相似，但这里的离去基团更好。



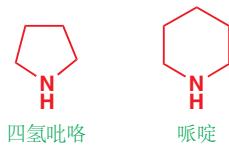
像这样的烯基酮，双键的末端有两个氢原子的，被称作 **外-亚甲基化合物** (exo-methylene compounds)；它们非常活泼，不容易简单地制备或储存。它们当然不能像我们之前见的烯基酮一样

→ 在 Chapter 39 中有更多关于 Cannizzaro 反应机理的内容。

### Mannich 反应



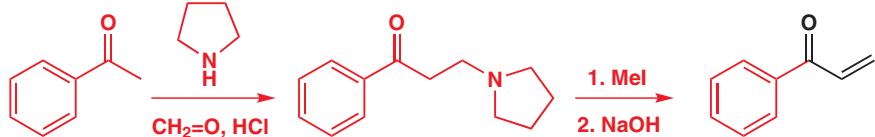
Interactive mechanism for the Mannich reaction



由羟醛反应制备。解决办法是制备 Mannich 产物，将其储存，在需要时烯基化时再将其烷基化并消除。我们在 Chapter 25 中已经见到了，它在 Michael 反应中发挥了很大价值。

如果我们需要的是烯基酮，那么仲胺可以任意选择，因为它不会存在于最终的分子中，更方便（挥发性更低，气味更小）的是用环状胺，通常使用的是四氢吡咯和哌啶。带有单取代双键的，亲电性很强的烯基酮可以用此方法制备。

用四氢吡咯完成的 Mannich 反应



### 有亲电性但不能烯醇化的羰基化合物

好的交叉羟醛缩合，需要一种化合物可烯醇化，作为亲核试剂，另一种物质不可烯醇化，作为亲电试剂。下表显示了能阻止烯醇化的羰基取代基，它们迫使羰基化合物扮演亲电试剂的角色。大致按照活性的顺序排列，对于烯醇盐的亲核进攻最活泼的位于表格的最顶端。当然，您需要两个取代基阻止烯醇化，因此典型的羰基化合物也被列入表中。注意最后两个例子——酯和酰胺——它们通常不会与烯醇盐发生羟醛反应，而是会扮演酰基化试剂，您稍后会遇到这类内容。

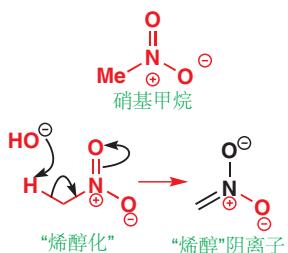
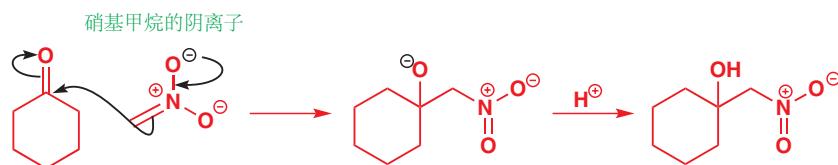
#### 阻止烯醇化的羰基取代基

	取代基	典型化合物	注释
最亲电的	H		需要特殊方法： 见 Mannich 反应
	$\text{CF}_3, \text{CCl}_3$		烯醇卤代制得 (Chapter 20)
叔烷基	$t\text{-Bu}$		很多其他的叔烷基亦可
烯基	$\text{Ph-CH=CH}_2$		亲核进攻可能进攻烯烃： 见 Chapter 25
芳基	$\text{Ph}$		很多其他的芳香环也可 以，例如杂环
	OR		甲酯或甲酸酯
最不亲电的	$\text{NR}_2$		这是 DMF；其他的酰胺很 不活泼

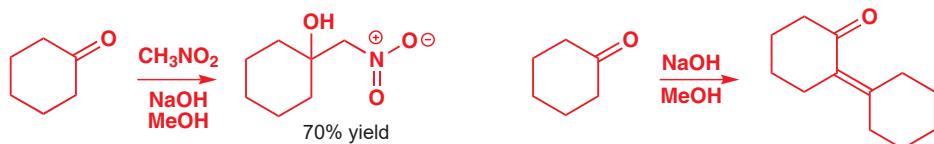
### 可以烯醇化但不亲电的化合物

我们可以用相反的类型来补充这类选择性。有没有什么可以烯醇化，但不能作为亲电试剂的化合物呢？没有任何的羰基化合物可以填补这个角色，但在 Chapter 25 (p. 585) 中我们见到一些完全

没有羰基，但却可以“烯醇化”的化合物。这类化合物中最出名的是硝基烷烃。硝基烷烃的去质子过程不是烯醇化，所得产物也不是烯醇离子，但整个过程与烯醇化过程十分相似，并值得我们将它们放在一起考虑。所得的阴离子有时被称作 **nitronates**，您在 Chapter 25 中见过它们与 Michael 受体反应，另外，它们也可以和醛、酮很好地反应。

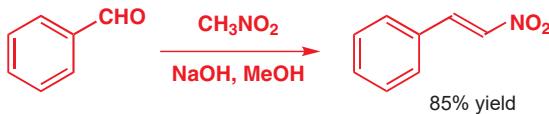


这个特别的例子，使用环己酮作为亲电试剂，硝基甲烷作为生成“烯醇盐”的原料，反应在  $\text{NaOH}$  做碱的甲醇溶液中很好地进行，并以可接受的产率得到“羟醛”产物。这个反应也包含一个选择。两个化合物确实都可以烯醇化，在基本相同的条件下，环己酮也可以很好地与自己反应。



虽然环己酮在没有硝基甲烷存在下会形成烯醇盐，但当酮和硝基烷烃同时存在时，碱会更愿意夺去硝基甲烷上的质子。这是一个可用  $\text{pK}_a$  值解决的简单问题。典型的酮的  $\text{pK}_a$  是 20，而硝基甲烷的则为 10. 甚至用像  $\text{NaOH}$  ( $\text{H}_2\text{O}$  的  $\text{pK}_a = 15.7$ ) 这样的强碱来为硝基甲烷去质子都是多此一举的：胺就可以完成这份工作 ( $\text{R}_2\text{NH}_2^+$  的  $\text{pK}_a$  大约为 10)，通常使用的是仲胺。

硝基化合物消除的步骤也很容易发生，并且在芳香醛的反应中是很难避免的。现在您便知道了 Chapter 22 中我们用的硝基烯烃 Michael 受体是如何制造的了。



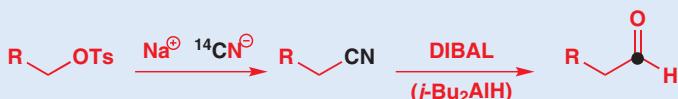
### 硝基烯烃作为白蚁防卫化合物 (termite defence compounds)

白蚁是群居昆虫，每个种都有自己的“士兵”白蚁来保卫巢穴。原鼻白蚁属 (*Prorhinotermes simplex*) 的兵蚁有巨大的头部，用于向它们的敌人喷射有毒的硝基烯烃。

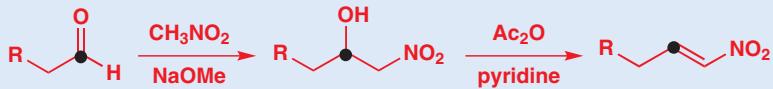
白蚁兵蚁的防御硝基烯烃



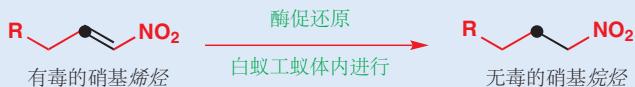
虽然这个化合物可以杀死其他昆虫，甚至其他种的白蚁，但它对于相同种的工蚁是没有效果的。为了了解原因，Prestwich 用羟醛反应制得了一些放射性的化合物。首先，通过放射性的 ( $^{14}\text{C}$ ) 氯离子与对甲苯磺酸酯的  $\text{S}_{\text{N}}2$  反应制备腈，紧跟着 DIBAL 还原 (Chapter 23) 制得十二醛。每个化合物中  $^{14}\text{C}$  原



子的位置都以黑色显示。然后用硝基甲烷和乙醇钠引发羟醛反应，给出硝基羟醛。最后用吡啶中的醋酸酐发生消除反应，得到需要的防御化合物 (*E*-硝基-1-十五烯)。四步产率为 37%。



当白蚁工蚁被喷上带有标记的的化合物后，它们用一种酶将其还原为硝基烷烃以使之无害。仅从同种的工蚁体内能重新分离得到仍具放射性的、带有标记的硝基烷烃：其他昆虫没有这种酶。



如果一个羟醛反应满足以下三个标准：

- 仅一个可烯醇化的化合物
- 仅一组可烯醇化的质子
- 一个比可烯醇化的化合物更活泼的羰基亲电试剂

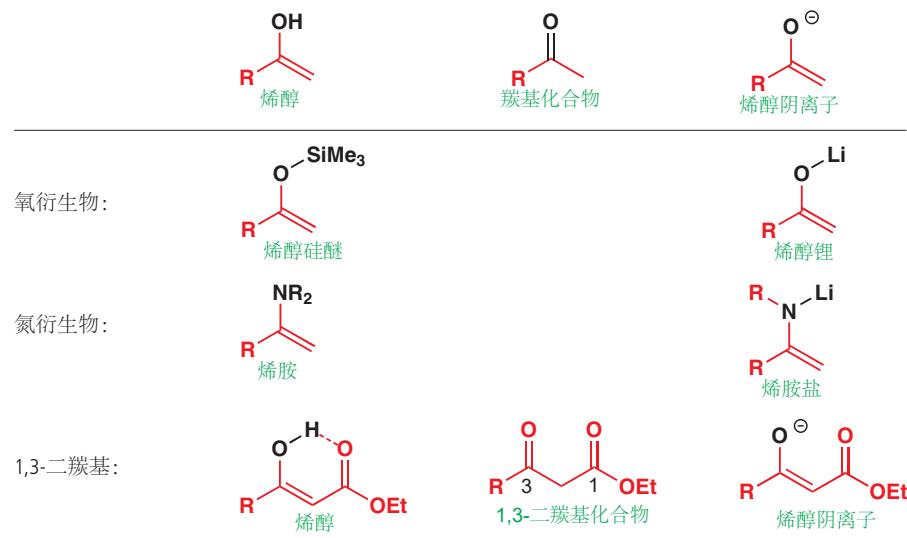
那么您十分幸运，交叉羟醛缩合的方法可以工作。但大多数羟醛反应并非如此：它们是有多种不同的可烯醇化质子，有各种各样的反应性的醛和酮发生的交叉缩合。大多数羰基化合物对的交叉羟醛反应会给出令人绝望的产物混合物。在所有不满足以上三个标准的情况下，都需要特别的烯醇等价物的帮助：一个化合物必须定量地转化为一种烯醇等价物，再在另一个单独的步骤中与亲电试剂反应。这就是下一节要叙述的内容——您会发现其中的一些方法与我们在 Chapter 25 中用于烷基化的方法有许多共同之处。

■ 这是一种泛论，我们在 Chapter 41 中讨论不对称合成时，会有它的反例。

## 特别的烯醇等价物用于控制羟醛反应

在 Chapter 25 中，我们看到，最简单的控制烯醇盐烷基化的方法是由羰基化合物制备特别的烯醇等价物。这同样是控制羟醛反应的最佳方法。下表将帮您回忆一部分最有用的特别烯醇等价物。

重要的特别烯醇等价物



(我们需要的) 特别烯醇等价物应当是具有烯醇或烯醇盐反应性的中间体，但又足够稳定，进而可以由羰基化合物以高产率制备。这是我们在 Chapter 25 中需要知道的。而当下，进一步的威胁是形成了一半的烯醇盐等价物，与其未烯醇化的母体之间的反应，我们应当补充给“在特别烯醇盐等价物的制备中，不应发生羟醛反应。”

- 特别烯醇等价物应当是有烯醇或烯醇盐反应性的中间体，并且有足够的高产率由羰基化合物生成的稳定性，而且在生成过程中没有任何羟醛反应发生。

对于合适的特别烯醇等价物，明智的选择将允许几乎任何羟醛反应成功地进行。刚才列表中的前两个化合物，烯醇硅醚和烯醇锂，有着尤其广泛的应用，我们会先着眼于它们的工作方式。如表所示，烯醇硅醚更像烯醇：它们都无碱性，且并不是非常活泼。烯醇锂更像是烯醇阴离子：它们是碱性的，而且活泼。它们适用于不同的情形。

### 羟醛反应中的烯醇锂

烯醇锂通常在低温下的 THF 中，用大空阻氨基锂碱(通常是 LDA) 制备，由于强的 O–Li 键，它在这些环境下稳定。烯醇盐的生成由 Li–O 键的形成开始，然后是碱性氮原子夺去邻位质子的过程。

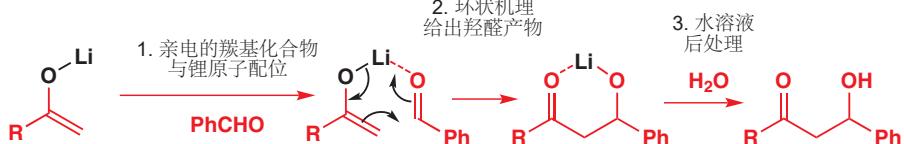


这个反应很快地发生——这种快速致使生成一半的烯醇盐并没有机会在质子的去除未完成时，与未烯醇化的羰基化合物反应。



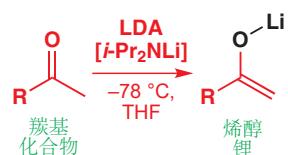
现在，如果加入一个仲羰基化合物，它也会与相同的锂原子络合。这使得羟醛反应在锂原子的配位层 (coordination sphere) 中以环状机理发生。现在的羟醛反应是一个很有利的，六元环过渡态的分子内反应。产物起初是羟醛的烷氧基锂盐，它在后处理中得到羟醛。

### 烯醇锂参与的羟醛反应



即使在亲电组分是一个可烯醇化的醛时，这个反应也能很好地工作。下一页的例子中，一个不对称醛(一侧被芳香环阻挡)做烯醇组分，以很好的产率与另一个非常容易烯醇化的醛反应。这是我们向您展示的第一个只能用特别烯醇等价物完成的羟醛反应：注意，最重要的一点是它以两步完成：

- 首先，形成特别烯醇等价物(此处是低温下形成烯醇锂)
- 然后，加入亲电试剂



► 烯醇锂的生成在 Chapter 25 中已经讨论。

► Interactive mechanism for lithium enolate formation

■ 醛是一个例外。您可以从例如  $i\text{-PrCHO}$  的醛中制备烯醇锂，但通常自缩合很快地发生，因此不想要的羟醛自缩合产物仍会在烯醇锂制备时析出。制备醛的特别烯醇盐，我们需要用另一类衍生物：稍后会见到。

■ 一个锂阳离子含四个配位点——我们没显示出来的其他位点都被溶剂分子占据。羟醛反应发生前，其中一个溶剂分子被亲电的羰基组分替代。

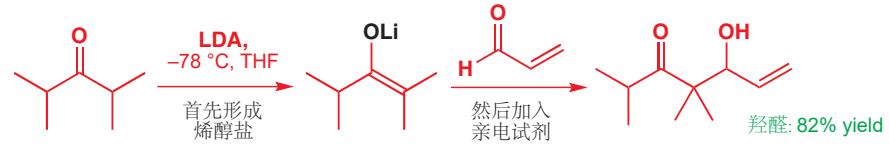


这与本章早期论述的那些，可烯醇化的化合物、碱、亲电试剂在一步中混合的交叉羟醛反应不同。

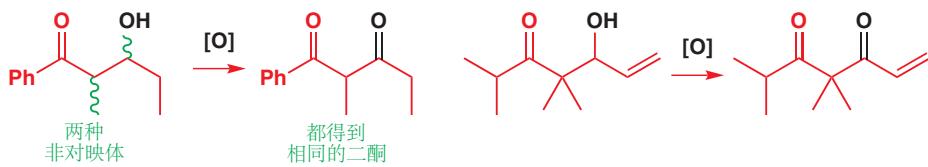
下一个例子尤其令人印象深刻。烯醇组分是一个对称的酮，有非常大的空阻——每侧仅有一个氢原子。亲电组分是一个共轭的烯基醛，不能烯醇化，但可以通过共轭加成接受一个亲核试剂。尽管有这些潜在问题，这个反应以极好的产率进行。

■ 烯醇锂的加成过程为六元环机理，因此它通常并不进行共轭加成。对于可以共轭加成的烯醇等价物，见 Chapter 25.

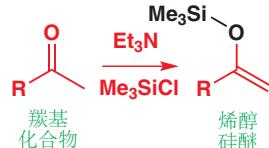
■ 符号 [O] 表示用常规但又含糊的氧化试剂氧化，这个符号来自著名威尔士化学家 Owen Brackets 的实验室。这里用 Swern 氧化是最佳的（见 Chapter 23）。



您可能想知道为什么在本页的第一个例子中我们没有提到立体化学。有两个新的立体中心形成了，产物是非对映体的混合。事实上，这两个反应的产物都用做氧化为 1,3-二酮，这样原本的立体化学也就无关紧要了。如下图所示，羟醛反应也（还有 Claisen 反应）可以用于制备二酮。



### 羟醛反应中的烯醇硅醚



烯醇硅醚可以由其母体羰基化合物，在弱碱，例如叔胺下形成少的平衡浓度的烯醇阴离子，并非常有效地被亲氧的亲电试剂  $\text{Me}_3\text{SiCl}$  捕获。烯醇硅醚的稳定性足以使其能够被分离，但通常它还是作为中间体使用，不会被储存。

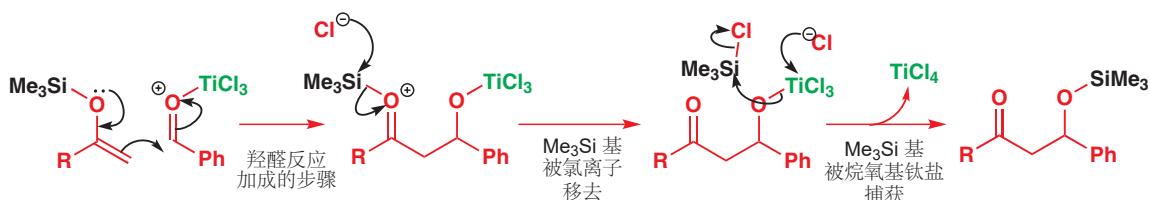
之前的内容中，烯醇硅醚是对于质子、溴相当活泼的烯烃（Chapter 20），但它们与醛和酮的反应则不能在没有催化剂的条件下进行：它们远没有烯醇锂活泼。与烷基化一样 (pp. 595 和 609)，需要 Lewis 酸催化剂推动羟醛反应进行，受欢迎的一种是 Ti(IV) 化合物  $\text{TiCl}_4$ .



中间体事实上是羟醛产物的烯醇硅醚，但它会在后处理中水解，并以好产率形成羟醛。过程中，Lewis 酸想必会与亲电试剂的羰基氧成键。

现在羟醛反应可以发生了：钛络合的羰基氧上的正电荷使醛足够活泼，足以被不那么亲核的烯醇硅醚进攻。氯离子移去硅基后，硅基又被烷氧基钛盐捕获。您不应当对最后一步惊讶，任何烷氧基

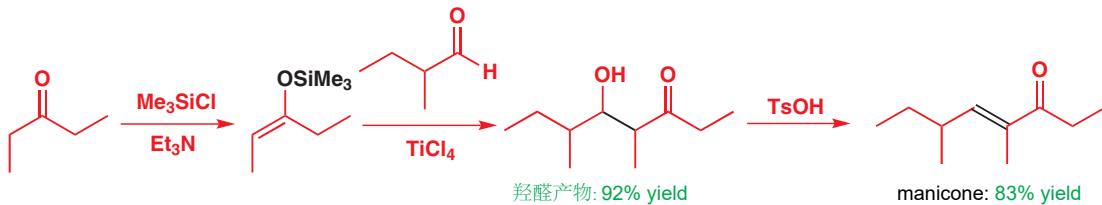
阴离子(例如 $\text{MeOLi}$ )都会与  $\text{Me}_3\text{SiCl}$  反应以形成烯醇硅醚。



这个机理看似复杂，它也确实复杂。事实上，我们写下的这些细节也不一定正确：钛也许会在反应中与两个氧都很好地络合，我们分开表示的一些步骤可能会协同发生。然而，任何合理的机理都会同意以下两点，也是您必须理解的：

- 烯醇硅醚的反应需要 Lewis 酸的存在。
- 关键的步骤是烯醇硅醚与 Lewis 酸络合的亲电试剂发生的羟醛反应。

烯醇硅醚的使用可以在 manicone 的合成中得到说明，这是一种共轭的烯基酮，蚂蚁用它留下通向食物资源的轨迹。它可以通过 3-戊酮 (作为烯醇组分) 和 2-甲基丁醛 (作为亲电组分) 的羟醛反应获得。两个组分都可以烯醇化，因此我们需要由酮形成特别烯醇等价物。烯醇硅醚能很好地工作。羟醛产物会是非对映体的混合物，但可以通过消除得到单一化合物。



烯醇硅醚不经分离，而是立刻用酸处理，以极好的产率得到羟醛。酸性的对甲苯磺酸 (TsOH) 溶液下脱水给出烯基酮。您可以从羟醛反应的高产率中发现，其中任何一个组分都没有显著的自缩合发生。

### 共轭的 Wittig 试剂做特别烯醇等价物

我们介绍 Wittig 反应的时候 (Chapter 11) 只是把它简单地看作了烯烃合成反应。如下的一组由  $\alpha$ -卤代羰基化合物 衍生的 Wittig 试剂，还可以被我们看作是合成不饱和羰基化合物时可选用的烯醇等价物。

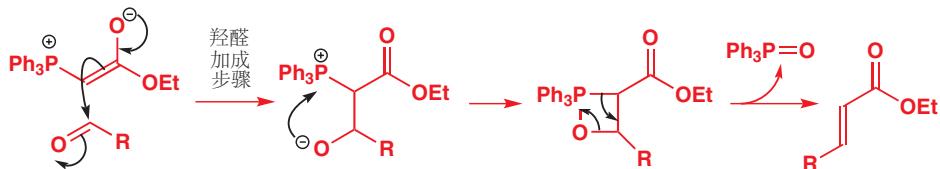


您注意到，我们将中间体叶立德画作烯醇盐的形式，这是为了强调它是一个烯醇盐衍生物：它同样可以表示为叶立德的形式，或与叶立德等价的  $\text{C}=\text{P}$  “正膦”结构。如果我们仔细观察这类 Wittig 反应的细节，我们会发现叶立德的形成就像是烯醇阴离子的形成 (事实上它就是烯醇阴离子的形成过程)。这种烯醇盐的生成仅需要弱碱，因为烯醇盐被  $\text{Ph}_3\text{P}^+$  稳定。

► 我们将在 Chapter 27 再次讨论叶立德，和 Wittig 反应的详细机理。



Wittig 反应的第一步类似于羟醛反应，包含烯醇盐对亲电的羰基化合物的进攻。但由于形成“羟醛”产物不同的是，进攻所得的加合物直接形成了不饱和羰基化合物。



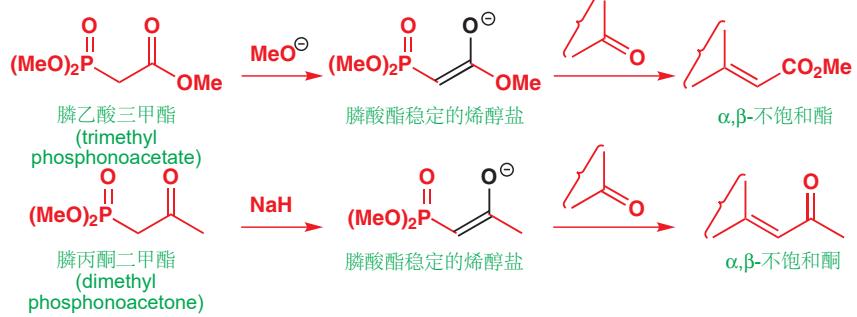
最后的一步，遵循您在 Chapter 11 已遇到过的 Wittig 机理：现在，您还可以把它们看作“羟醛”脱水的特殊情形，由氧化膦和不饱和羰基化合物的形成推动。

由醛、酮和酯衍生的共轭的叶立德，都足够稳定，可以在市面上买到——仅有的，您真正可以购买的特殊烯醇盐等价物中的一个例子。乙醛的烯醇盐对应的叶立德是一种固体，m.p. 185–188°C，可以很好地与其他醛，包括可烯醇化的醛反应。



用  $(RO)_2P=O$  取代  $R_3P^+$  的烯烃生成反应被称为 Horner-Wadsworth-Emmons 反应 (Horner-Wadsworth-Emmons reaction)。Horner-Wadsworth-Emmons 反应只能用于生成共轭烯烃。

这里所用的大括号 (brace) 通常像 “R” 一样使用——它表示分子的剩余部分对所讨论的反应不重要，可以是任何事物。



这几个试剂中的阴离子同时被邻位羰基 (以烯醇盐的形式) 稳定，也被邻位的  $P=O$  基稳定，它们是两个吸电子基稳定的烯醇阴离子的众多例子中的一个。这类化合物中最重要的成员是 1,3-二羰基化合物的烯醇盐，它是下一节的主体。

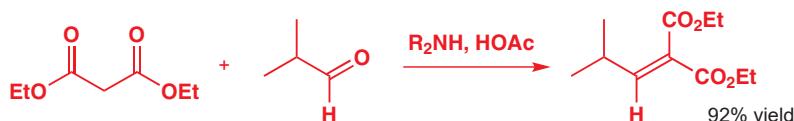
### 1,3-二羰基化合物的特殊烯醇等价物

这类化合物是在特殊烯醇等价物的选用中最古老的，但如今它们仍然被广泛应用着，因为它们不需要特别的条件——不需要低温，也不需要严格的无水条件。最重要的两个是缩苹果酸衍生物和乙酰乙酸乙酯。



乙酰乙酸乙酯在一般条件下部分烯醇化。因此您会问，为什么它不会通过羟醛反应立刻与自己缩合呢？这个问题的答案包含两个方面。第一，生成的烯醇非常稳定（见 Chapter 20 中完整的讨论）；第二，未烯醇化的少部分样品中的羰基是亲电性很差的酯或酮羰基。当一个一般的羰基化合物用催化量的酸或碱处理时，会在大量的未烯醇化的亲电试剂中出现少量的可反应的烯醇或烯醇盐，这时羟醛反应（自缩合）就会发生了。而在 1,3-二羰基化合物中，占大部分的是稳定的（也因此不活泼）烯醇，仅有少量活泼的未烯醇化的化合物，因此没有羟醛反应发生。

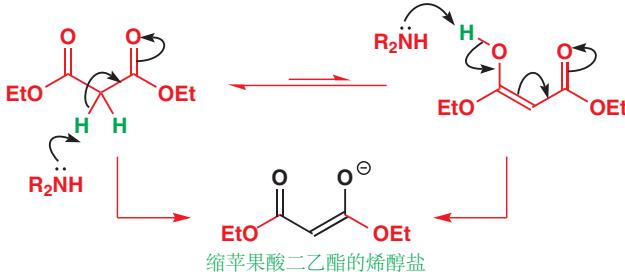
如果我们想用 1,3-二羰基化合物 完成交叉羟醛反应，我们只需要随同弱酸或弱碱，加入第二种亲电的羰基化合物，例如乙醛。催化剂通常用的是羧酸和仲胺的混合物。



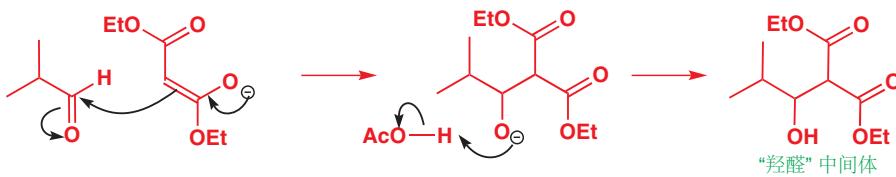
■ 这些条件下，1,3-二羰基化合物的羟醛缩合有时以其十九世纪的发现者命名为 Knoevenagel 反应 (Knoevenagel reaction).

毫无疑问，反应是通过胺产生的烯醇离子进行的，而羧酸用于缓冲溶液，中和产物并阻止醛的烯醇化发生。胺 ( $R_2NH_2^+$  的  $pK_a$  大约 10) 的碱性足够由 1,3-二羰基化合物 ( $pK_a$  大约 13) 形成显著浓度的烯醇盐，但并不足以由醛 ( $pK_a$  大约 20) 生成烯醇。烯醇盐的生成可以在缩苹果酸酯的两种互变异构体中的任意一种上画出。

→ 异构体指通过互变异构现象连接的两种异构体：见 Chapter 20, p. 451.

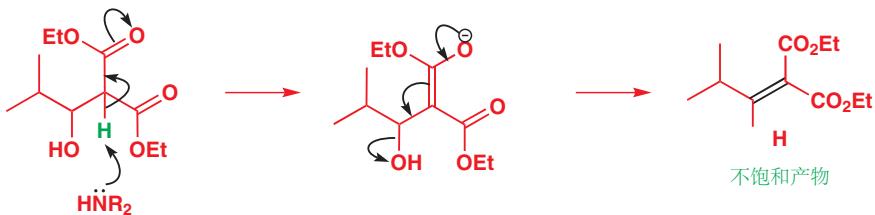


现在烯醇阴离子可以以通常的方式进攻醛，酸的缓冲作用在反应混合物中产出羟醛产物。

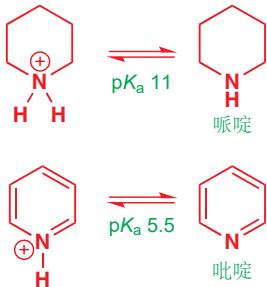


两个羰基间仍有一个质子很容易烯醇化，烯醇阴离子生成后脱水得到不饱和产物。

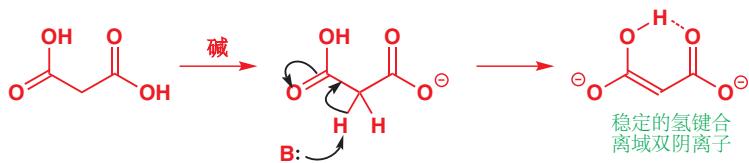
Interactive mechanism for the Knoevenagel reaction



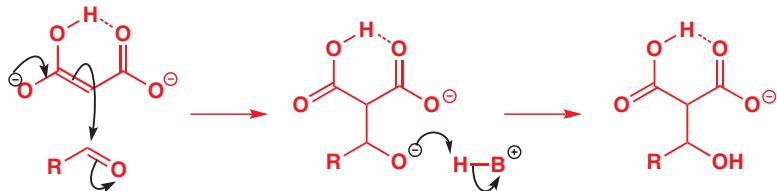
您也许不想要有两个酯基的产物，我们在 Chapter 25 中讨论了，两个 1,3-相关的酯基可以通过水解和脱羧的过程，去除其中一个。羟醛反应有一个更好的途径。如果，所用的不是缩苹果酸酯，而是缩苹果酸，那么在反应过程中脱羧就会自发进行。这时使用的催化剂通常要用碱性更强的哌啶、吡啶混合物。



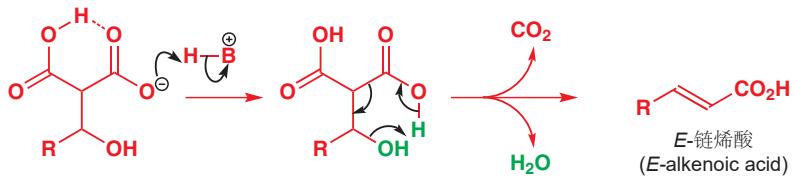
这个反应推测是由缩苹果酸的单羧酸阴离子的烯醇阴离子完成的。虽然这个烯醇阴离子是一个双阴离子，它广泛的离域作用和分子内氢键使其事实上相当稳定。



下一步是羟醛步骤。二阴离子进攻醛，质子转移后羟醛得以形成(在这个碱性溶液中，仍以单羧酸阴离子的形式存在)。



最后是脱羧的步骤，可以通过环状机理发生(与 Chapter 25 中的脱羧机理对比)。脱羧产物中的双键可以是 E 型也可以是 Z 型，这取决于以  $\text{CO}_2$  形式失去的羧基是哪一个。更稳定的 E 产物的过渡态是低能的，于是生成的产物具有 E 几何结构。



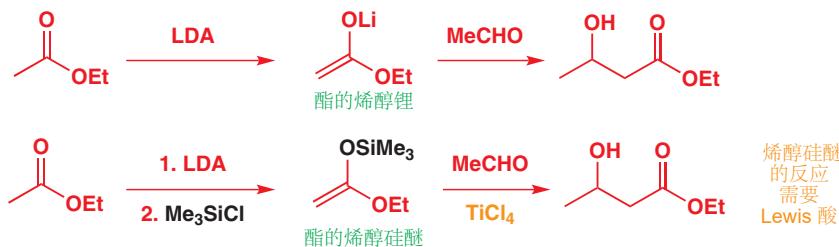
在本章的第一部分，我们考察了控制交叉羟醛反应的问题的一些通用解决方案。现在，我们将转向这些解决方案应用于不同类别的可烯醇化化合物时的细节。

## 如何控制酯的羟醛反应

在羧酸衍生物的烯醇盐中，酯的应用最为广泛。酯的烯醇盐不能用于发生于醛的交叉羟醛反应，因为无论是烯醇化的能力还是亲电性，醛都超过酯。醛会自己发生缩合，并忽略酯。酮亦是如此。因此酯烯醇盐羟醛反应的成功，需要用到酯的特别烯醇等价物。

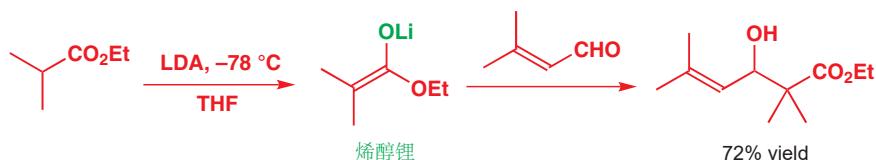
幸运的是，由于这是一个经典的问题。现在以及有了很多解决方案。您可以使用烯醇锂或者烯醇硅醚，通常通过烯醇锂的反应是最好的。

■ 上文中，我们已经介绍了苹果酸酯、膦乙酸酯这两种特例。现在我们要考虑的是更为普遍的酯烯醇盐。

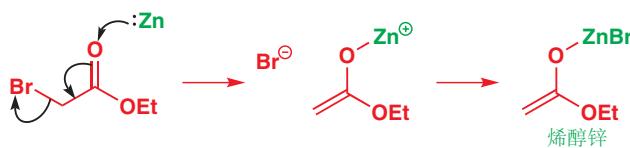


一个好例子是由 Oppolzer 和 Snowden 完成的，天然产物 himalchene 的合成的第一步。虽然酯和醛都因为取代基而拥挤，但通过酯的烯醇锂，羟醛反应仍能很好地工作。(烯醇锂的) 环状机理确保了醛直接进攻，而非共轭 (Michael) 攻进羰基。

■ 请原谅我提醒您，在烯醇硅醚的反应中，Lewis 酸是必要的。

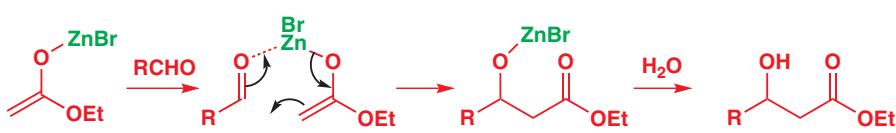


由溴代酯可以制备烯醇锌 (zinc enolates)，一种很好的酯烯醇锂的替代物。烯醇锌生成的机理应当能让您想起格式试剂的形成过程。



使用烯醇锌时，不需要有任何关于自缩合的担心，因为烯醇锌不会与酯发生反应。它们会干净地与醛、酮反应，经过后处理得到羟醛。您会意识到，烯醇锌特别地只对酯适用：您不能从 2-溴代醛或  $\alpha$ -溴代酮制备烯醇锌，因为那样您会得到自缩合产物。

■ 如是的烯醇锌生成，与烯醇锌的羟醛反应被称作 Reformatsky 反应 (瑞福马斯基反应, Reformatsky reactions).



■ 如果想制备这种羟醛的脱水产物，则最好直接由我们之前讨论的 Wittig 变体 (p. 628) 制备。叶立德合成的起始原料是相同的溴代酯。

● 酯的烯醇盐等价物

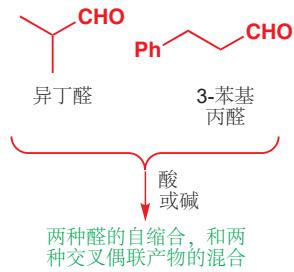
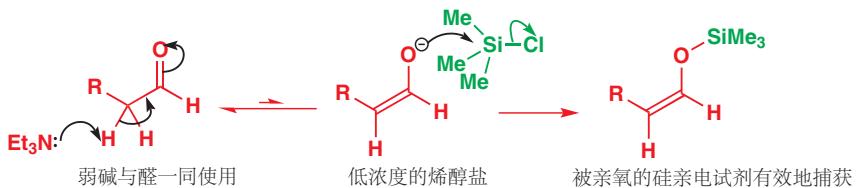
对于酯烯醇盐参与的羟醛反应，可选用：

- 烯醇锂 或
- 烯醇硅醚 或
- 烯醇锌。



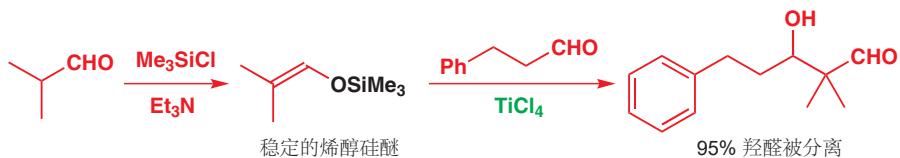
## 如何控制醛的羟醛反应

醛能很轻易地烯醇化，而自缩合同样相当容易。醛的烯醇盐不能干净地被制备，因为甚至在  $-78^{\circ}\text{C}$  下，自缩合反应也能像 LDA 下的烯醇化一样快速地发生。烯醇硅醚是一个远远胜过它的选择。它们显然不能通过烯醇锂制备，通过选用胺做碱。每分子的烯醇盐都在平衡中产生，继而会被硅基化试剂有效地捕获。

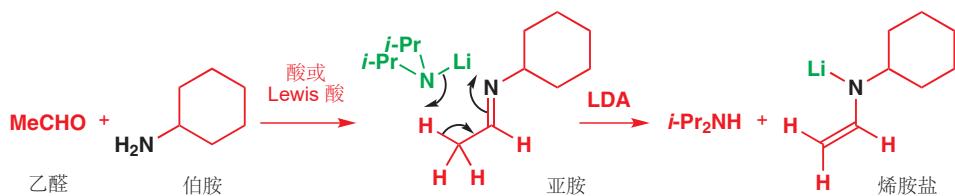


烯醇硅醚可能是发生醛做亲核组分（烯醇或烯醇盐）的羟醛反应最好的方法。一个例子是不太容易烯醇化的异丁醛和非常容易烯醇化的 3-苯基丙醛间的反应。直接混合，然后加入碱，毫无疑问会导致放荡的自缩合和交叉偶联的混合。

烯醇硅醚可以由两个醛中的任一个，在另一个不存在的情况下提前制备，因为  $\text{Me}_3\text{SiCl}$  捕捉烯醇盐的速率要快于自缩合发生。这里我们需要由异丁醛制备烯醇硅醚。随后，另一个醛同必要的 Lewis 酸，这里是  $\text{TiCl}_4$  一起加入。机理在 p. 627 中已经给出，后处理后以极好的 95% 产率得到羟醛。其他反应的发生不超过 5%。

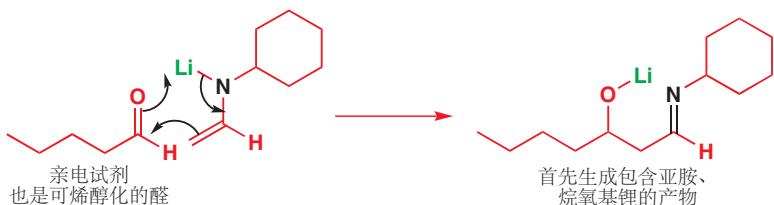


对于醛和酮，其他有用的烯醇等价物是烯胺和烯胺盐 (aza-enolates)，您在 Chapter 25 中的烷基化反应中已经用过的两个。烯胺盐——由醛衍生的亚胺的烯醇锂——在羟醛反应中也是很有用的。甚至是乙醛，也能与环己胺得到一个有理由稳定的亚胺，并可以得到分离，在 LDA 作用下锂化得到烯胺盐。机理与烯醇锂的形成相同，锂原子与烯胺盐中的氮原子成键，就像在烯醇盐中与氧成键一样。

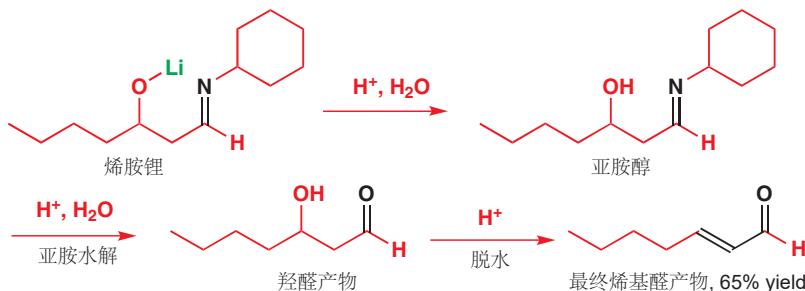


■ 亚胺对于水解非常敏感，最好不要经过储存，而应现制现用。想要完整地理解这些反应，您需要确保您对 Chapter 11 中亚胺的形成和水解熟悉。

烯醇盐干净地与另一个醛或酮反应，得到羟醛产物。甚至是最具挑战性的一种交叉偶联——进攻另一个相似的可烯醇化醛——都可以以很好的产率进行。



起初的产物是一个新的亚胺，在酸性水溶液的后处理中很容易水解。烷氧基被质子化，亚胺水解，所得的羟醛经脱水给出烯基醛——这个例子的全过程产率为 65%。



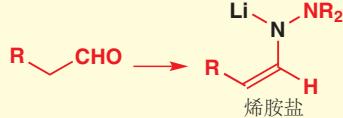
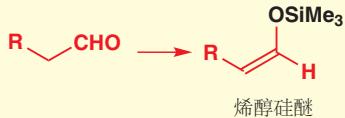
用烯胺盐时，成功的关键是在相对较弱的碱性下，先让醛和伯胺形成亚胺，在弱碱条件下亚胺的生成快于自缩合。等亚胺生成之后，再加入 LDA，这时自缩合仍然不能发生，因为已经没有剩余的醛了。

除了某些情况（您会在 Chapter 41 遇到其中的一些），烯胺并不是羟醛缩合中的通用方法，部分地因为它们活性不够，主要是因为它们与羰基化合物本身处在平衡中，这会导致自缩合，以及错误的交叉偶联。您不久会见到，当我们用更活泼的酰氯来酰基化烯醇时，烯胺就会发挥它们的用途。

### ● 醛的烯醇盐等价物

对于醛做烯醇组分的交叉羟醛反应，可选用：

- 烯醇硅醚 或
- 烯胺盐。



对于醛烯醇盐的酰基化（稍后见到），可选用烯醇硅醚或烯胺。

## 如果控制酮的羟醛反应

对于酮的烯醇化，除非它们是对称的，否则都会抛出一个特别的问题。除了要阻止它们自缩合（虽然这个问题比醛的稍微轻些），酮的烯醇化在羰基的那一侧发生也是我们需要考虑的。本节中，我们会介绍不对称酮的羟醛反应，必须控制生成两种可能的烯醇或烯醇盐中的一种。

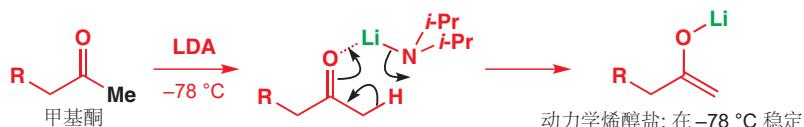
### 制取少取代烯醇盐等价物：动力学烯醇盐

用LDA处理甲基酮，通常给出的烯醇锂处在甲基一侧。这一侧的烯醇盐形成得最快，因此被称作动力学烯醇盐。它生成得快是因为：

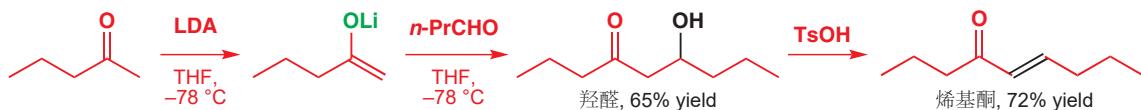
- 甲基一侧的质子酸性更强；
- 甲基一侧有三个质子，比另一侧多；
- 羰基另一侧受LDA进攻时存在空阻。

► 动力学烯醇盐和热力学烯醇盐的介绍在 Chapter 25, p. 601.

Gilbert Stork 出生于布鲁塞尔，在 1948 成为哈佛大学化学助理教授。从 1953 起，Stork 开始在纽约的哥伦比亚大学工作。他开创了一些新的合成方法，其中很多都包含烯醇盐和烯胺。

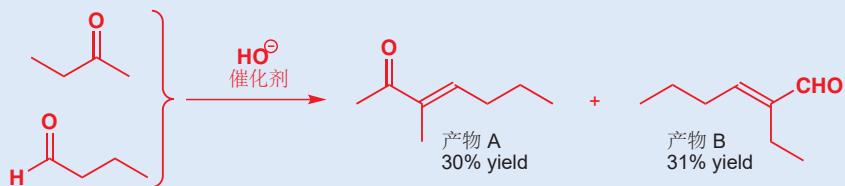


这一反应的首次报道，是 Gilbert Stork 和他的小组在 1974 年完成的，这是一个 2-戊酮和丁醛缩合给出羟醛，然后通过酸催化脱水得到烯基酮 4-壬烯-3-酮的简单例子。产率可能有点失望，但只是首个不饱和酮与可烯醇化的醛的交叉缩合，并以还算合理的产率，只给出一个羟醛产物的例子。

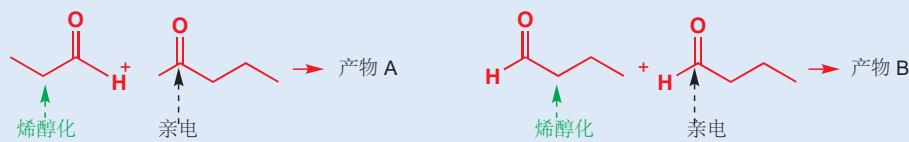


### 不受控制的酮的羟醛反应

在丁酮与丁醛通过烯醇盐等价物发生特定的羟醛缩合的方法被发明前，一个更典型的，用碱催化，试图交叉缩合的结果如下所示。两个产物都以低产率被分离。



产物 A 来源于酮在多取代侧的烯醇盐和醛的反应，产物 B 是醛自缩合的产物。

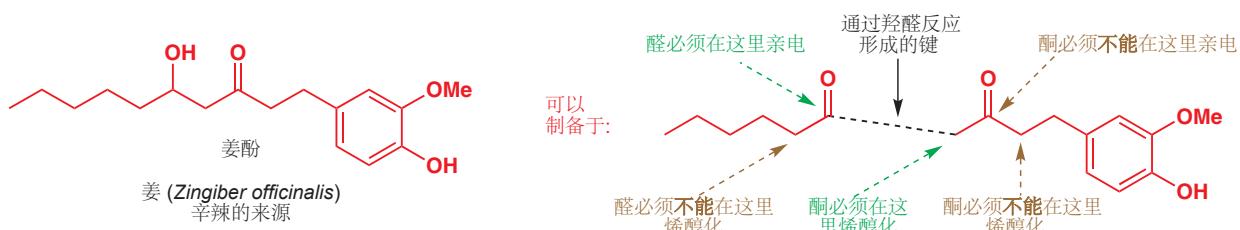


这些动力学的烯醇锂在 THF, -78°C 下短时间稳定，但可以以其烯醇硅醚形式在室温下保存。

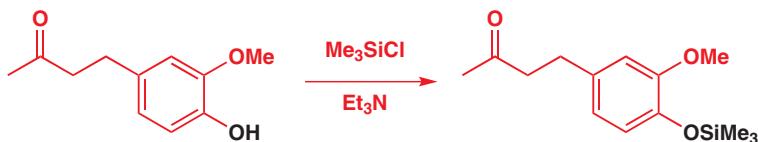


无论烯醇锂还是烯醇硅醚，都可以发生羟醛反应。我们将用姜的味道的化合物的合成作为例子。

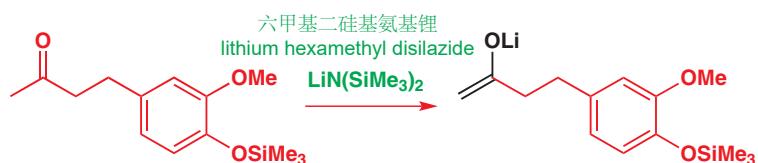
姜的辣味来源于“姜酚 (gingerol)”——姜“辛辣的来源”。姜酚是一种 3-羟基酮，因此我们会考虑用羟醛反应制备它。我们会需要在不对称酮甲基一侧生成烯醇（或烯醇盐），以与一个作为亲电组分的简单的醛（戊醛）发生羟醛反应。戊醛是一个可烯醇化的醛，因此我们必须阻止它烯醇化。下图总结了可能的羟醛反应。



我们会在烯醇锂和烯醇硅醚中考虑。由于我们需要的是动力学烯醇盐（烯醇盐在酮少取代的一侧形成），我们会使用烯醇锂来制备烯醇硅醚，率先尝试这种方法是明智的。另有一个问题。酮在环的远端有一个自由的 OH 基会妨碍反应。我们需要先将其保护为普通的硅醚（不是烯醇硅醚）。



现在我们可以用大空阻的氨基锂做碱，来制备动力学烯醇。事实上，这里选用的是比 LDA 空阻更大的碱，在氮原子上有两个 Me3Si 基。



### 六甲基二硅基氨基锂

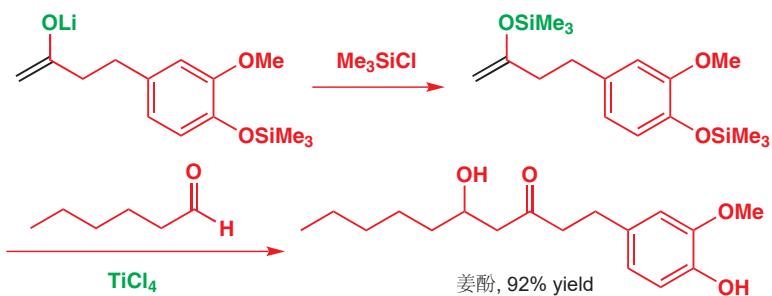
六甲基二硅基氨基锂 (Lithium hexamethyldisilazide, 简写作 LiHMDS) 比 LDA 的空阻稍大，碱性稍弱。它通过 BuLi 为六甲基硅基氨基 (hexamethyldisilazane) 去质子制得。



上述烯醇锂与戊醛的羟醛反应成功进行，保护基（硅醚）在后处理的水解过程中被请以去除，并得到姜酚本身。然而产率只有 57%。然而如果配合 TiCl4 做 Lewis 酸，并用烯醇硅醚参与反应，则

东京理科大学(从前在东京工业大学和东京大学)的 Teruaki Mukaiyama(向山光昭)是他所生活的年代最重要的日本化学家之一,他的工作显著地影响了羟醛反应,和其他有机合成领域的发展。

产率会跳至 92%。这是 Mukaiyama 所发明的羟醛反应方式的很多成功案例中的一个。



### 制取少取代烯醇盐等价物：热力学烯醇盐

作为一个烯烃, 烯醇和烯醇盐在取代基较多时也较稳定。因此在两种烯醇盐能相互转化的条件下, 所得的是多取代的烯醇盐等价物: 平衡会给出更稳定的形式。您在 Chapter 25 (p. 599) 中以及看到过, 如何通过用  $\text{Me}_3\text{SiCl}$  和一个弱碱处理酮, 得到其少取代的烯醇硅醚, 但这些热力学的烯醇硅醚在羟醛反应中应用较少。一个成功的案例是 1-苯基-2-丙酮的热力学烯醇硅醚: 在共轭的一侧烯醇化在热力学上压倒性地有利。与一个 2-酮醛 的羟醛反应也专一地在更活泼的醛基上进行。

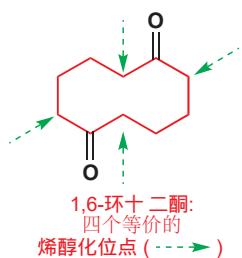


这就总结了我们对于羟醛反应中特别烯醇盐的普查。接下来您将看到, 很多相同的试剂也应用于碳上的酰基化。我们还剩下一些尤其容易解决的反应。

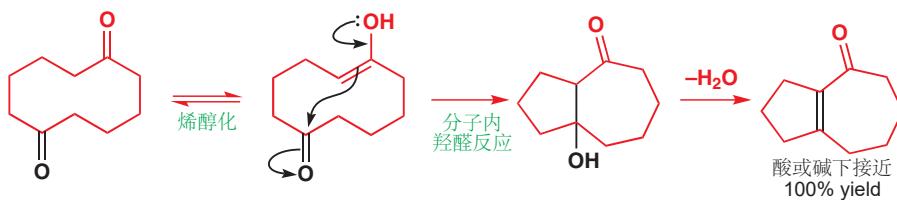
### 分子内羟醛反应

现在来看一些简单的内容。当一个羟醛反应可以以五元环或六元环发生时, 您将无需再担心用特别烯醇等价物或其他的什。由于分子内反应比分子间反应快, 用弱酸或弱碱建立平衡的方法, 对于通过分子内羟醛反应给出环状产物就是足够的了。我们将考察一系列越来越复杂的二酮的环化来说明分子内反应, 我们将以一个能形成四种等价的烯醇的二酮开始: 1,6-环十二酮。

对于烯醇化无需过多考虑, 因为生成的都是同一种烯醇。烯醇生成的一刻, 也只有一种合理的将要做的事: 进攻另一个酮并形成稳定的五元环。它还会给出一个合理的稳定七元环, 但那是顺便进行的事。在弱酸或弱碱下, 仅有少比例的羰基会烯醇化, 因此两次烯醇化发生于同一分子的机会很少。没有发现分子间缩合, 而由分子内反应生成双环烯基酮的产率几乎是 100% (用  $\text{Na}_2\text{CO}_3$  贡献 96%)。

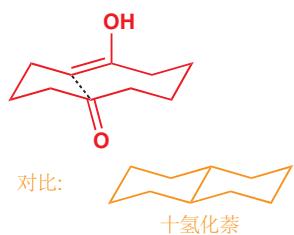


关于环的大小与稳定性  
的讨论位于 Chapter 16.



看起来，烯醇穿过是元环抵达另一个酮的距离很远，但侧边栏画出的构象显示了它们可以多近。您应当将这个构象与十氢化萘的构象 (Chapter 16) 对比。

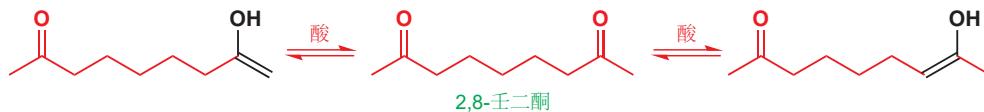
对于分子内羟醛反应，需要牢记的关键点是：



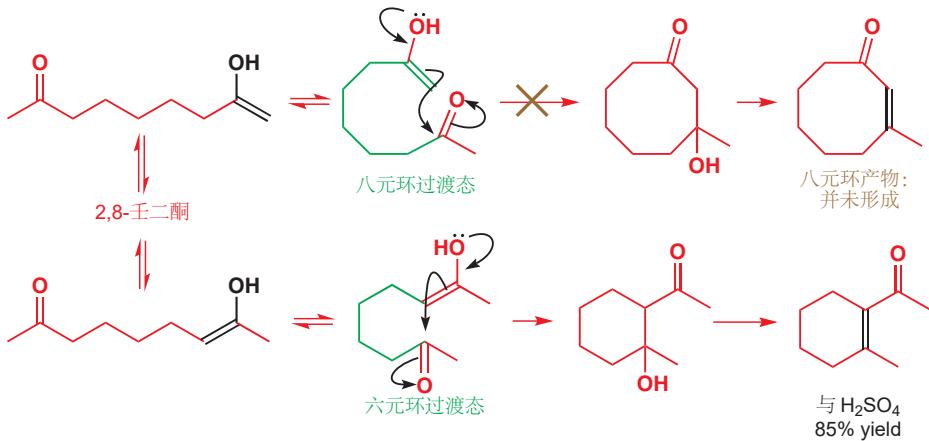
- 产生五元或六元环的分子内反应，比产生有张力的三元或四元环，或中环(八到十三元)的反应更加有利。

→ 我们将在 Chapter 31 重新回到对环大小的重要性的讨论。

对称酮 2,8-壬二酮 在酸催化下的环化反应会给出两种烯醇。

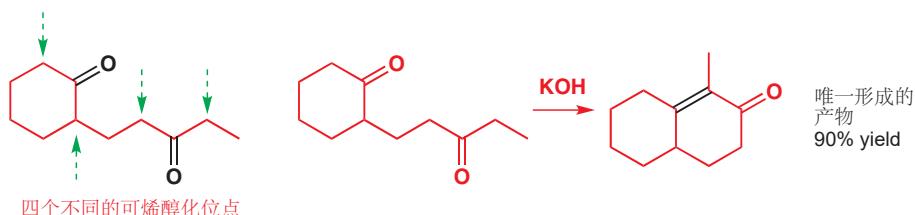


其中一个烯醇可以经八元环过度态环化，而另一个则经历六元环过渡态。两种情形都先生成羟醛，然后再水解为与刚才过渡态的环的大小相同的环状烯基酮。实践中，只生成较小张力的六元环，烯基酮以 85% 产率被分离。

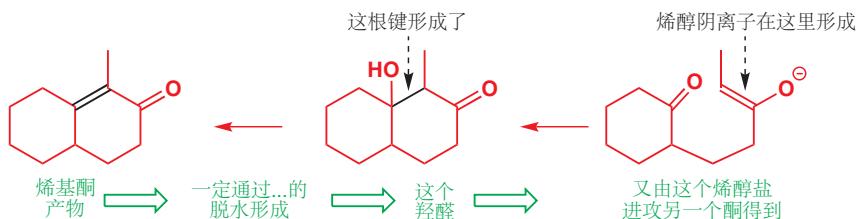


Interactive mechanism for intramolecular aldol reactions

大多数二酮缺乏对称性，并会有四个潜在的烯醇化位点。请考虑当下面的二酮用 KOH 处理时发生的变化。同样，有两个不同的亲电羰基，因此会有很多种分子间或分子内的缩合方式。但其中只有一种产物得以形成，并以 90% 产率。



我们可以简单地从产物的结构逆推反应机理。双键由我们可以预言出的羟醛中的一种烯醇，由此我们又知道了形成哪种阴离子，和哪个酮做亲电组分。



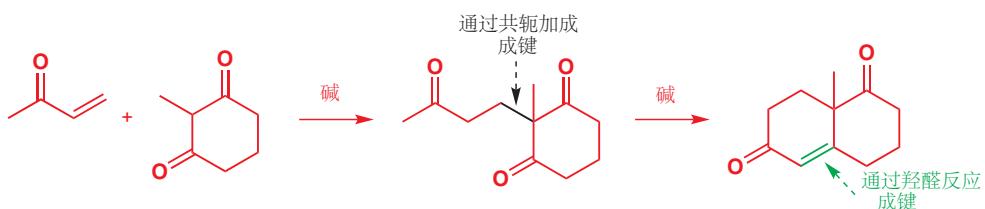
我们必须要论证是这个烯醇盐，比其他的三个都更容易形成吗？当然不是。四种烯醇盐的差异都较小，而其中三种由  $\text{CH}_2$  基生成的更是差异小。但我们可以论证只有这个羟醛反应，所得的产物是在六元环中的稳定的共轭烯基酮。下面是机理；其他的都因过于缓慢而难以完成。质子化和脱水照例发生。



其他的三种情况，给出的要么是不稳定的四元环，要么是不稳定的桥环体系，它们都会转化回烯醇盐的反应物。当反应在平衡条件下完成时，整个过程会退回初始的二酮，最终我们所观察到的环化（六元环的）会占主导。侧边栏上的桥环化合物最终不生成的关键点，是因为它的脱水是不可能的。由于桥头碳不能处于平面型（Chapter 17, p. 389），烯基酮产物将不能存在：棕色结构中标记的（●）碳原子需要在同一平面内。羟醛完美地有一个可以接受的构象，但消除却不能发生。羟醛产物与其他产物保持平衡，但只有一种羟醛可以消除——并且那是不可逆的，因此最终原料结束与单一的烯基酮。

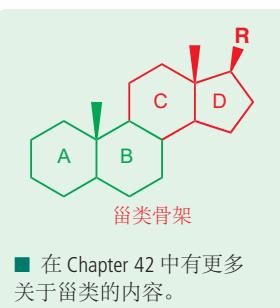
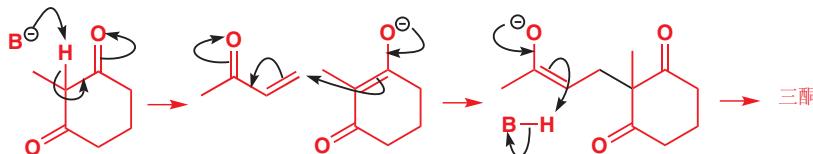
### Robinson 增环反应 (罗宾森增环反应, Robinson annelation)

分子内羟醛反应最重要的应用之一是分两步进行的环合成（增环反应, annelation 或 annulation）。第一个例子中由 Robinson 合成的化合物，是一个包含甾类基本结构中环 A 和 B 的双环二酮。两步所形成的键在图中已被标记。

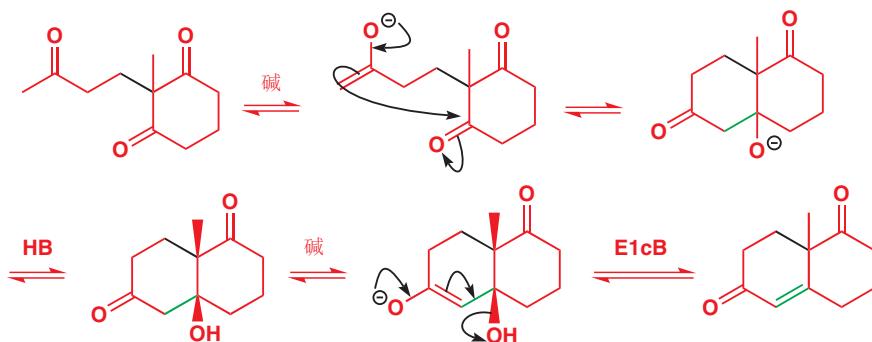


Robert Robinson (1886–1975), 英国化学家，于 1947 年因其在生物碱合成上所做的工作而获得诺贝尔奖。

由 1,3-二酮 形成稳定的烯醇盐仅需要弱碱，烯醇盐随后对烯基酮进行共轭加成 (Chapter 25). 中间体三酮可以被分离，但通常不这样做。

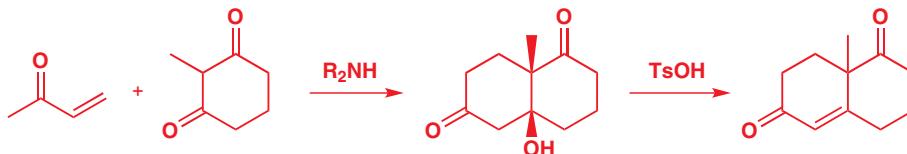


第二阶段开始于分子内羟醛反应。不同的进攻位置得到的六元环的替代品，要么是四元环，要么是桥环产物。所生成的顺式立体化学的羟基酮，也可以被分离，但通常经 E1cB 机理的消除完成羟醛流程。



Interactive mechanism for  
Robinson annelation

完成同一反应的其他方法是使用仲胺作为弱碱。它以极好的产率给出羟基酮，继而可以与酸作用转化为烯基酮。



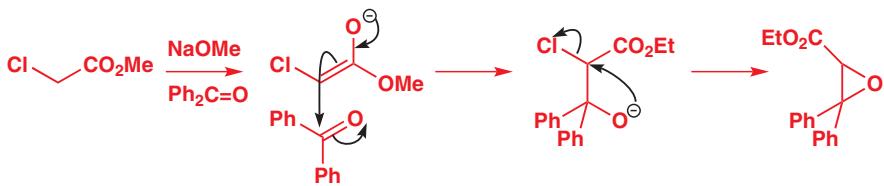
您会在 Chapter 41 中发现，使用天然氨基酸脯氨酸做碱，有利于产物形成一种单一对映体。

按照上述流程，新环一定要成在旧环的一侧，但这是不必要的。任何容易烯醇化的化合物(不需要有环)和一个烯基酮的组合都可能给出 Robinson 增环产物。一个简单的例子，将一个不能烯醇化的烯基酮与乙酰乙酸乙酯结合起来，以极好的产率给出环己烯酮 (cyclohexenone). 这些化合物都很结实，可以选用强碱。



## Darzens 反应

从前我们接触过，用串联反应可以制取环丙烷，即第一个反应生成的烯醇盐发生紧接着发生 C-烷基化 (见 Chapter 25, p. 586); 而如果 O-烷基化 紧跟着羟醛反应，则可以制取环氧 (epoxide). 这种环氧应用于药物达卢生坦 (darusentan) 的合成中。



这种环氧生成方法是烯烃和 *m*-CPBA 反应的方法的补充，因为它包含 C–C 键的构建。由  $\alpha$ -卤代羰基化合物形成环氧的反应被称作 **Darzens 反应** (达森反应，Darzens reaction)。

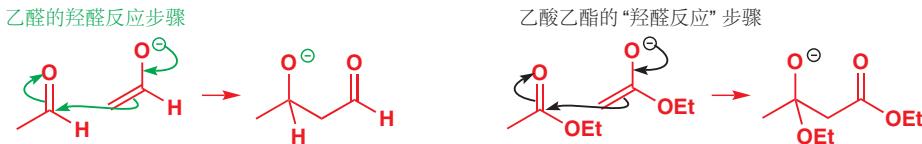
## 碳上的酰基化

### 引入: Claisen 酯缩合和羟醛反应的对比

我们曾以碱处理下乙醛的变化开始这一章。此变化的首步为烯醇阴离子的形成，然后发生羟醛反应。而本节则将开始于，当您用碱处理乙酸乙酯时，发生的变化。第一步上，这两者差异并不大。我们会用烷氧基阴离子而不是氢氧根做碱，因为氢氧根会使酯水解，但尽管如此第一步仍然是相似的。它们在就并排位于下面。



两种情形的第二步都是烯醇阴离子对未烯醇化的羰基化合物的亲核进攻。烯醇阴离子的浓度低，每一个烯醇阴离子都被未烯醇化的醛或酯分子包围着，因此这个反应如您所料发生。醛和酯发生此步的过程，均如下所示。

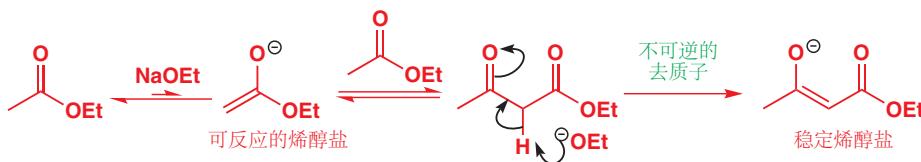


只有现在，才会产生一些区别。醛的二聚物仅仅从溶剂中捕获质子，并给出羟醛产物。而酯的“羟醛”(事实上根本不是羟醛)有一个离去基团， $\text{EtO}^-$ ，替代氢原子，它实质上是羰基亲核加成形成的四面体中间体。对比如下两个步骤。



虽然最后一步是不同的，但两个产物相当相似。它们都是原始的二碳链的二聚体，也都在链的一端带有羰基，在三号位带有氧取代基。它们显然是同一类的反应，但却通常用不同的名称描述。酯的反应有时被称为 **Claisen 酯缩合反应** (克莱森酯缩合反应, Claisen ester condensation)，有时还被称作 **Claisen–Schmidt 反应** (克莱森–施密特反应 Claisen–Schmidt reaction)。相比于记忆反应名称，更重要的是熟悉它的机理。

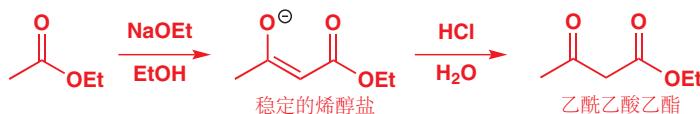
这是碱的强度不足以将酯全部转化为烯醇盐的另一个反应。仅产生少量平衡浓度的烯醇盐与酯亲电试剂反应。这个反应的副产物是乙氧基例子，因此乍一看我们重新得到了催化剂——如果您记得，羟醛反应的碱是催化剂。但在 Claisen 反应中不是这样。反应的第二步事实上也在一个平衡中，而正向进行的原因恰恰就是产物可以不可逆地被副产物乙氧基阴离子去质子，这个过程中小号乙氧基阴离子。回顾，羟醛反应在有一种附加的驱动力推动时，通常很好地工作——例如脱水成烯基酮。相似地，当产物与烯醇阴离子反应，得到稳定的烯醇阴离子时，酯的二聚反应进行得最好。



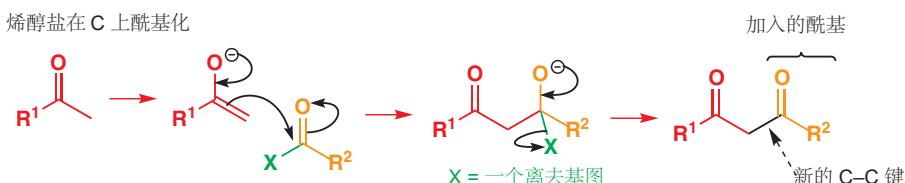
Interactive mechanism for Claisen ester condensation

关键在于碱的选用，乙氧基阴离子  $\text{EtO}^-$  的碱性很弱 ( $\text{EtOH}$  的  $\text{pK}_a$  大约 16) 不足以彻底地移去乙酸乙酯的质子 ( $\text{pK}_a$  大约 25)，但却足以移去乙酰乙酸酯产物的质子 ( $\text{pK}_a$  大约 10)。在反应条件下，产生少量的乙酸乙酯烯醇盐——就足够让反应发生——但产物则会彻底地转化为其烯醇盐。中性的产物，乙酰乙酸乙酯本身，会在酸性后处理中生成。

完整的 Claisen 酯缩合过程

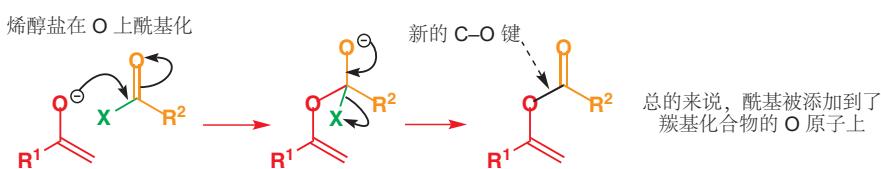


最终产物通过酯的烯醇盐在碳上的酰基化形成。更普遍的过程——碳上的酰基化 (acylation at c-carbon)——是本章的第二个主题。在这个例子中，酰基化试剂碰巧是另一分子的相同酯，而对于普遍的过程，我们会用各种各样的烯醇、烯醇盐、特别烯醇等价物，以及各种各样的酰基化试剂完成，但最基础的思想仍是一种羰基化合物的烯醇盐在碳原子上加入一个酰基 (这里是橘色的  $\text{R}^2\text{CO}$  基)。



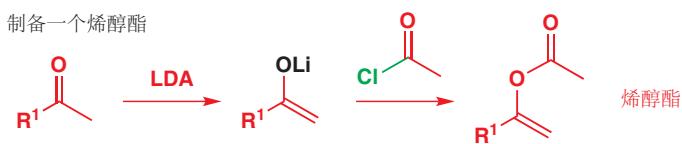
## 在碳上烷基化的问题

烯醇盐酰基化最主要的问题是，反应相比于在碳上进行，更倾向于在氧上进行。



■ 您之前已经见过了氧上发生的反应。烯醇盐与硅亲电试剂的反应发生在氧上，产物在很多延伸反应中有用的烯醇硅醚。烯醇酯也有它们的用处——例如作为烯醇锂的前体。您在 p. 454 见过烯醇酯生成的反应。

在氧上酰基化的产物为烯醇酯 (enol ester)。通过氧进攻的趋势，在活泼的烯醇与活泼的酰基化试剂间的反应上体现得最明显。例如，烯醇锂与一个酰氯的结合，毫无疑问给出烯醇酯。



如果我们想在碳上酰基化，则需要满足这两个条件中的一个：

- 活性较差的特别烯醇等价物，例如烯胺或烯醇硅醚，与活泼的酰基化试剂，例如酰氯反应；或
- 活泼的烯醇，例如烯醇阴离子本身，与活性较差的酰基化试剂，例如酯反应。

我们用第二类反应的一个例子开了头，而我们也将继续深入 Claisen 酯缩合和相关反应的细节。

### 在氧上反应—在羟醛反应中不成问题

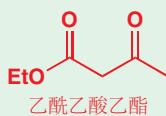
本章前期，我们提到羟醛反应中，并没有在氧上反应的麻烦。这听起来很令人震惊，但考虑到我们已经讨论过的酯亲电试剂，醛、酮做亲电试剂事实上并无两样。我们可以通过观察酮被烯醇盐中的氧原子进攻时的变化来解决这个问题。



中间体中，唯一有道理的离去基团是烯醇氧：返回反应物。

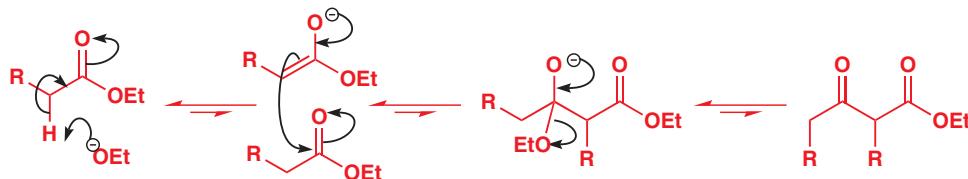
### Claisen 酯缩合和其他自缩合

■ 我们曾考察过乙酰乙酸乙酯的反应：现在您知道它是如何合成的了。

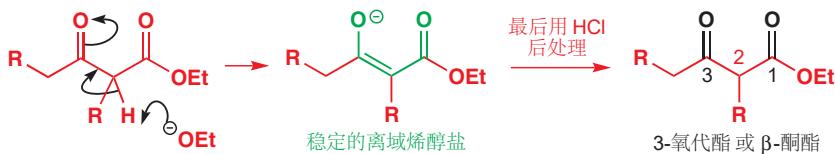


乙酸乙酯的自缩合是 Claisen 酯缩合最为著名的例子，它在方便的条件下以好产率工作。产物 (乙酰乙酸乙酯) 也正是因为这个原因可在市面上买到——因此您不太可能需要自行完成这个特定的例子。

一个更普遍的实用反应是简单的取代乙酸酯  $\text{RCH}_2\text{CO}_2\text{Et}$  的自缩合。它在相同的条件下 ( $\text{EtOH}$  中的  $\text{EtO}^-$ ) 很好地工作。首先在平衡中生成了低浓度的烯醇阴离子，它然后发动对充裕的未烯醇化酯分子的亲核进攻。



这些步骤本身都不利于平衡，得到很少量的产物。然而，我们刚才提到的，这个反应能够工作，是因为由产物生成稳定、离域烯醇盐的基本不可逆的过程拉动了平衡。

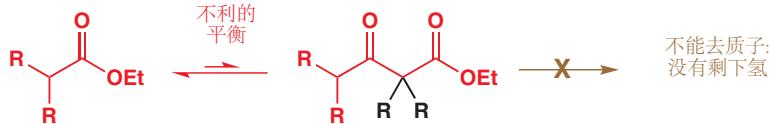


最终，反应在酸中后处理，并形成  $\beta$ -酮酯产物。注意，Claisen 酯缩合的所有产物都以 1,3-二羰基关系。这些化合物在特定烯醇等价物的制备中十分有用，您在 Chapters 20、25，以及本章中都看到了它们的作用。

我们将 在 Chapter 28 中论述 1,3-关系的重要性。

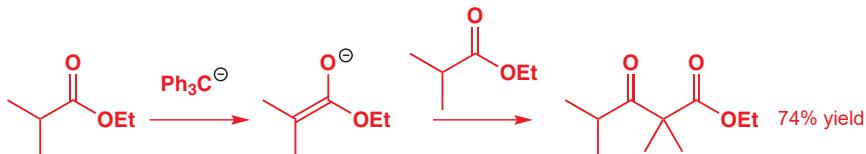
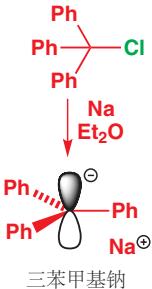
### 我们是如何知道去质子推动反应的？

如果最初的酯在  $\alpha$  碳原子 (酯的 C2) 上有两个取代基，没有氢原子可以移去，产物稳定的烯醇盐形式就不再能够得以生成。



您也许料到了，所有的平衡现在都是不利的了，反应并不能在一般的平衡条件 (EtOH 中的 EtO<sup>-</sup>) 下很好地进行。如果加入强碱，可以以合理的产率反应。传统上，选择的是三苯甲基钠 (triphenylmethyl sodium)。它通过金属钠与 Ph<sub>3</sub>CCl 制备，是一个非常共轭的碳阴离子。

三苯甲基碳阴离子是一个强碱，可以将酯完全转化为其烯醇盐。烯醇盐与第二分子的酯以好产率给出酮酯。



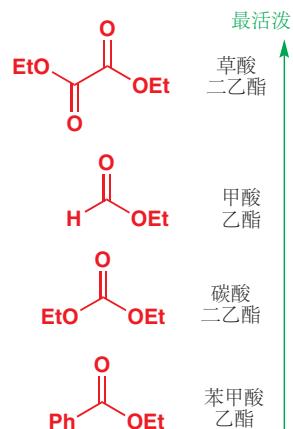
### 交叉酯缩合

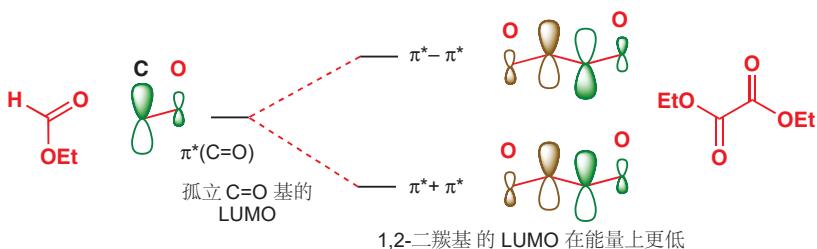
这里的大部分论证，都同样适用于羟醛反应。我们必须相当地确定自己知道哪个化合物将要做烯醇组分，哪个化合物将要做酰基化试剂组分。

### 不能烯醇化的活泼酯

有很多实用的这类酯，其中侧边栏的四个最为重要。它们不能作为烯醇组分，而前三个还比大多数酯更加亲电，会比将被烯醇化的酯本身更快地酰基化酯烯醇盐。

这四个化合物以其对于亲核试剂的活性型排序，最亲电的处在顶端，最不亲电的处在底端。草酸酯 (Oxalates) 非常活泼，因为每个羰基都使得另一个羰基更加亲电。LUMO 分子轨道是两个  $\pi^*$  轨道的总和，并会比先前任意一个都更低能。





甲酸酯看起来有点像醛，但它作为酯的身份占主导。氢原子只是让它更为亲电，因为它们缺乏一般酯的  $\sigma$  共轭（也缺乏一般酯的空阻）。

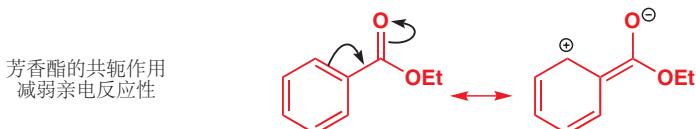
碳酸酯 (Carbonates) 尤其实用，因为它们在烯醇盐上引入了一个  $\text{CO}_2\text{R}$  基。它比普通酯更加亲电的原因可能不那么清晰。普通酯比酮的亲电性（稍）弱，其原因是氧原子贡献的孤对电子的钝化作用，在这里共轭作用要比氧原子的吸电子诱导作用更为重要。



结果来源于这两种效应发挥过程中的一点小差异。在碳酸脂中，两个氧原子位于同一个羰基上。此时它们仍都可以发挥全部的诱导效应；但由于  $\pi^*$  轨道仅能由一对孤对电子占据，两个氧原子不能同时发挥它们的共轭作用。平衡因此改变——结果是，诱导效应胜出了一——碳酸酯相比普通的酯更加亲电。



最后，芳香酸酯不能烯醇化，但由于芳环的共轭作用，它们比普通酯的亲电性弱。但我们还会见到，它们仍然有用。



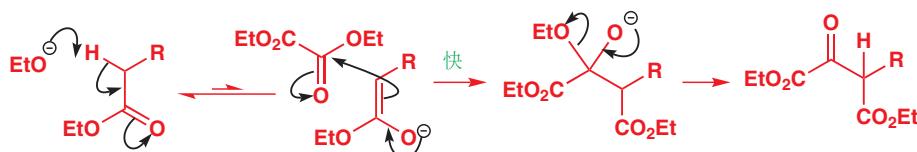
### 两种不同酯间的交叉 Claisen 酯缩合

为了说明几个容易进行的 Claisen 反应，我们现在将给出几个普通酯与我们刚刚讨论过的化合物间的交叉 Claisen 酯缩合。首先，是一个简单线性酯和草酸二乙酯，在烷氧基做碱的平衡条件下发生的反应。弱碱意味着烯醇盐的浓度较少。

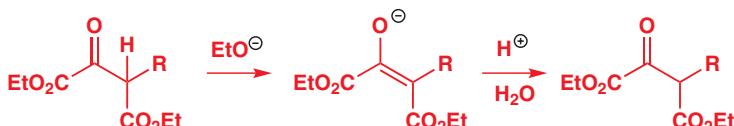


只有简单酯可以给出烯醇盐，低浓度的这种烯醇盐优先与更亲电的草酸二乙酯，通过经典的碳

上酰基化的过程反应。由于草酸酯更加亲电，不会有普通酯的自缩合发生。



产物含有一个酸性氢原子，因此它立即转化为稳定的烯醇盐，后续在酸的水溶液的后处理中质子化，重新给出三羰基化合物。



另一个重要的例子成为了苯基缩苹果酸二乙酯的制备方法。这个化合物不能通过缩苹果酸二乙酯的“烷基化反应”制备，因为芳香卤不能发生亲核取代反应 (Chapter 22)。

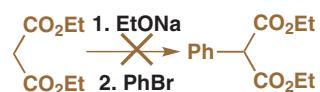
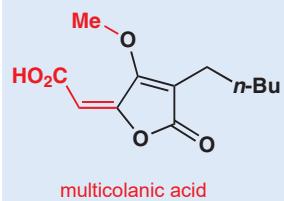
在平衡条件下，非常容易烯醇化的苯乙酸乙酯与不能烯醇化，但亲电性强的碳酸二乙酯，委实非常好地发生了交叉 Claisen 酯缩合。



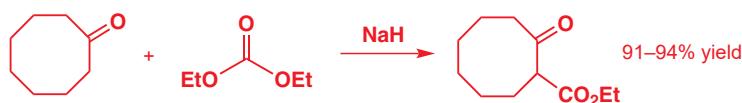
### 酮与酯间的 Claisen 缩合

Claisen 缩合通常是包含酯做亲电组分的酰基化反应，而另一个烯醇组分，则其他羰基化合物的烯醇盐——如酮的——也同样能胜任。在与碳酸酯的反应中，只有酮可以烯醇化，活泼的碳酸酯又比另一分子的酮更亲点。下面环辛酮的例子就很好。无需考虑在羰基的哪一侧烯醇化——它们都是一样的。

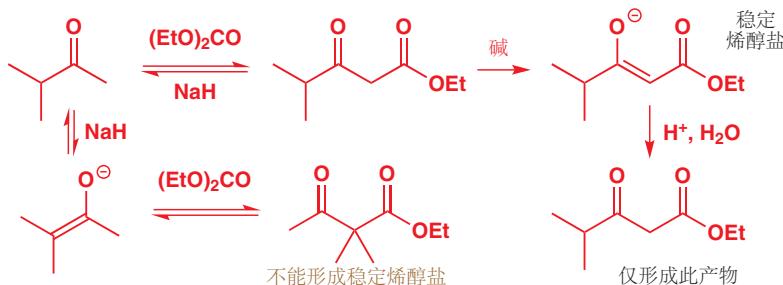
这个化合物在一种青霉菌的代谢物，multicolanic acid 的合成中被使用。很容易看出这个天然产物中的哪些原子（黑色所示）是通过我们刚刚得到的化合物经很简单的一步得到的。



■ 这里酯的所指也包括碳酸酯：它们是碳酸的酯。



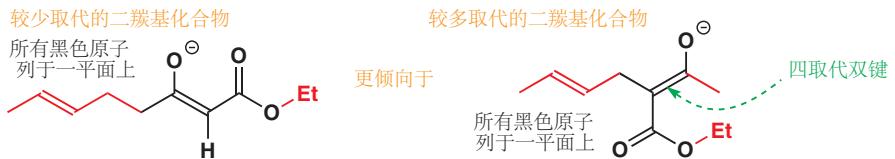
即使没有特别烯醇等价物的使用，不对称酮也通常给出单一产物，因为反应通常在较少取代的一侧发生。这是最终不可逆的烯醇化步骤带来的另一结果。在下面的例子中，两种产物都可能生成，但只有一个可以继续形成稳定烯醇盐。在反应的平衡条件下，只有最终的烯醇盐是稳定的，所有产物都会结束于所示的异构体。



不对称酮甚至在一侧是甲基，一侧是伯烷基链时也能很好地工作。这个反应给出令人赞叹的产率，并且如您所料，远端烯烃不会影响反应。



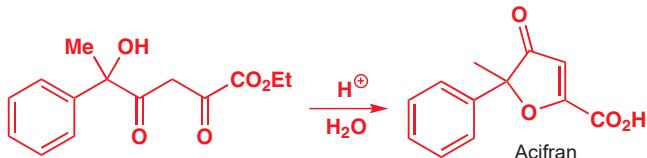
两种烯醇盐都能够形成，但更倾向于形成的是少取代的二羰基烯醇盐，这是因为在烯醇盐双键构成的有空阻的平面上，两种烯醇盐分别为三取代和四取代，少取代烯醇盐挤入其中的取代基更少。



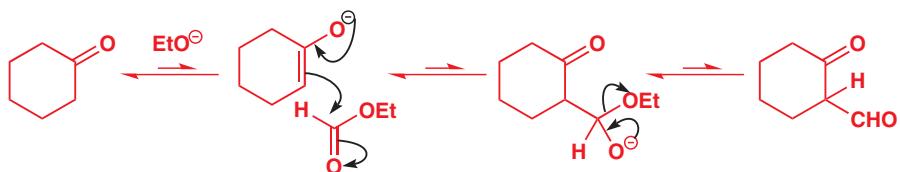
草酸二乙酯也可以与酮给出可控的缩合，我们将以一个新药的合成作为例子。预防心脏病的一种方式就是碱减少血液中“坏的”脂蛋白的含量。药物 Acifran 就是这样起到作用的。其合成的关键一步是草酸二乙酯与甲基酮的碱催化缩合。



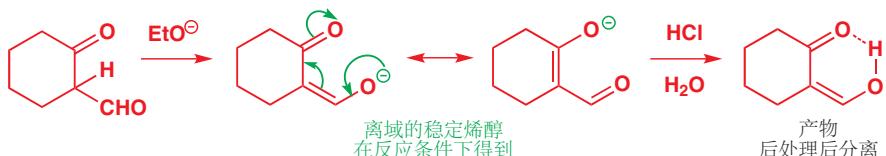
注意酮中的羟基不会干扰反应。毫无疑问，第一分子的碱移去 OH 质子，而第二分子则用于形成烯醇盐（两个分子中唯一可能的烯醇盐）。紧接着是与高亲电性的草酸二乙酯快速的缩合。所得产物简单地用酸处理即可得到药物本身。



另一个我们在 p. 643 提到的不可烯醇化的酯，也可以与酮进行交叉缩合。与甲醛不同的是，甲酸酯表现得很好——不需要像羟醛化学中对应的 Mannich 反应那样特殊处理。下面是它与环己酮反应发生的变化。



产物醛不会受到亲核进攻的威胁，因为它在碱中生成后就立即烯醇化。在后处理中，产物同样以稳定的烯醇生成，带有分子内氢键。



## 通过 Claisen 反应制备酮酯的总结

在这里，我们有必要停下来总结一下我们讨论过的两种简单的制备酮酯的方法，分别被称作：

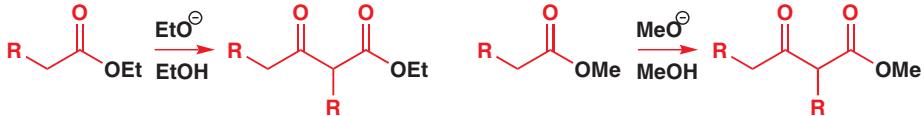
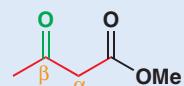
- Claisen 酯缩合
- 酮与碳酸酯的烷基化

乙酰乙酸乙酯（3-氧代丁酸乙酯）当然可以由乙酸乙酯的自缩合制备。这个酯很便宜，通常直接购买，而其同系物，可由其他酯自缩合的得到，则通常在实验室中制取。不管酯中酯化基团如何（OEt, OMe, etc.），需要保证的是使用与之相同的烷氧基阴离子做碱。

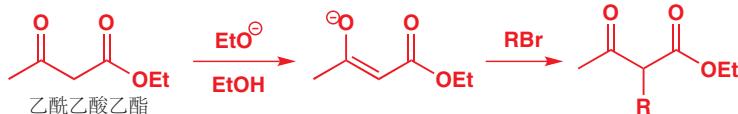
### $\beta$ -酮酯

我们在 p. 643 中已指出，Claisen 反应生成 1,3-二羰基化合物。下面的例子归属这类化合物的一个子集：它们是  $\beta$ -酮酯。

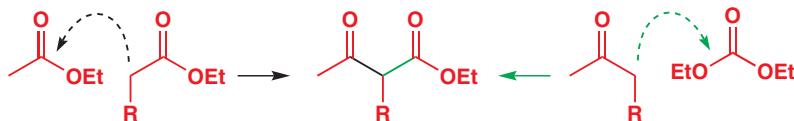
一种  $\beta$ -酮酯



仅含有一个 R 取代基在这个结构中的化合物也很容易制备。如果 R 取代基在 C2 上，最好的引入方法是用未取代的酯烷基化（见 Chapter 25, p. 595）。



试图通过 Claisen 酯缩合制备这个化合物，则需要选择下图中的一种方式。虚线弯曲箭头显示了缩合需要进行的大致方向，染色的键代表如果反应进行，会形成的键。



但这两个反应都不会发生！黑色的路线需要控制的是两种可烯醇化的酯的缩合——给出产物的混合。而上文所示的简单烷基化则不需要控制。绿色的路线是不对称酮与碳酸二乙酯的缩合，这个反应不需要控制，但给出的产物恰恰是我们不想要的。如您在 p. 645 所见，Claisen 缩合倾向于给出少取代的二羰基化合物，因此缩合会发生在酮甲基的一侧，并给出另一种不对称酮酯。因此这种异构体也很容易值得。



### ● 制取 $\beta$ 酮酯：清单

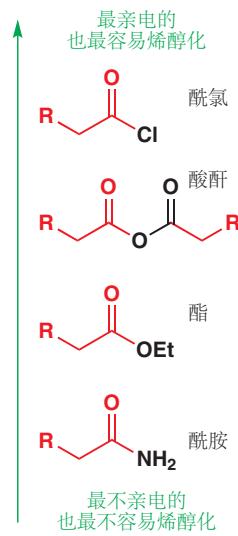
自缩合，与碳酸二乙酯的缩合，以及由这些方法制备的酮酯再发生烷基化，它们将允许我们制取大多数我们想要  $\beta$  酮酯。下面是您需要留意的，烯醇盐化学中的常见问题，如果有其中一个问题存在，请试试烷基化路线。

- 烯醇化的是正确的羰基化合物吗？
- 如果是一个酮，烯醇化发生在正确的一侧吗？
- 烯醇盐会与正确的烷基化组分反应吗？

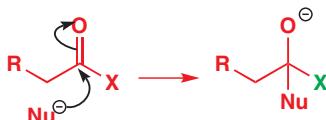
## 通过特别的烯醇等价物控制酰基化

在本章的第一部分，我们已经考察过特别烯醇等价物用于控制羟醛反应的情况了。现在我们要着眼于相同类型的等价物在控制烯醇盐酰基化上的情况，并将我们的讨论拓展到羰基衍生物的特别烯醇盐上。

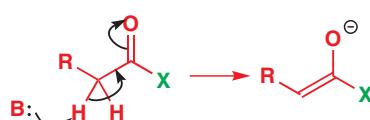
我们在 Chapter 10 中建立起了羧酸衍生物亲电性的等级制度，您现在应当很熟悉这个内容——酰氯位于顶端，而酰胺位于底端。但它们中位于 R 和羰基间的  $\text{CH}_2$  基烯醇化的等级制度又如何呢？您现在可能能够解决这个问题。其原则基于这两个过程的机理。



亲核进攻的机理



烯醇盐形成的机理



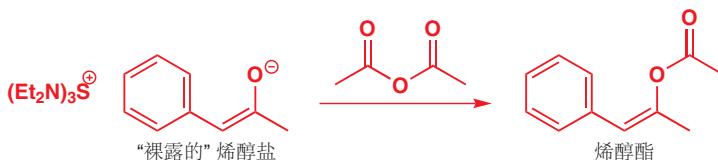
您会发现这两个机理的相似性。尤其是，在羰基本身的变化上是完全相同的。电子流入  $\text{C}=\text{O} \pi^*$  轨道： $\text{C}=\text{O}$  键转变为  $\text{C}-\text{O}$  单键，同时负电荷出现于氧原子上。因此并不会让您感到惊讶的是，烯醇化的反应性次序与受亲核进攻的反应性次序相同。醛比酮更加亲电，也更容易烯醇化；酮比酯更加亲电，也更容易烯醇化，尽管确切地一对一对比醛和酮，一对一对比醛和酸衍生物是不明智的。

在 Chapter 20 我们曾说过，烯醇盐可以由酰氯生成，但它会分解为烯酮。由酰胺生成烯醇盐是很困难的，因为伯酰胺或仲酰胺中的 NH 质子很有可能替代它被移去。本节的剩余部分，我们将会看到酸、酯、醛和酮的特定烯醇等价物的制取。

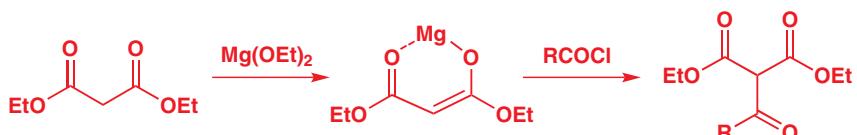


### 酯的定位 C-酰基化

我们需要面对的危险是，酰基化有发生在氧上的趋势，而不是发生在碳上。在极端条件下，裸露的烯醇盐（完全不参与配位的阴离子）与酸酐或酰氯，干净地在氧上烯醇化。

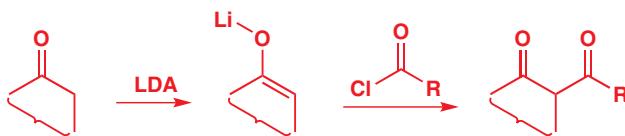


幸运的是，我们之前讨论过的用于羟醛反应的试剂（烯醇锂和烯醇锌），也在碳上酰基化而不是在氧上酰基化。即使与酰氯反应，烯醇镁，尤其是 1,3-二羰基化合物的烯醇酶，会给出可靠的 C-酰基化。镁原子与氧原子紧密成键，降低了它们的有效负电荷。

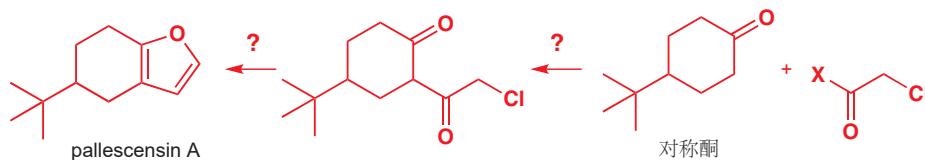


然后通过水解和脱羧的通常方法，可得到酮酯或酮酸。在较常见的用于烯醇烯醇盐的金属中，锂是最有可能给出好的 C-酰基化 过程的，就像镁一样，它能形成紧密的 O-金属键。用简单的烯醇锂与可烯醇化的酰氯进行酰基化是可行的。

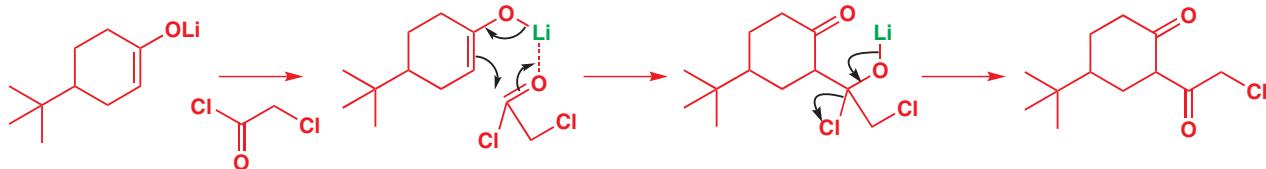
见 p. 597 对于脱羧的讨论。



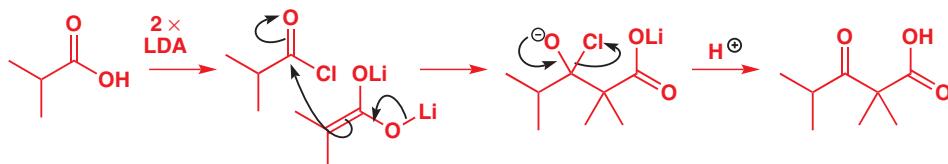
我们将描述两个将此反应应用于天然产物的合成中的例子。第一个是 pallescensin A，海绵的一种代谢物。这是一种相当简单的化合物，米兰的一些科学家设想它可由如下所示的氯代二酮合成的，而氯代二酮则可以通过一种对称酮的酰基化制得。



所选的路线是 4-叔丁基环己烷 的烯醇锂与正确的酰氯的反应。这个反应很好地工作，并一并完成了 pallescensin A 合成的剩余部分。关键的一步，烯醇锂的酰基化是很有趣的，因为烷基化反应可能替代它发生(酰氯做卤代烃)。而在这个反应，酰氯比氯代烷更加亲电，而烷基化则发生于下一步中发生。注意观察在反应中，锂原子是如何将两个分子团结在一起的。



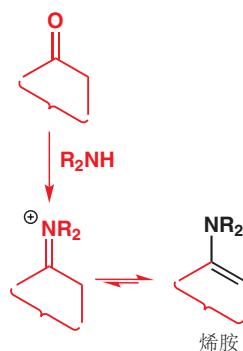
即使是羧酸，用两分子的 LDA 处理所得的二锂衍生物 (dilithio derivatives)，也可以与酰氯发生很好的反应。在这些反应中，不需要考虑最终产物里两个羰基间是否还留有质子，因为反应是强亲核试剂和强亲电试剂间发生的，它是动力学控制的。



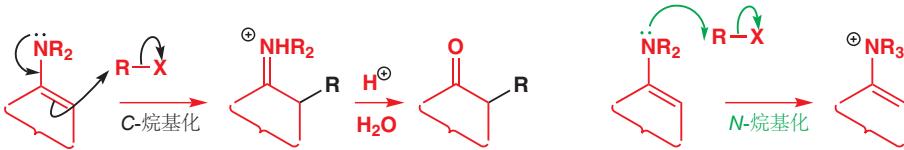
更常见的是用烯胺或烯醇硅醚与酰氯发生烯醇化。这是更通用的方法——醛和酮都能很好地用烯胺反应，而烯醇硅醚则适用于全部羰基化合物。将两个可烯醇化的分子用这些方法，专一地结合是可能的，我们接下来将考虑它们。

### 酮通过烯胺或烯胺盐的酰基化

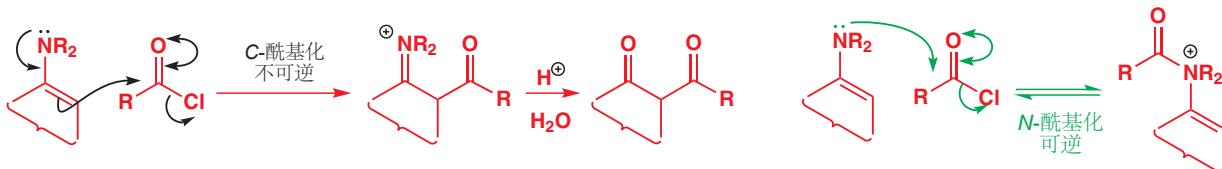
烯胺由醛或酮与仲胺通过亚铵盐制取：您在 Chapter 11 遇到了它们，并在 Chapters 20 和 25 考察了它们的功能。在 Chapter 25 中我们见到，烯胺可与活泼的卤代烃和  $\alpha$ -卤代羰基化合物发生可



靠的 C-烷基化，而对于简单的卤代烃(不活泼的)，则会出现不想要的 N-烷基化与它的竞争。本章早期我们也提到，由于它们不够活泼，因而很少用于羟醛反应。

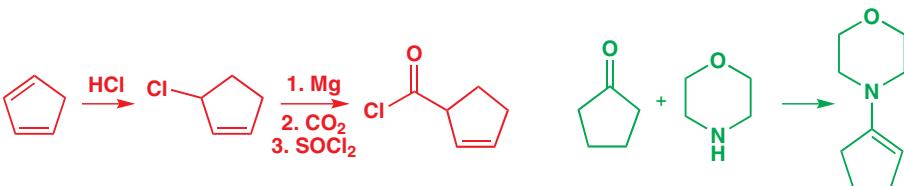


与大大活泼的酰氯发生的酰基化，也遵从上面两条，但有一个很大的不同。那就是 N-酰基化 的产物是一个不稳定的盐，N-酰基化 是可逆的。而在碳上酰基化，是不可逆的。由于这个原因，烯胺会可靠地结束于在碳上的酰基化。

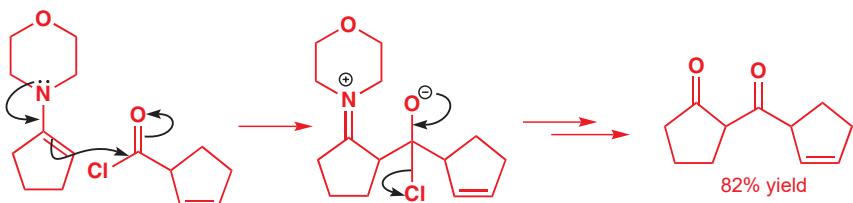


瑞士化学家 Oppolzer 将这个反应用在了天然产物长叶烯 (longifolene) 的合成中。他首先由环戊二烯制备了一个酰氯，并从环戊酮和仲胺吗啉制备了烯胺。

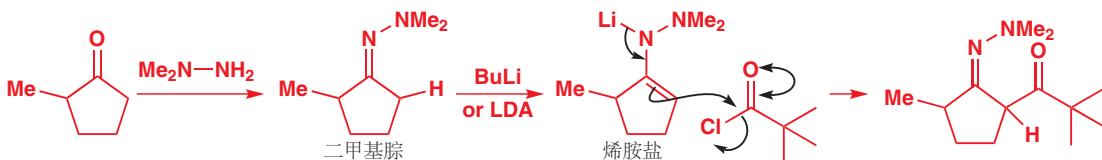
■ 吗啉在烯胺的制备中经常被选用。见 p. 592.



烯胺与酰氯的结合，以 82% 的产率给出干净的碳上的酰基化，最终成功合成了长叶烯。



烯胺盐也同样能与酰氯，干净地在碳上反应。一个好的例子来源于酮的二甲基腙 (dimethylhydrazone). 当酮不对称时，即使只是伯碳、仲碳的差异，烯胺盐也在较少取代的一侧形成。而我们从前最好的区域选择性酰基化反应，仅能区分甲基与较多取代的碳原子。



不会令您惊讶的，直接的产物会在后续互变为被分子内氢键所稳定的酰基烯胺。温和的酸性后处理可释放二酮产物。整个步骤可能听起来有些复杂—— $\text{Me}_2\text{NNH}_2$ ，然后碱，然后酰氯，然后酸性甲醇——但它们都在单个烧瓶中进行，而起产物，1,3-二酮，又以几好的产率生成了——上述情形总产率为 83%。

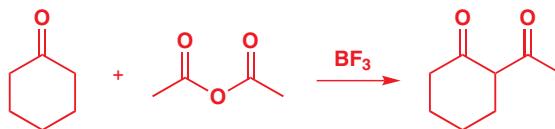


■ 酰的亲电性，我们在 p. 232, Chapter 11 曾阐述，远小于酮。甚至碱的使用可以是 BuLi：它不会进攻  $\text{C}=\text{N}$  键。

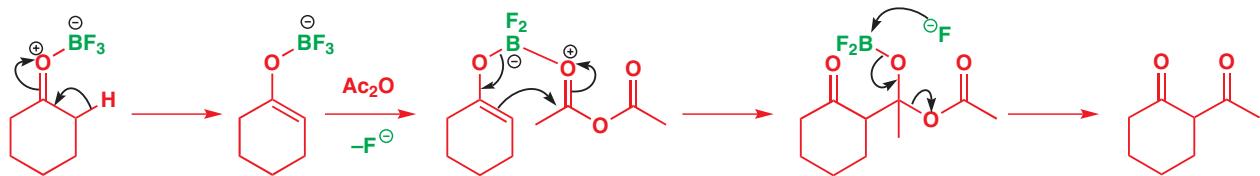
Interactive mechanism for hydrazone enolate alkylation

### 酸性条件下酮的酰基化

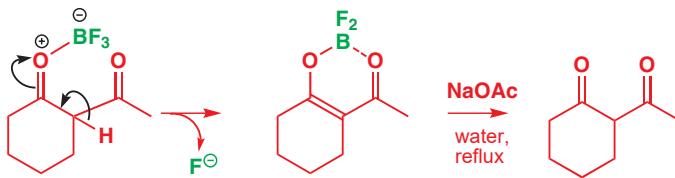
酮烯醇与酸酐的烯醇化被 Lewis 酸，例如  $\text{BF}_3$  催化。这个过程会让您想起 Friedel-Crafts 酰基化反应 (p. 477)，但更好的类比不如有金属 (如锂) 参与，将试剂团结在一起，并通过六元环进行的羟醛反应。



机理显然包含酮的烯醇 (或“烯醇硼 boron enolate”) 对酸酐发动的进攻，由 Lewis 酸催化。可能的过程是硼原子将试剂团结在一起，非常像烯醇锂的羟醛反应中锂原子的作用 (p. 625)。

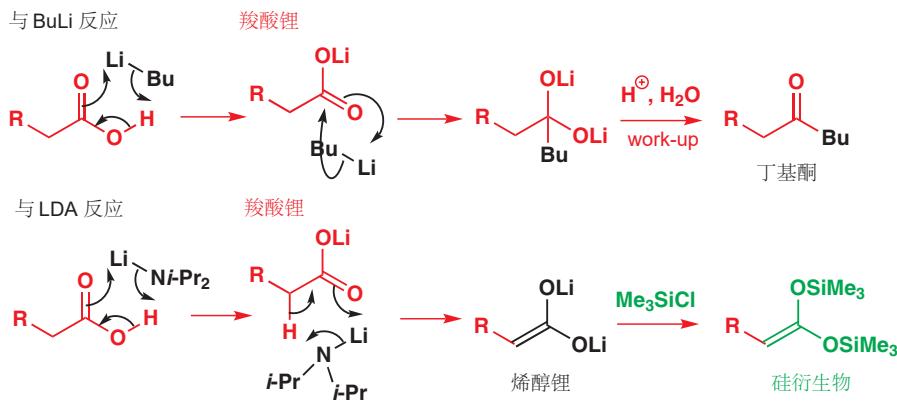


在反应条件下，产物以烯醇硼形式生成，并需要用回流的乙酸钠水溶液处理，以分解得到二酮。



### 游离羧酸的酰基化

您可能会认为，羧酸中酸性质子的存在，建立了一个任何烯醇衍生物的生成都不可逾越的屏障。事实上，这在烯醇锂和烯醇硅醚的生成上都不构成问题。像羧酸中加入  $\text{BuLi}$  或  $\text{LDA}$ ，立即发生酸性质子的脱去，所得是羧酸的锂盐。如果用的是  $\text{BuLi}$ ，下一步会是  $\text{BuLi}$  对羰基的进攻，最终形成酮 (见 Chapter 10, p. 218)。但如果用的是  $\text{LDA}$ ，就可能形成羧酸锂 (衍生物) 的烯醇锂。



■ 酸或酯的烯醇硅醚被称作烯酮缩醛 (silyl ketene acetal)。详见 p. 609.

烯醇盐衍生物有两个  $\text{OLi}$  基在同一个双键上，这相当奇异，但它可以干净地转化为对应的烯醇硅醚。由酸得到的烯醇锂和烯醇硅醚都可以用于羟醛反应。

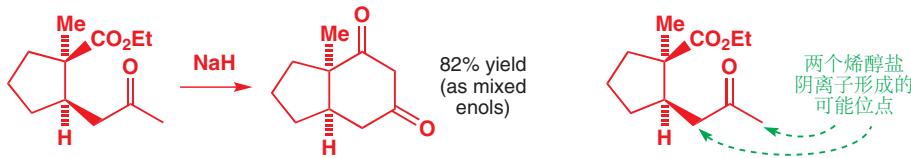
#### ● 用于羟醛反应和在碳上的酰基化的实用的烯醇盐

烯醇盐类别	醛	酮	酯	酸
烯醇锂	×	√	√	√
烯醇硅醚	√	√	√	√
烯胺	√	√	×	×
烯胺盐	√	√	×	×
烯醇锌	×	×	√	×

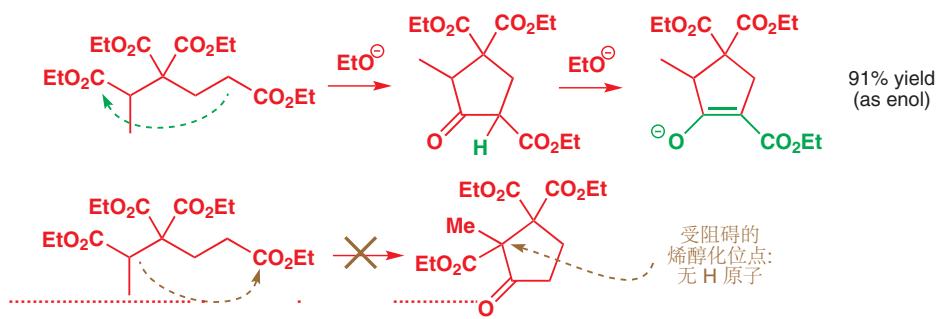
这就结束了我们对于碳上酰基化的特别烯醇盐的普查了。现在还剩下一些尤其容易处理的反应 (历史总是惊人的相似)。

## 分子内交叉 Claisen 酯缩合

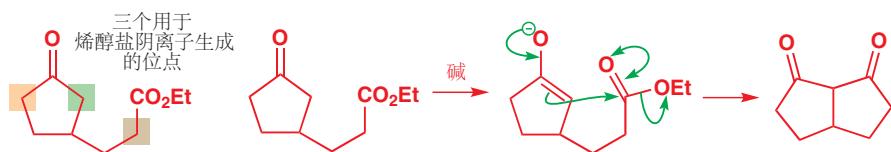
由于它与分子内交叉羟醛反应的反应方式相同，我们也不需要过多地考虑如何控制烯醇化位点，因为总有一种产物是比其他的产物都更稳定的一一例如，我们能得到五元或六元环的产物 (而不是得到四元环，或得到八元环的一个)一一并且我们在平衡条件下完成这个反应。下面的几个例子将说明我们的观点。虽然烯醇盐阴离子的形成有两个位点，但其中一个给出四元环，并因此可被我们忽略，而另一个则给出一个稳定的六元环。



在下一个例子中，两个烯醇盐阴离子形成的可能位点，都会导向稳定的五元环的生成。而正确的产物会在反应条件下形成稳定的烯醇盐阴离子，另一个则由于两个羰基间没有氢原子而不能如此。



在下一个例子中，有三个可用于烯醇阴离子形成的位点，但最终产物仍只有一个，且产率良好。如果我们考虑这三种可能的阴离子，那么就会很容易做出选择。首先，反应委实发生了。烯醇阴离子在酮的绿色位点形成，并紧跟着在碳上的酰基化。产物是一个稠环，而不是桥双环结构（橘色位点反应），因此很容易形成稳定烯醇阴离子。



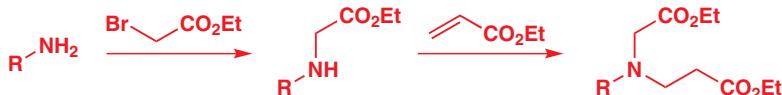
我们可由在酮中橘色的位点生成烯醇阴离子，继而以相同的方式进攻酯。而产物会是一个桥双环二酮它并不会生成（见上文）。第三个可能的烯醇化位点（棕色）可能给出羟醛反应，但产物也会是桥双环化合物，并也不会生成。

### 分子内交叉 Claisen 缩合中的对称性

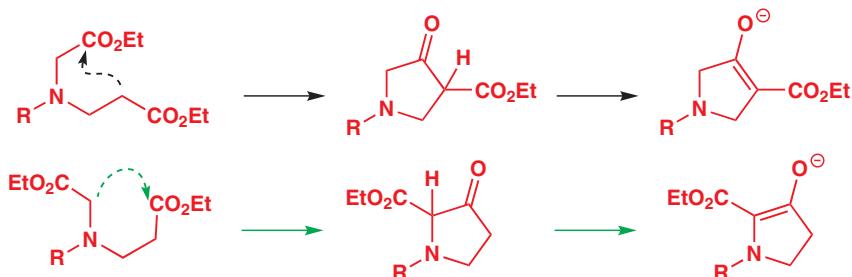
如果环化之后又有脱羧跟着，那么一个诡计就诞生了。通过  $S_N2$  反应向一个  $\alpha$ -卤代酯添加胺，紧跟着对不饱和酯的共轭加成，可由给出 Claisen 酯环化的底物。

### 桥环化合物

在 Chapter 32 中我们会讨论稠环化合物（共用一根键）、螺环化合物（共用一个院子），以及桥环化合物（两个环通过两个非相邻原子相连）的区别。下面每种化合物的例子都傲寒两个五元环。

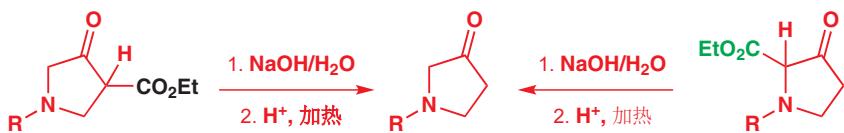


这个二酯是不对称的，因此很可能导致两种不同的酮酯的形成。每一种都可以形成稳定的烯醇盐，因此它们都委实形成了。产物是混合物，这听起来像个坏消息。

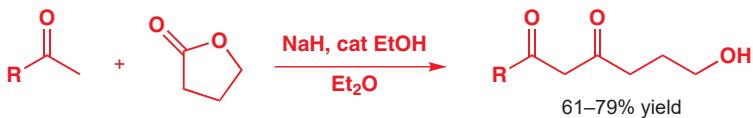


而我们的诡计在于，两个产物中，酮与氮原子在五元环中的相对位置是一样的。唯一有区别的是

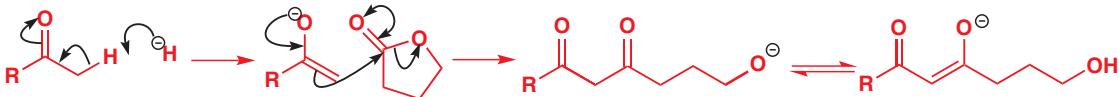
$\text{CO}_2\text{Et}$  基的位置。当这两种产物都水解、脱羧后，所得的是相同的氨基酮！



在平衡条件下，两种不同的自缩合都发生，并均给出可烯醇化的产物的情况偶尔发生。一个值得注意的例子是甲基酮和内酯的碱催化反应。用氢化钠——一个可以将这两种原料都完全转化为其烯醇阴离子的强碱——以良好的产率，获得了酮的烯醇盐对亲电的内酯进攻的产物。



在酮的甲基上形成动力学烯醇盐，并紧跟着与内酯的酰基反应。相比于非环状酯，内酯向当地亲电，但上述过程的控制仍然引人注目。注意稳定的烯醇盐是如何从首个形成的产物中通过质子转移形成的。



## 羰基化学——下一站？

本章总结了从 Chapter 6 开始，羰基化合物的反应，最初我们考察的是在  $\text{C}=\text{O}$  基上的加成反应，然后接连完成下面几个阶段：

Chapter 9: 通过向  $\text{C}=\text{O}$  添加有机金属来构筑  $\text{C}-\text{C}$  键

Chapter 10:  $\text{C}=\text{O}$  (羧酸衍生物) 上的取代反应

Chapter 11: 伴随羰基 O 离去的  $\text{C}=\text{O}$  上的取代反应 (缩醛、亚胺，等等)

Chapter 20: 烯醇和烯醇盐

Chapter 25: 烯醇盐的烷基化

Chapter 26: 向  $\text{C}=\text{O}$  基添加烯醇和烯醇盐：羟醛反应和 Claisen 反应

羰基是允许化学家将分子组合在一起的“挂钩 (hooks)”，在下下章中 (Chapter 28 逆合成分析)，我们会讨论如何用羰基化学思考合成的科学。我们会重新考察很多您见过的反应，也包含后面将要学的反应——尤其是杂环的合成 (Chapter 30)，以及非对映选择性、对映选择性的反应 (Chapters 33 和 41)。

## 延伸阅读

S. Warren, *Chemistry of the Carbonyl Group*, Wiley, Chichester, 1974: section 5 is ‘Building Organic Molecules from Carbonyl Compounds.’ 更后期的手段见：P. Wyatt and S. Warren, *Organic Synthesis: Strategy and Control*, Wiley, Chichester, 2007, chapters 3–6. 所有类型的羟醛反应的最终来源为 A. T. Nielsen and W. J. Houlihan, *Organic Reactions*, 1968, **16**, whole volume. 对于 Claisen 方式的缩

合, J. P. Schaefer and J. J. Bloomfield, *The Dieckmann Condensation*; G. Jones, *The Knoevenagel Condensation: Organic Reactions*, 1967, **15**, whole volume.

F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry B, Reactions and Synthesis*, 5th edn, Springer 2007, chapter 2.

## Check your understanding

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To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 27

# 有机化学中的硫、硅和磷

## 联系

### → 基础

- 羰基化学 ch6, ch10, & ch11
- Wittig 反应 ch11
- 动力学和热力学控制 ch12
- 立体化学 ch14
- 消除反应 ch17
- 共轭加成 ch22
- 还原反应 ch23
- 烯醇(盐)化学 ch25 & ch26

### 目标

- 有机 S 和 Si 化学
- 烯烃合成中的 S, Si, 和 P
- E/Z 控制的重要性
- 控制 E/Z 几何结构的方法
- 烯烃的平衡给出反式构型
- 光的作用和我们的视力
- 实践中的 Julia 成烯反应和 Wittig 反应
- 可靠的炔烃还原反应

### → 展望

- 非对映选择性 ch33
- 周环反应 ch34 & ch35
- 碎片化 ch36
- 自由基和卡宾 ch37 & ch38
- 不对称合成 ch41

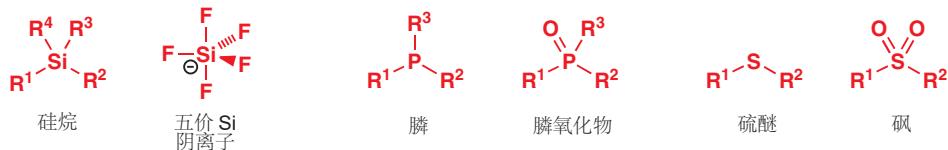
## 有用的主族元素

### 电负性

C (2.5)	N (3.0)	O (3.5)	F (4.0)
Si (1.8)	P (2.1)	S (2.5)	Cl (3.0)

有机化学家使用周期表中的大部分元素：您已经见到了包含 Li, B, F, Na, Mg, Al, Si, P, S, Cl, K, Cu, Br, 和 I 的有机化合物——但这仅仅是开始。其中三种最重要的，是硫、磷和硅。它们都可以形成稳定的有机化合物，并且在有机化学中起到像氧、氮和卤素一样重要的作用。它们是第三周期元素，紧挨在碳、氮、氧的下方，因而它们也有些相似之处。电负性（侧边栏所示）从右上到左下递减。

与 C, N, 和 O 主要的区别在于，Si, P, 和 S 可以形成更多根键。这是因为它们有更多的轨道：在一个 3s 和三个 3p 的基础上还另有五个 3d 轨道。硅可形成与烷相当像的硅烷 (silanes)，但还可以形成稳定的五价阴离子。磷可形成类似于胺的膦 (phosphines)，但还可以形成四面体型的氧化膦。硫的配位数可由零直到七，形成类似于醚的硫醚 (sulfides, thioether) 和四面体型，硫连接六根键的砜 (sulfones)。我们将从硫谈起。



### 硫的英文拼写

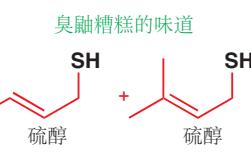
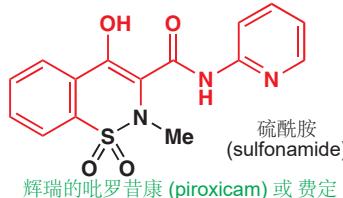
如果您查阅牛津英语词典，您会看到 "sulphur" 一词 (以及 "sulphuric", "sulphate"...)。它们是英式独有的拼写方式，几年前全世界的化学家已将其统一为：“sulfur”。

## 硫：充满不一致的元素

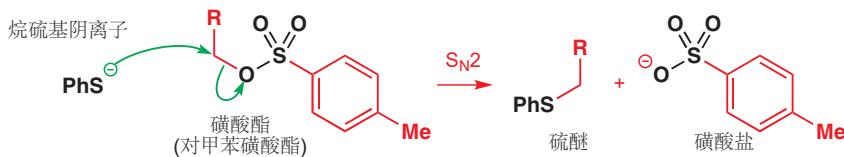
本书中最先涉及的有机硫化合物，是臭鼬的可怕味道和松露的绝妙味道。对于松露的味道，猪可用透过一米深的土壤侦察到这种气味，它的味道令人很愉悦，以至于它的价格超过等重的黄金。

硫化合物可以用作还原剂、氧化剂、阴离子、阳离子, 亲核试剂、亲电试剂, 以及, 它的味道可以是臭的, 也是可以是甜的。

有用的硫化合物, 包括麻风药物达普颂 dapson (Chapter 6), 关节炎药物费定 feldene (Chapter 20), 能保护大多数生命体面对氧化剂的, 包含天然氨基酸半胱氨酸的谷胱甘肽 glutathione (Chapter 22), 当然, 还有几章前提到的, 著名的抗生素盘尼西林 penicillins,.



硫的重要的反应, 包括在  $S_N2$  反应中作为亲核试剂、离去基团, 包括芳环的碘化反应 (Chapter 21), 二硫缩醛的形成和还原反应 (Chapter 23). 如下的  $S_N2$  反应使用了一个硫亲核试剂和一个含硫离去基团 (磷酸根)。



## 一些有关硫的事实

硫是位于 VI 族 (16 族) 的 p-区元素, 紧挨在氧的下方, 在磷和氯之间。我们自然会将其与氧比较, 但我们还会, 奇怪地, 将其与碳比较。

硫的电负性远低于氧; 事实上, 它与碳的电负性相同, 因此试图用 C–S 键的极性解释任何问题都是捕风捉影! 它能与碳成颇 (reasonably) 强的键——足够使化合物稳定, 但又在比它强得多的 C–O 键的存在下足够不稳定以被选择性断裂。它也能与自己成还算 (fairly) 强的键。黄色结晶硫单质以  $\text{S}_8$  分子形式存在——硫原子构成的八元环。

因为硫在周期表中处于第三周期, 因此它能形成许多氧不能形成的化合物种类。与很稳定, 可以被分离的 S–S 和 S–卤 键对比, O–卤 和 O–O 化合物是不稳定, 通常易爆的。硫的 d 轨道使其氧化态涵盖 0, 2, 4, 和 6, 配位数 (注: 化合价) 由 0 到 7. 这里选择了一些化合物展示。

## 硫的化合物

氧化态	S(II)			S(IV)			S(VI)	
配位数	0	1	2	3	4	4	6	7
例子	$\text{S}^{2-}$	$\text{RS}^-$	$\text{R}_2\text{S}$	$\text{R}_2\text{S=O}$	$\text{SF}_4$	$\text{R}_2\text{SO}_2$	$\text{SF}_6$	$\text{SF}_7^-$

## 硫是一个多才多艺的元素

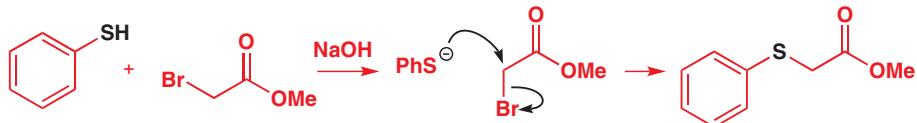
与氧化数的多样性一样, 硫在功能上也不时地展现出令人惊喜的多功能性。如您所预料的, 硫含



典型键能,  $\text{kJ mol}^{-1}$

X =	C	H	F	S
C–X	376	418	452	362
S–X	362	349	384	301

高能的非键孤对电子 ( $3sp^3$  而非氧上的  $2sp^3$ )，因而简单 S(II) 化合物是好的亲电试剂。用硫醇 thiol (RSH, 醇的硫等价物) 和 NaOH 的混合物与卤代烷反应，可以单一地给出通过  $RS^-$  的亲核进攻得到的硫醚。



▶ 亲核试剂的“软或硬”性质随  $S_N2$  反应在 Chapter 15 中大致讨论。

■ 亚砜酰氯  $SOCl_2$  在硫上亲电，而砜酰氯  $SO_2Cl_2$  则在氯上亲电。又一个不一致！

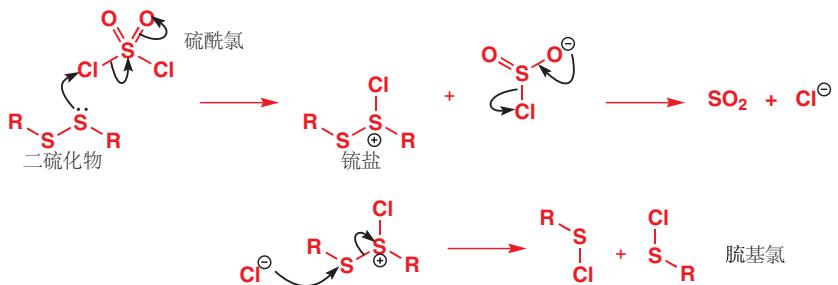
注：砜基氯不是正式名称，这大概是由于根本没有“砜”字所致，本书中所有“砜”替换作“硫”即是正确命名。

注：砜/砜，亚砜酰/亚砜分别是大同小异的。例如：砜/砜酰化合物 (eg.  $\text{W}_2$ , 亚砜/亚砜酰化合物 (eg.  $\text{W}_2\text{IV}$ ), 简单化合物命名亦可见砜酰基 (sulfuryl)、亚砜酰基 (thionyl)。

硫醇 thiol/mercaptan (RSH) 的酸性比醇强，因此第一步是由硫醇与氢氧根离子间快速的质子转移。随后烷硫基阴离子 (thiolate anion, 硫醇的共轭碱) 在烷基溴上发生一个非常有效的  $S_N2$  取代反应，以给出硫醚。注意，烷硫基阴离子不会进攻羰基。小的、碱性强的氧阴离子电荷密度高，而轨道低能——它们是硬亲核试剂，倾向于进攻质子和羰基。而大的、碱性弱的烷硫基阴离子的轨道高能，是软的亲核试剂，它们倾向于进攻饱和碳原子。硫醇和烷硫基阴离子都是好的软亲核试剂。

● 硫醇 (RSH) 比醇 (ROH) 酸性强，但硫化合物对于饱和碳原子 ( $S_N2$ ) 是比氧化合物好的亲核试剂。

它们同样是好的软亲电试剂。砜基氯/烃砜基氯 Sulfenyl chlorides (RSCl) 很容易通过二硫化物 d-isulfides (RS-SR) 和砜酰氯 sulfuryl chloride ( $SO_2Cl_2$ ) 的反应制备。这种氯化 S(VI) 带有亲电的氯原子，可被亲核试剂二硫化物进攻，给出两分子的 RSCl 和一分子气态  $SO_2$ 。这其中包含了许多硫化学内容！我们将从二硫化物中的一个硫原子发起的亲核进攻开始。中间体包含一个三配位的砜阳离子或砜盐 (sulfonium salt)。然后氯离子进攻中间体的另一个硫原子，得到两分子 RSCl。起始二硫化物中的每个硫原子都形成了一根 S–Cl 键。一个硫原子是对氯的亲核试剂，另一个则是亲电试剂。

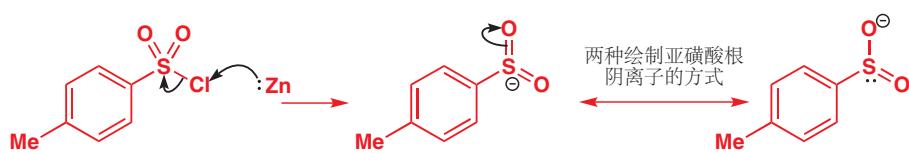


这个反应的产物，砜基氯，也是一个好的，对碳原子的软亲电试剂，尤其是对于烯烃。这个反应非常像 Chapter 19 中的溴化反应，只是将溴𬭩离子中间体换成了三元环锍 (锍𬭩) 离子。这个反应是立体专一性的，产物为 anti 构型。

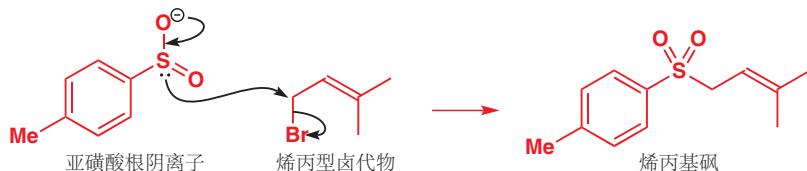


氧化态越高，硫上带有的正电荷就会越高，化合物就会变成越硬的亲电试剂。在本章和前面的章节中，我们提到过对甲苯磺酰氯 (tosyl chloride),  $TsCl$ ，它可作为对烷氧基阴离子的亲电试剂。

在较高氧化态下，硫看起来并不像好的亲核试剂，但请思考  $TsCl$  与金属锌反应的结果。锌提供两个电子，将化合物转化为一个阴离子。这个阴离子可以以两种方式绘制。



意外的是，这个阴离子也是一个好的、软的亲核试剂，并可从硫原子进攻饱和碳原子。在下面的情形中，进攻发生在烯丙型溴代物较少取代的一端，并给出烯丙基砜，我们稍后会用到。



- 硫化合物可以做好的亲核试剂和好的亲电试剂。

### 以硫为基础的官能团

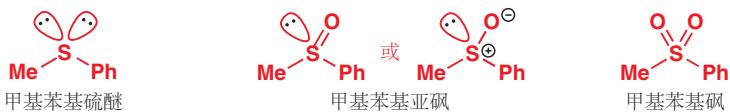
您已经遇到了不少含硫的官能团：下表将它们总结以用于参考。

名称	结构	价值	例子	注释
硫醇	RSH	味道浓郁，通常不好闻，但在低浓度下可能令人愉悦		咖啡和西柚的气味和味道
烷硫基阴离子	RS-	好的软亲核试剂		
二硫化物	RS-SR	蛋白质交联		胱氨酸
氨基氯	RS-Cl	好的软亲核试剂		
硫醚	R-S-R	连接分子		菠萝的气味和味道
锍盐	R <sub>3</sub> S <sup>+</sup>	重要的试剂		环氧化物中使用的叶立德
亚砜	R <sub>2</sub> S=O 或 R <sub>2</sub> S <sup>+-</sup> O <sup>-</sup>	很多反应；可具有手性		DMSO (二甲亚砜)
砜	R <sub>2</sub> SO <sub>2</sub>	阴离子稳定基		
磺酸	RSO <sub>2</sub> OH	强酸		对甲苯磺酸，TsOH
磺酰氯	RSO <sub>2</sub> Cl	将醇转化为离去基团		对甲苯磺酰氯，TsCl

随着本章的发展，您将看到硫多功能性的其他例子。您将看到，它可以通过氧化或还原从有机化合物中移除，您也会看到，它可以稳定邻位碳原子上的阴离子或阳离子。对阴离子的稳定化作用是本章的第一个主要节。

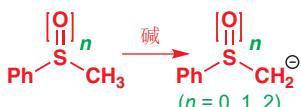
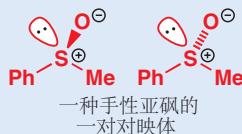
## 被硫稳定的阴离子

硫醚、亚砜和砜对阴离子的稳定化作用，是贯穿本章的主题。硫在其外壳层有六个电子。对于硫醚，则因此带有两对孤电子。在亚砜中，其中一对孤对电子用于与氧原子成键——亚砜可以表示为至少两种极限式，它们是等价的。砜中的硫原子用其全部孤对电子与氧成键，通常表示成含有两根 S=O 双键的结构。

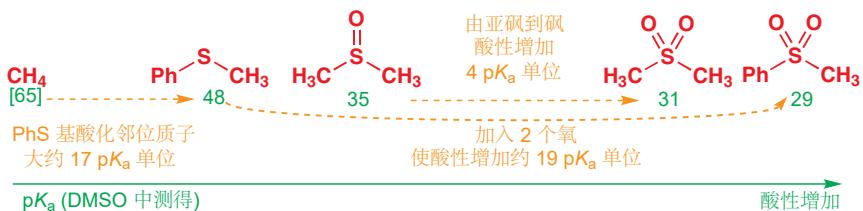


### 亚砜的手性

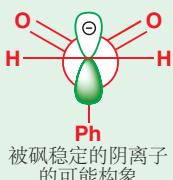
亚砜具有形成手性的潜力——四面体硫原子被四个基团包围（此例中为 Ph, Me, O, 和孤对电子）；并且不像胺中的四面体氮原子，亚砜的四面体构型较稳定。我们会在本章中回到有关亚砜手性的内容。



用强碱处理上面任意一种化合物，则都会在原先的甲基上产生阴离子。硫如何稳定阴离子？这个问题曾被多次作为辩论的主题，但我们并没有足够时间详细地一一讨论。包含至少两个因素，第一个是从对砜、亚砜、硫醚官能团旁边质子的  $pK_a$  数值的跟踪上得到的证据。



■ 在砜旁的碳阴离子是平面型的，而在亚砜、硫醚旁的则是金字塔型的 ( $sp^3$  杂化)。



洞若观火，氧原子是重要的——最好的阴离子稳定体是砜，其次是亚砜，然后是硫醚。您可以对比砜的去质子和酮的去质子（给出烯醇阴离子，Chapter 20）。烯醇阴离子包含一个平面型的碳原子，其负电荷主要在氧原子上。被砜稳定的碳阴离子有两个氧原子，其阴离子型碳原子很有可能也是平面型的，带有负电荷的 p 轨道正对两根 S=O 键之间。



但附着于其上的氧原子，并不是导致与之相邻的阴离子稳定的唯一原因，因为即使是硫醚官能团，也能很显著地酸化邻位质子。对于这一现象的确切原因，有一些争议，但通常的解释是硫的 3s 和 3p 电子的极化作用（它们更加松散，因此比氧的 2s 和 2p 电子更易极化）对稳定化有所贡献。

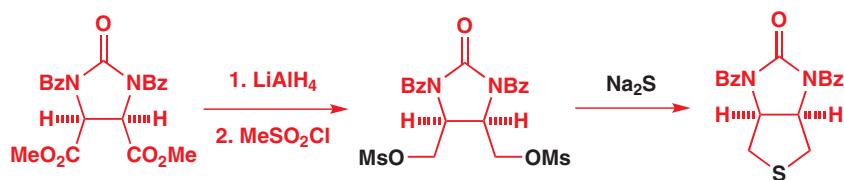
### 邻位硫稳定阴离子

长期以来，人们认为进入硫的空 3d 轨道的离域提供了所需的对阴离子的稳定化作用，但近 20 年左右的理论工作提出，可能并非如此。从头计算法 (*ab initio* calculations) 提出， $\text{CH}_2\text{SH}$  中的 C-S 键比  $\text{CH}_3\text{SH}$  中的长。如果进入硫 d 轨道的离域是重要的，那么现象则应正好颠倒。离域起到半双键的作用，因而会使键缩短。更有可能作为附加因素的，是进入 C-S 键在硫原子另一端的  $\sigma^*$  轨道的离域现象——二噻烷（更多有关二噻烷请见 p. 662）中硫旁边的平伏质子比直立质子酸性更强，平伏阴离子也更加稳定，由于它可以离域入 C-S 键的  $\sigma^*$  轨道。



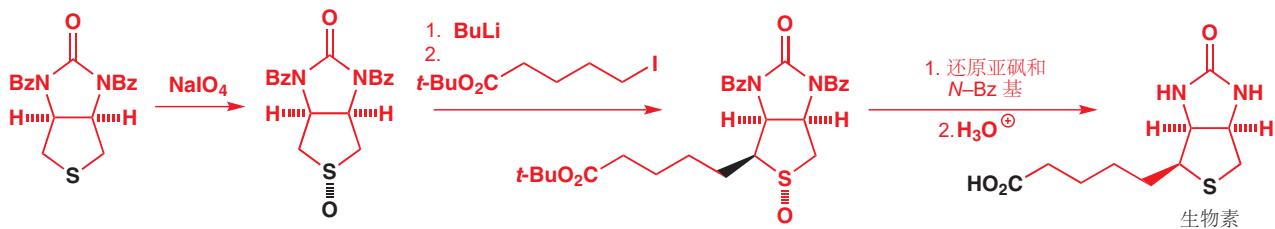
### 被亚砜稳定的阴离子应用于合成

亚砜基化组成了重要的维生素生物素 (biotin) 的合成中关键的一步。生物素包含一个稠合在另一个五元环上的五元杂环硫醚，这种双环结构容易由简单的对称酯制得。最重要的步骤是在两个伯碳原子上的两个  $\text{S}_{\text{N}}2$  反应。



下一步是烷基链的引入——最好的做法是首先用高碘酸钠，将硫醚氧化为亚砜。亚砜随后被 *n*-BuLi 去质子，并与一个包含被叔丁酯保护的羧基的碘代烷发生烷基化。然后，经过亚砜的还原和叔丁酯的水解，给出生物素。

合成中还包含一些立体化学，我们会在 Chapter 32 中再访。

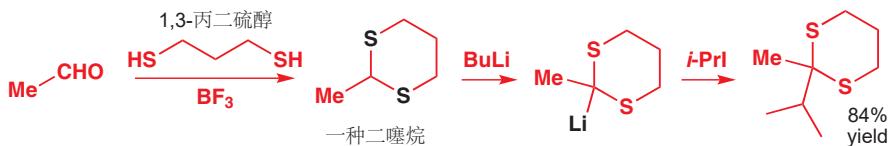


### 硫缩醛

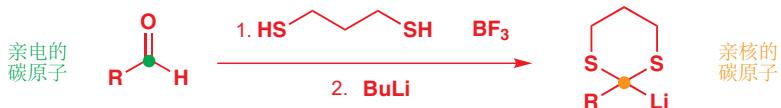
尽管硫醚本身可以去质子，但与两个硫醚硫原子同时相邻的质子的酸性还要更强，硫缩醛 (thiaoacetal) 的烷基化相当容易发生。



一般而言，硫缩醛也可用与“一般”(氧基)缩醛相似的方式制取——用硫醇和酸催化剂处理醛或酮——对于酸性催化剂，相比于质子酸，更常用 Lewis 酸，例如  $\text{BF}_3$ 。最容易制备的，面对水解最稳定的，面对烷基化最活泼的硫缩醛，是由 1,3-丙二硫醇衍生的，被称作二噻烷(dithianes)。



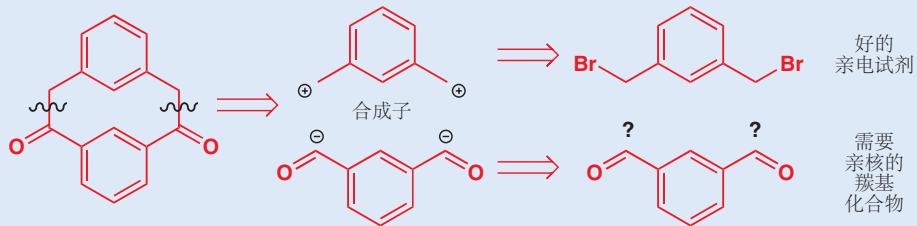
二噻烷在有机合成中是极其有用的化合物，因为由羰基化合物形成硫缩醛的过程会使携带官能团的碳原子极性翻转。您很清楚，醛在  $\text{C}=\text{O}$  碳原子上是亲电的，但二硫缩醛，通过去质子化为阴离子，则可在相同的碳原子上做亲核试剂。



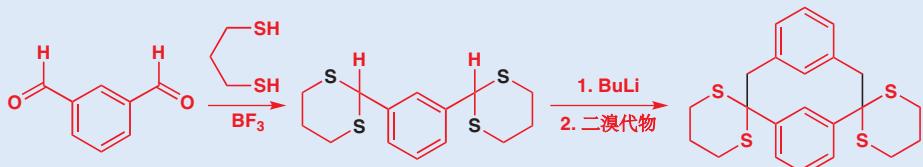
### 二噻烷应用于合成

一个例子：一些化学家想制取如下左侧这个化合物(一个“间环蕃/间环芳烷 metacyclophane”)以研究在小环中受阻的苯环的独立旋转。理想的方法是将亲电的溴苯添加到亲核的羰基上，这建立在羰基可亲核的情况下。

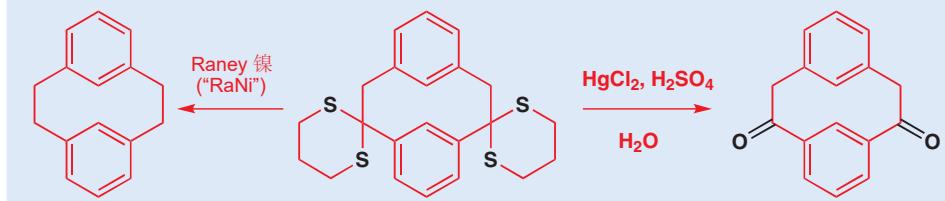
关于这些敞开的“逆合成”箭头以及“合成子”一词的阐释，请见 Chapter 28.



二溴代物和二醛都是可得的——他们真正需要的，是二醛的亲核等价物，以使之能与二溴代物反应。因此他们制取了二噻烷。硫的碱性比氧弱，在相同的 pH 下质子化的物种浓度更低；并且硫的 3p 孤对电子相比于氧的 2p 孤对电子，较不容易与碳形成稳定的  $\pi$  键(注：即相比缩醛不易水解)。



二噻烷被烷基化后，它们可以水解变回羰基。或者，用 Raney 镍催化氢化，可以将硫缩醛变为  $\text{CH}_2$  并给出未取代的环蕃。



二噻烷相比缩醛稳定很多，它水解为羰基的过程需要特殊的试剂协助。硫比氧的碱性弱，在相同 pH 下质子化物种的浓度更低；而硫的 3p 孤对电子相比于氧的 2p 孤对电子与碳成的  $\pi$  键更不稳定。

反应得差...



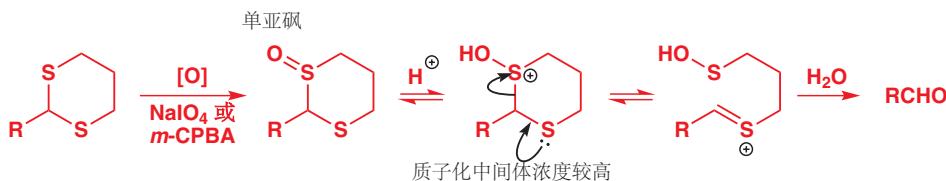
反应得好...



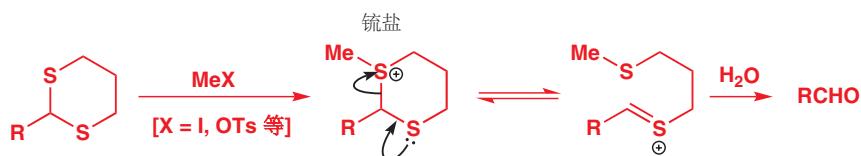
### ● 硫化合物的碱性弱于氧化合物， $C=S$ 化合物的稳定性差于 $C=O$ 化合物。

这个问题最显然的解决方法，是为硫提供一个相比于质子更好的亲电试剂。汞，Hg(II)，就是其中一种方法。另一种方法，则是将硫氧化为亚砜；这样质子化就可以发生在亚砜碱性较强的氧原子上，质子化的中间体的浓度得以提高。

由于硫醇 (Thiols) 捕获汞的倾向，它也被称作 **mercaptans** (mercury capture).



第三种解决办法是甲基化，这利用了硫比氧还好的对于饱和碳亲核性。所得的锍盐可以以缩醛分解的相同方式分解，以释放醛。二硫缩醛的水解还有更多其他方法，这种多样性会让您怀疑其中没有一个是非常好的。



► Raney 镍的介绍: p. 537.

硫醚和硫缩醛中 C–S 键的氢化均使用 **Raney 镍** (用碱 alkali 处理镍–铝合金，以溶解其中的铝制得的细小分散状的镍) 完成。它既可以作为催化剂，和氢气一起完成氢化；由于它在新制时通常吸附有充足的氢 (由铝与碱的反应得到)，也可以单独完成还原。硫缩醛化反应加 Raney 镍还原是一种将 C=O 基替换为 CH<sub>2</sub> 的实用方法 (Mozingo 反应, p. 540)。

### ● 二噻烷是“酰基阴离子等价物”

羰基化合物先装扮为硫衍生物，与亲电试剂发生烷基化，然后再转变回羰基的流程是一次亲核酰基化 (nucleophilic acylation)。这些羰基化合物的亲核性等价物被称为酰基阴离子等价物 (acyl anion equivalents)。用 Chapter 28 中的逆合成术语来说，即是酰基阴离子合成子对应的 d<sup>1</sup> 试剂。

## 砜的阴离子

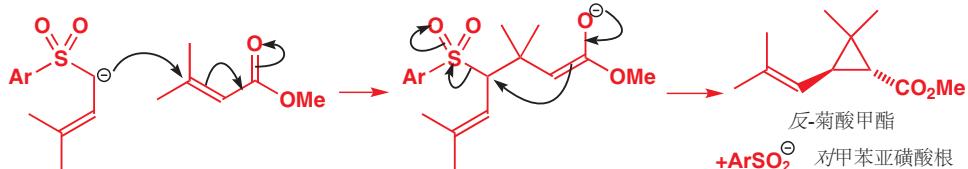
如果硫的氧化态较高，则邻位阴离子的形成会容易得多，砜便是如此。之前我们所制取的烯丙型砜 (p. 659) 可以通过去质子并加成到一个不饱和酯上，以得到环丙烷。注意，由于阴离子会被砜和烯烃共同稳定，这里所需的碱是很弱的 (MeO<sup>-</sup>)。

■ 在锍盐的节中，您会看到更多这类，硫原子起到既扮演阴离子稳定基又扮演离去基团的双重角色的反应。



第一步是高度稳定的阴离子的共轭加成。中间体烯醇盐会通过十分有利的在烯丙型碳原子上的取代反应，使三元环关环。离去基团是一个亚磺酸根阴离子，立体化学来源于闭环过程的过渡态中最有利的构象。产物是在自然界中发现的重要的除虫菊杀虫剂，菊酸 (chrysanthemic acid) 的甲酯。

■ 在 Chapter 22 我们提出，亲核试剂越稳定，反应越可逆，也会越倾向于发生共轭加成。



## 锍盐

硫醚在没有去质子时也是亲核试剂——硫原子可进攻卤代烷以形成锍盐。当然，这与您熟悉的胺的反应性模式相似，并且您也曾见过，𬭸以类似的方式形成。



这个反应是一个平衡，对于活性较弱的硫醚(例如空阻较大的)的锍盐的制取，可用较强的，带有非亲核性反荷离子的烷基化试剂，例如  $\text{Me}_3\text{O}^+$   $\text{BF}_4^-$ ，四氟合硼酸三甲基锌(也被称作 Meerwein 盐)完成。硫原子从  $\text{O}^+$  上捕获一个甲基，其逆过程不会发生，并且  $\text{BF}_4^-$  阴离子也不是一个亲核试剂。二甲醚不仅是一个弱的亲核试剂，并且也是会从反应混合物中离去的气体。相同的原则也被用于由一种硫醚制备另一种硫醚。



锍盐最重要的化学性质基于以下两种属性中的一条或两条：

1. 铌盐是亲电试剂：亲核取代掉一个中性的硫醚离去基。
2. 铌盐可被去质子以给出锍叶立德 (sulfonium ylids)。

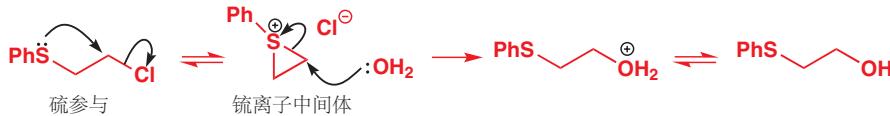
## 锍盐做亲电试剂



一战期间，芥子气 (mustard gas) 被发展为一种化学武器——它会导致皮肤出现水泡，并对呼吸道有强烈刺激作用。它对于人体组织的活性与如下观察有关，这也是对于锍离子强大的亲核性的恐怖证据。



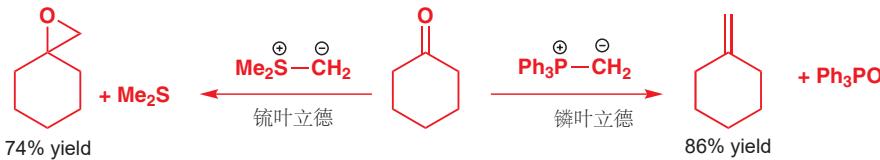
芥子气与人体组织的反应与如上反应的活性，均为硫原子对氯离子离去基的分子内取代所致——或者我们可以称其为**硫参与 (participation by sulfur)**——给出一个三元环锍离子中间体 (或**环锍乙烷离子 episulfonium/thiiranium ion**)。在这个亲电的锍离子上，水或皮肤中结构蛋白的亲核进攻，都非常快。当然，芥子气可以如是反应两次。下一节中，您会看到更多锍离子中间体在其中做亲电试剂的例子。



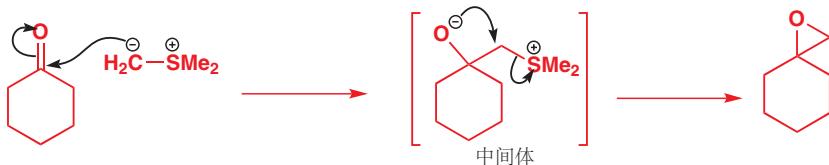
## 锍叶立德

锍盐中的硫原子带有正电荷，这意味着与之相邻的质子酸性显著地比硫醚中的更强，因而锍盐可被去质子以给出**锍叶立德/sulfonium ylids**。

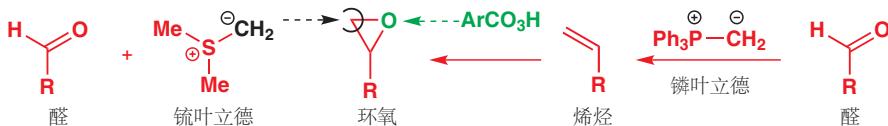
在 Chapter 11 中我们讨论了𬭸叶立德与羰基化合物发生的 Wittig 反应。锍叶立德也能与羰基化合物反应，但反应方式却很不同——对比如下两个反应。



𬭸叶立德给出烯烃，而锍叶立德给出环氧。这是为什么？Wittig 反应的驱动力是强 P=O 键的形成——但对于硫类似物来说，驱动的能力就小得多了 ( $\text{Ph}_3\text{PO}$  中  $\text{P}=\text{O}$  键的键能为  $529 \text{ kJ mol}^{-1}$ ； $\text{Ph}_2\text{SO}$  中  $\text{S}=\text{O}$  键的键能为  $367 \text{ kJ mol}^{-1}$ )。反应的第一步是相同的：叶立德的阴离子进攻羰基，发生亲核加成反应。Wittig 反应的中间体会环化给出四元环，但在锍叶立德中并不会如此。相反，中间体会通过氧阴离子对  $\text{Me}_2\text{S}$  的亲核取代反应直接分解。

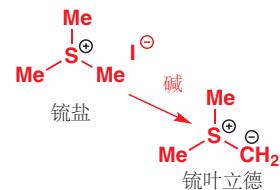


锍叶立德因此适用于由醛、酮制备环氧的过程；另一种您学过的，制备环氧的反应可用由可通过𬭸叶立德制备的烯烃开始 (Chapter 19)。



在研究一些潜在  $\beta$ -受体阻滞剂 药物的化学家需要如下的环氧，由于 4-环丙基苯甲醛 比 4-环丙基苯乙烯更易得，它们计划用醛作为起始原料，并用锍叶立德完成的一步反应制备环氧。

➡ 参与 (Participation) 将在 Chapter 36 中更详细地讨论。

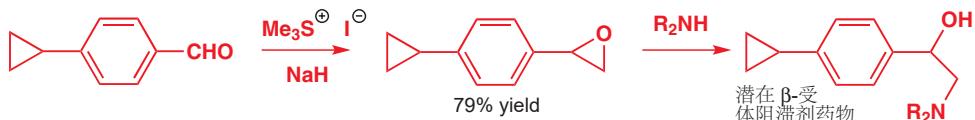


注：有时也被称作“硫叶立德 (sulfur ylides)”，包括本书原书中也是如此，译本中一律改作“锍叶立德”。

■ 提醒。叶立德指带有在相邻两个原子上的正电荷和负电荷的物种。

➡ 铑叶立德的 Wittig 反应于 p. 237 被介绍，丙会在本章的结尾，p. 689 再次出现。

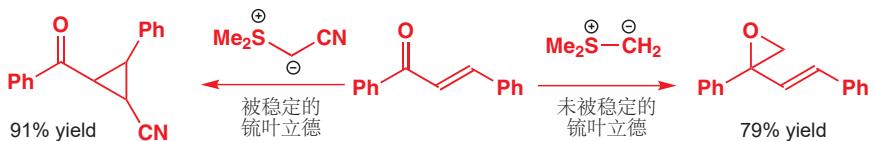
Interactive mechanism for epoxide formation using sulfonium ylids



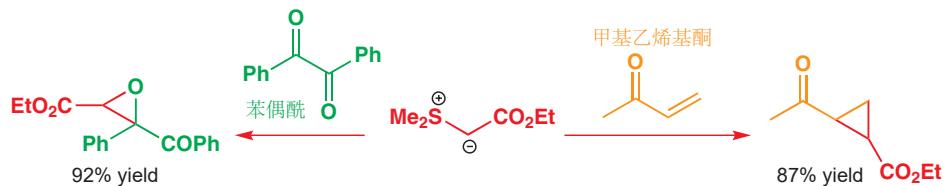
“被稳定的” 镜叶立德

如果叶立德的阴离子碳与一个基团共轭，那么叶立德就比较稳定，它的反应性也可能改变。如您已经学过的，由这个  $\alpha,\beta$ -不饱和酮 和简单锍叶立德的反应，可给出环氧；但“被稳定的 (stabilized)” 叶立德则会给出环丙烷。

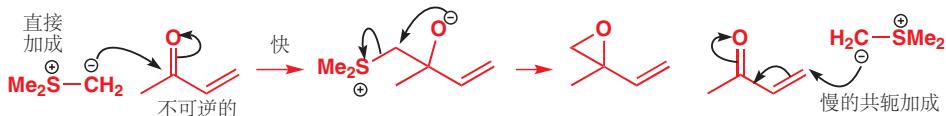
→ 在 Chapter 26 中您遇到了烯醇盐反应形成环氧 (Darzens 反应, p.639) 或环丙烷的相似反应。



若无与羰基共轭的烯烃存在，则两种类型的叶立德都给出环氧——例如被酯稳定的叶立德，会与被称作苯偶酰（benzil）的二酮反应给出环氧，但会与甲基乙烯基酮（3-丁烯-2-酮）反应给出环丙烷。

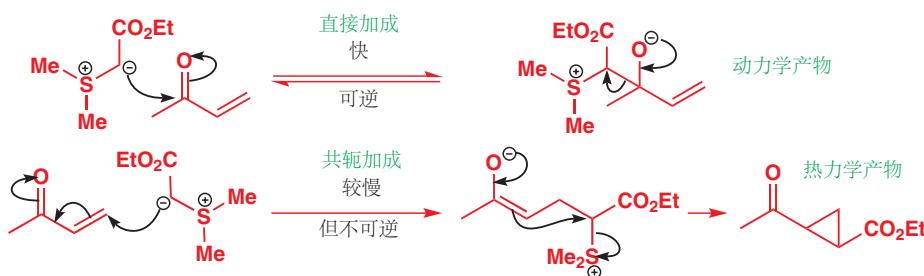


为什么被稳定的叶立德倾向于与双键反应呢？烯基酮有两个亲电位点，但在 Chapter 22 中我们已讨论了亲核试剂在 Michael 受体上区域选择性的进攻，直接的 1,2-加成 是较快的反应。这个步骤是不可逆的，因为继而发生的烷氧基阴离子对硫醚离去基团的取代会产出环氧。环丙烷是否是更稳定的产物对于反应来说都是无关紧要的：环氧生成得更快，因而是动力学产物。



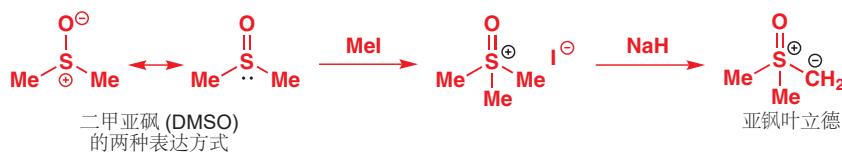
但叶立德被稳定时，对羰基的直接加成事实上可能还是较快的反应。但在这个情形中，起始原料足够稳定使反应变得可逆，锍叶立德会在环氧得以形成前被重新赶走。与此同时，一些叶立德以 1,4 (Michael 或 共轭) 方式加成。1,4-加成，虽然较慢，但在能量上是有利的，因为 (相对) 弱的 C=C π 键，而不是 (相对) 强的 C=O π 断裂时，获得了更有利的新 C-C 键，并因而它是不可逆的。最终，所有叶立德结束与 1,4-加成，生成烯醇盐，并环化为热力学产物环丙烷。这是另一个动力学与热力学控制竞争的经典例子，请将其记在头脑中。

→ 其他例子可以在 pp. 266 和 505 找到。



## 亚砜叶立德

还有另一类非常重要的被稳定的锍叶立德，它们的稳定性并非来源于附加的阴离子稳定基，而是来源于硫基团阴离子稳定能力的提升。它们就是**亚砜叶立德/亚砜锍叶立德 (sulfoxonium ylids)**，由二甲亚砜与卤代烷通过  $S_N2$  取代反应制取。注意，二甲亚砜中尽管有阴离子的贡献，氧原子仍不如硫原子亲核。硫高能的孤对电子（软）与饱和碳原子发生  $S_N2$  取代——很少部分取决于电荷吸引的反应 (Chapter 15)——反应得更好。



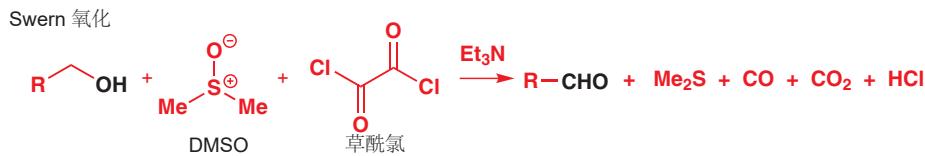
亚砜叶立德与不饱和羰基化合物的反应方式，与您从前遇到过的被稳定的叶立德的反应方式相同——它们形成环丙烷，而非环氧。下面的例子展示了这种反应性模式的一种结果——用锍叶立德或亚砜叶立德与一个不饱和羰基化合物（一种被称作香芹酮 carvone 的萜）反应，则可高产率地得到环氧或环丙烷。



Interactive mechanism for three-membered ring formation with sulfonium and sulfoxonium ylids

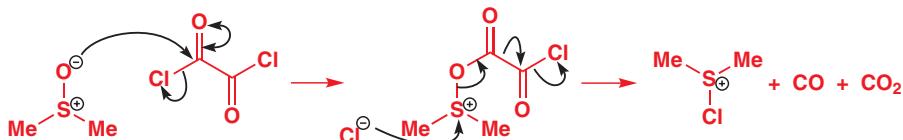
## Swern 氧化

我们在 Chapter 23 中曾简要地讨论了这个反应的特征，它是一种重要的由醇氧化为醛的方法。在当时，我们说过，这个有趣的反应的讨论将在稍后进行，而现在已经是时候了。



翻回 p. 545, 是关于 Swern 氧化和其他相似反应的对比。

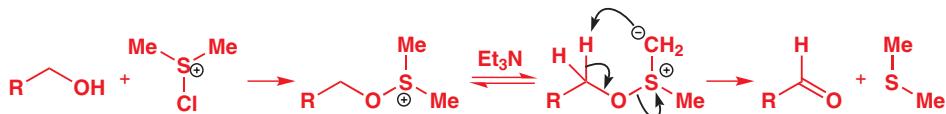
第一步中，DMSO 与草酰氯 (oxalyl chloride) 反应给出亲电的硫化合物。对于进攻羰基的，是带电的氧原子而不是软的硫原子，您应当不会感到惊讶。这个酰基化反应中释放的氯离子随后进攻带正电的硫原子，并脱去一个相当值得讨论的碎片化三份—— $\text{CO}_2$ 、 $\text{CO}$  和一个氯离子的离去基团。熵使反应有利。



以上过程中，醇始终作为旁观者，等到氯代锍离子 (chlorosulfonium ion) 形成时，就可以与之反应给出一个新的锍盐。锍盐被碱 ( $\text{Et}_3\text{N}$ ) 去质子，形成叶立德。最后一步以一个氧化还原反应完成：质子转移到阴离子碳上并给出一个醛。整个过程是二甲亚砜 (DMSO) 转变为二甲硫醚 (DMS) 的还原反应。

### Interactive mechanism of the Swern oxidation of alcohols

► 在 Chapter 35 中您会学到，最后一步是一个周环反应。



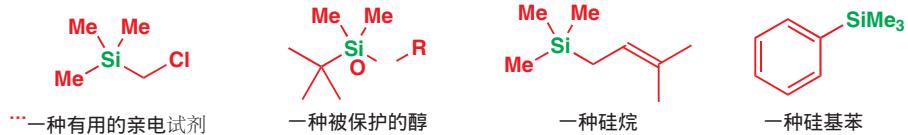
## 硅和碳的比较

元素周期表中，硅紧贴在碳的下方，它们最明显的相似之处是，两个元素一般都显四价以形成四面体型化合物。碳和硅的化学性质有重要的差异——硅没有那么重要，有很多专注于碳化学的书，但对于硅化学则相对较少。碳原子可形成很多稳定的包含  $\pi$  键的三角型和直线型化合物，但硅则很少如此。最重要的差异是 硅—氧  $\sigma$  键的强度 ( $368 \text{ kJ mol}^{-1}$ ) 和 硅—硅 键的相对脆弱 ( $230 \text{ kJ mol}^{-1}$ )。这两个因素组合在一起，即可解释，在地球的富氧气氛中，碳骨架可形成的大量结构，硅却无法进入其中的原因。

平均键能,  $\text{kJ mol}^{-1}$

X	H-X	C-X	O-X	F-X	Cl-X	Br-X	I-X	Si-X
C	416	356	336	485	327	285	213	290
Si	323	290	368	582	391	310	234	230
比例	1.29	1.23	0.91	0.83	0.84	0.92	0.91	1.26

表中的多个数值我们提供了深入了解碳和硅反应性差异的机会。硅与负电性元素成的键通常比碳的强，尤其，硅—氟 键是已知的最强单键之一；而硅与正电性元素成的键就较弱了。硅—氢 键远弱于碳所对应的，因而可被轻易地切断。下面是几种有机硅化合物。



本节中，我们主要会讨论含四根 Si-C 键的化合物。其中三根通常是相同的，因此化合物通常是在有机分子上附着  $\text{Me}_3\text{Si}$  基的形式。我们会讨论当其中一根 Si-C 键反应以变为新的 Si-F 或 Si-O 键时，有机分子上发生的有趣变化。我们也会讨论有机硅化合物作为试剂的情况，例如还原剂三乙基硅烷 triethylsilane ( $\text{Et}_3\text{SiH}$ )，而  $\text{Et}_3\text{C}-\text{H}$  则并不是还原剂。

碳–硅键足够强，能使三烷基硅基在分子的其余部分合成转移时仍存活；但它也足够弱，可在我需要时专一性地被切断。尤其，氟离子对于碳化合物是差的亲核试剂，但却非常容易进攻硅。另一个重要的因素是 C–Si 键长 (1.89 Å)——显著地长于一般的 C–C 键 (1.54 Å)。硅的电负性 (1.8) 比碳 (2.5) 小，因此 C–Si 键像碳极化。这使得硅易于接受亲核试剂的进攻。C–Si 键的强度意味着烷基硅烷是稳定的，而大多数有用的化学性质则产生于并非烷基的碳取代基上。



### 硅对负电性元素有亲和性 (affinity)

对硅最有效的亲核试剂，应是与硅形成强键的负电性原子。基于氧的亲核试剂和卤素离子 (氯离子、氟离子) 是其中最杰出的。您在 Chapter 23 中学习硅醚的选择性切断时就已利用过这一特点。氟化四丁基铵通常作为可溶于有机相的氟离子，反应后形成副产物氟代硅烷。此机理并不是一个简单的  $S_N2$  过程，并且在碳化学中也找不到直接的相似例子。它看起来像是在大空阻的叔中心上的取代反应，这应该几乎是不可能的。但硅的两个特征促进了这个过程：长 硅–碳 键缓和了空间相互作用，硅的 d 轨道为亲核试剂提供了一个并无与 C–O  $\sigma^*$  相同的几何阻碍的进攻目标。

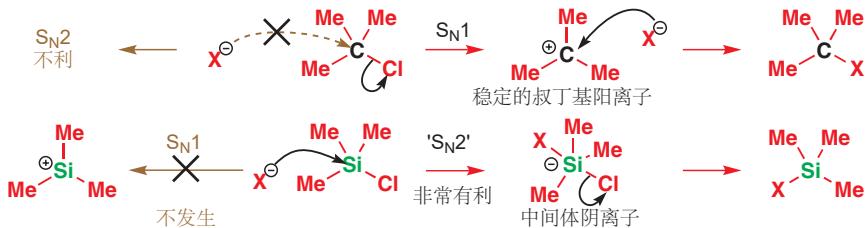


氟离子对空 d 轨道上的进攻，形成了一个带负电的五配位中间体，它随后会断裂并失去烷氧基阴离子。您可将这个五配位三角双锥型中间体，与与之具有相似形状的基于碳的  $S_N2$  反应的过渡态对比。在机理图中，它经常被忽略，这是因为它形成得很慢，而分解得很快，反应机理也仍被称为“硅上的  $S_N2$  反应”。

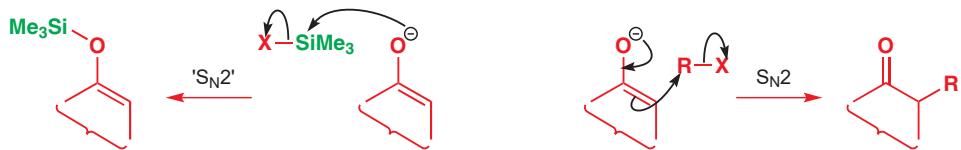
- 硅与氧形成强键，与氟形成非常强的键。

### 硅上的亲核取代反应

三甲基硅基氯，并不发生与您熟悉的碳化学类似物叔丁基氯一样的  $S_N1$  机理，这一点可能让您不解。事实上，对于  $Me_3Si^+$  阳离子的存在没有任何错误——例如，它可以被光谱法观察到。而原因仅仅在于，“硅上的  $S_N2$  反应”太过有利， $S_N1$  不足与之竞争。



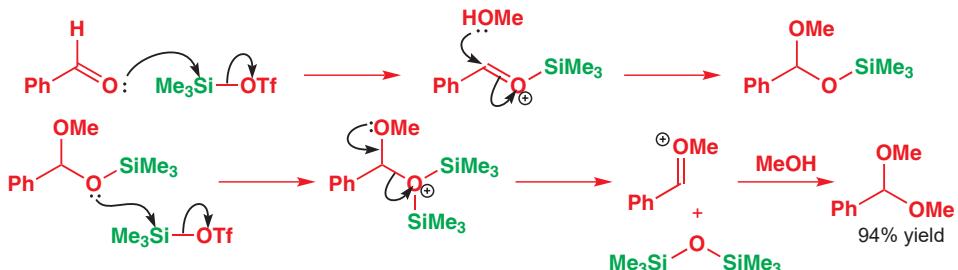
Si 和 C 上的  $S_N2$  取代反应，有一些重要的差异。卤代烷是软的亲电试剂，但硅基卤/卤代硅烷则是硬的亲电试剂。卤代烷与氟离子的反应非常缓慢，而硅基卤与氟离子的反应则快于与任何其他亲核试剂的反应。对于饱和碳原子最好的亲核试剂是中性的，或基于在周期表下方的元素 (S, Se, I)，亦或二者都满足；而对于硅最好的亲核试剂则是带电荷的，及基于高电负性原子 (主要为 F, Cl, 和 O) 的。您熟悉的一个例子，是烯醇阴离子与卤代烷在碳上反应，而与烯醇硅醚在氧上反应 (Chapter 20)。



当  $\text{Me}_3\text{Si}$  基被氢氧根从有机分子上移去时，产物并不是您也许以为的硅醇 (silanol)，而是硅基醚“六甲基二硅基醚/六甲基二硅氧烷 (hexamethyldisiloxane)”。



硬币的另一面，碳上的  $S_N2$  反应并不会过多地受到碳上部分正电荷 ( $\delta+$ ) 的影响；硅的 “ $S_N2'$ ” 反应则会被硅上的电荷影响。最亲电的硅化合物是三氟甲磺酸硅酯 (silyl triflates)，估计它与氧亲核试剂的反应比硅基氯的，要快差不多  $10^8$ ~ $10^9$  倍。三氟甲磺酸三甲基硅基酯，事实上是一个很好的 Lewis 酸，可用于由羰基化合物形成烯醇硅醚，或催化形成缩醛，并可使这二者发生羟醛式反应。这三个反应中，硅化合物均进攻氧。缩醛形成反应中，在羰基氧上发生了两次硅基化，得到最终的离去基团，六甲基二硅基醚。您应当将它与 Chapter 11 中叙述的一般的酸催化缩醛化对比，即在羰基氧上质子化两次，并得到作为离去基团的水。



### 烯醇硅醚是对于醇的万能保护基

基于硅的保护基对于醇，是最万能的，因而也是最好的。它们可用被氟离子或氧亲核试剂通过亲核取代反应去除，并且速率主要取决于硅基的空阻。最简单的三甲基硅基 trimethylsilyl ( $\text{Me}_3\text{Si}$  或简写作 TMS)，空阻最小，因而最容易去除。事实上，带有痕量碱或酸的水就可容易地去除它，因而若想使它保持在正确的位置上，需要特殊处理。对于这些保护基的讨论在 Chapter 23。

用空阻大得多的叔丁基替换其中一个甲基，则可得到叔丁基三甲基硅基  $t$ -butyldimethylsilyl (TBDMS)，它在一般的处理条件下是稳定的，并可在水溶液后处理，或硅胶柱层析过程中存活。在分离、纯化条件下的稳定性使 TBDMS (有时过度简写作 TBS) 成为在有机合成中非常流行的选择。TBDMS 的引入，通过在有咪唑的 DMF 中，在对应的硅基氯上发生取代反应完成。产率通常几乎定量，条件也温和。伯醇可在仲醇的存在下被保护。它的去除依赖氟离子对硅的亲核性，通常非常有效且具选择性。

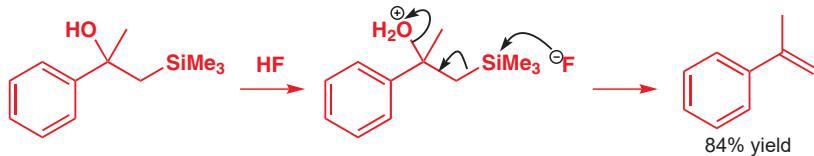
然而，对于一个保护基，仅当它可用高产率地，在不影响分子其余部分的情况下引入和去除，且可在范围很大的合成所用条件下存活时才是实用的。空阻极大的叔丁基二苯基硅基  $t$ -butyldiphenylsilyl (TBDPS) 在仲醇的存在下选择性地保护空阻较小的伯醇上是实用的。

常用硅基保护基中最稳定的一个 (三异丙基硅基 triisopropylsilyl 或 TIPS) 带有三个含支链的烷基取代基，保护中心硅原子免受会导致其断裂的亲核试剂的进攻。这三种大空阻硅基 (TBDMS, TBDPS, 和 TIPS) 都具有极佳的稳定性，但仍可通过氟离子去除。



## Peterson 消除反应

有机化学中有很多,  $\text{Me}_3\text{Si}$  基在其中充当质子的反应。如同酸性的质子可被碱移去一样, 硅很容易被硬亲核试剂, 尤其是  $\text{F}^-$  或  $\text{RO}^-$  移去, 这可用于促进消除反应。如下展示了一个例子。



Interactive mechanism for Peterson elimination

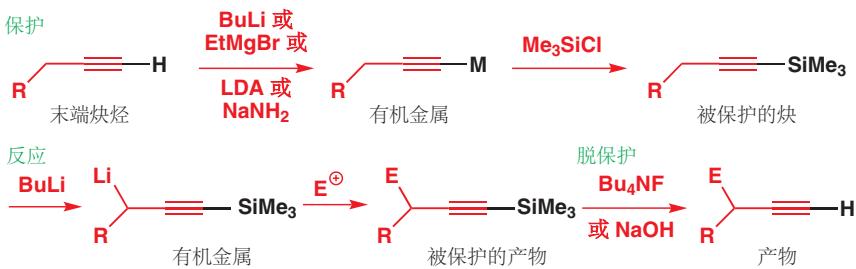
这个反应被称作 **Peterson 消除反应 (Peterson elimination)**, 它与 Chapter 17 中我们讨论的——酸性条件下醇消除给出烯烃的反应相当相似。但与那些反应不同的是, 它完全的区域选择性使之在其他方法可能产生错误的区域异构体或区域异构体的混合物时, 是非常有用的方法。在下面的例子中, 仅高产率地形成一个产物, 并包含环外双键。想想若无硅原子, 则可能发生什么(忽略在氧上的硅原子——它仅仅是保护基)。这个化合物, 事实上是重要抗癌化合物紫杉醇 (Taxol) 的一条合成路线的中间体。



Peterson 反应在制取用于与其他分子连接的末端双键、环外双键时尤其有用; 因为反应的起始原料 (如上所示的镁衍生物) 可容易地通过可获得的  $\text{Me}_3\text{SiCH}_2\text{Br}$  制取。

## 炔基硅烷用于保护和活化

末端炔烃含有一个酸性质子 ( $\text{pK}_a$  大约 25) 可被强碱, 例如有机金属试剂 (格氏试剂,  $\text{RLi}$ , 等) 移去。有时这是我们意欲完成的, 但有时它也许是我们在用有机金属试剂时的一个不需要的副反应, 会消耗有机金属试剂并干扰选择的反应。这些问题一个十分整洁的解决方案, 是利用炔烃的末端质子相对的酸性, 将其换作三甲基硅基。 $\text{SiMe}_3$  基可在反应中保护炔烃末端, 并随后可被氟离子或氢氧化钠脱除。一个经典的例子是在末端质子保护的情况下, 移去炔烃邻位质子。

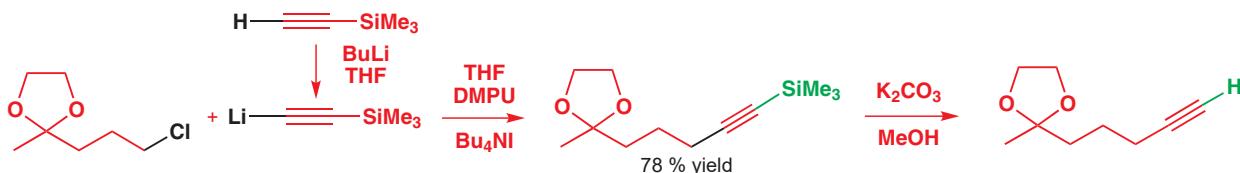


■ 炔烃邻位有时被称作“炔丙型 (propargylic)”位。  
炔丙醇 (Propargyl alcohol) 指  $\text{HC}\equiv\text{CCH}_2\text{OH}$ .

► 炔基锂和炔基格氏试剂在 Chapter 9 中曾以此方式制备。

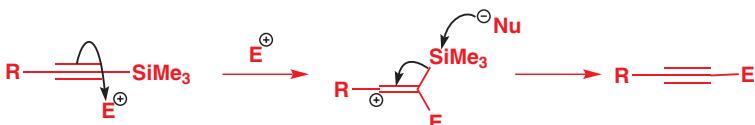
此外, 乙炔本身是一个有用的双碳积木, 但由于它是易爆的气体, 因而不方便处理。三甲基硅基乙炔是一个可蒸馏的液体, 由于它只有一个酸性质子, 因此涉及锂衍生物的反应中是对乙炔很方便的替代物。炔基酮的合成便是一个例子。丁基锂去质子, 提供与氯代烷反应的炔基锂, 碘离子在其中做亲核催化剂 (见 Chapter 15)。用乙醇中的碳酸钾脱去三甲基硅基, 可使炔烃在另一端发生后续

反应。



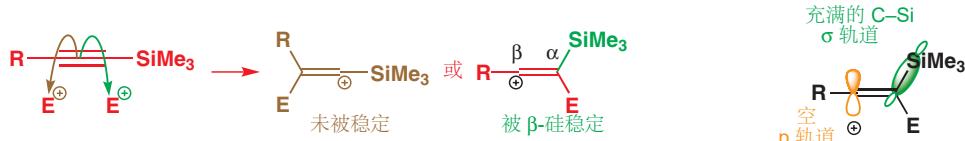
### 硅稳定在 $\beta$ 碳上的正电荷

与普通炔烃一样，硅基炔烃也是亲核试剂，能与亲电试剂反应。硅的存在对这个反应的区域选择性有引人注目的影响。这必然是由于中间体的阳离子被稳定所导致的。



我们在 Chapter 15 中阐释了这一现象。

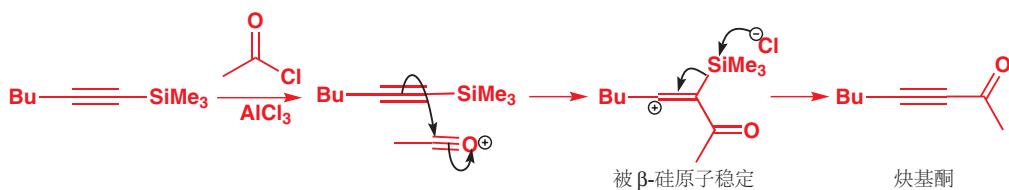
我们熟悉的碳阳离子稳定性的层级体系是一叔 > 仲 > 伯——正电荷被相邻的 C—H 或 C—C 键中与空轨道排列的恰当的几个（确切地说，是它们充满的  $\sigma$  轨道）所贡献的电子密度稳定。硅的正电性属性，使 C—Si 键成为更加有效的给体：正电荷  $\beta$  位的（附着在与正电荷相连的碳上的）硅基可很有效地稳定正电荷，并因而使涉及阳离子中间体的反应通常完全地得到控制。这是被  $\sigma$  给体作用稳定的情形。



由于 C—Si 键的脆弱，亲核试剂并不需要非常强。很多带有孤对电子的中性分子都可以完成，甚至三氟甲磺酸根 ( $\text{CF}_3\text{SO}_2\text{O}^-$ ) 都可以。

阳离子的稳定化也通过离域使 C—Si 键变得脆弱，进而易于断裂。亲核试剂（尤其是卤素或氧亲核试剂）在硅上的进攻可将其从有机碎片上移去，净结果是一个亲电取代反应，其中硅被亲电试剂取代。

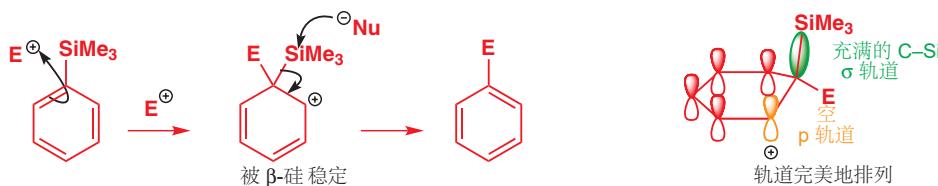
这在炔基酮的合成上是有用的，炔基酮很难直接用方便的有机金属试剂，如炔基—Li 或  $-\text{MgBr}$  合成，因为它们会在酮产物上进行第二次加成。炔基硅烷以 Friedel—Crafts 方式，在 Lewis 酸，例如三氯化铝的存在下与酰氯反应，给出酮。



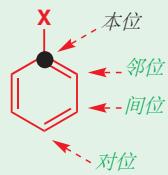
### 芳基硅烷与亲电试剂经历本位取代

芳基硅烷与亲电试剂在 Friedel—Crafts 条件下反应的机理解释与上文的反应完全相同。与通常取代基定位规则包含的邻位、间位，和对位取代不同的是，仅有一条规则：硅基会在亲电取代中被取代，取代发生于硅基所处的环的位点——即本位取代 (*ipso substitution*)。事实上，这个选择性来源

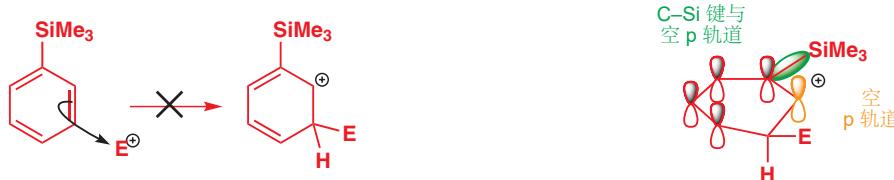
于与普通芳香取代相同的原则 (Chapter 21): 亲电试剂反应以产生最稳定的阳离子——此情形中则为硅  $\beta$  位的阳离子。任何亲核试剂都可切断被弱化的 C–Si 键, 进而得到本位产物。



■ 拉丁语 *ipso* (本位) 表示“自己”——指与  $\text{SiR}_3$  基自己所占据的位置。提醒:



对硅间位的进攻也会得到处于  $\text{Si}$   $\beta$  位的阳离子。但这个阳离子尤其不稳定, 因为 C–Si 键仍处在环平面当中, 进而空 p 轨道与 C–Si 键是正交的, 并不能发生相互作用。这说明, 理解基于分子轨道的效应的源头是比仅仅记住反应结果更重要的。



芳基硅烷的反应性, 被用于通过如侧边栏所示的反应, 将稳定的苯基二甲基硅基转化为更活泼的化合物, 例如醇。很多试剂可以做到这一点, 而它们都是通过向苯基硅烷引入本位取代实现的。与溴单质的反应是典型的; 溴苯与可继续被氧化的硅基溴一同产出。

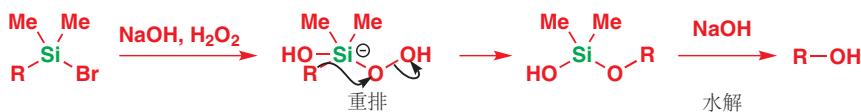
亲电去硅基化 (electrophilic desilylation) 的机理与芳香亲电取代反应的机理仅一点不同, 那就是被取代的是三甲基硅基而非质子。过渡态导向能被硅稳定的中间体阳离子, 速率也提高几个数量级。如下是与溴单质反应的第一步。



■ 一组相近的由 Si(带苯基的) 到 OH 的转化被称作 Fleming-Tamao 氧化反应 (Fleming-Tamao oxidations), 以其两位独立发现者命名。



反应流程的剩下部分包含  $\text{Br}^-$  被  $\text{HOO}^-$  取代, 氢氧根的加成, 重排, 和水解。



→ 这个机理应当让您回忆起硼烷的氧化机理, 通常在硼氢化反应之后进行——见 Chapter 19, p. 446.

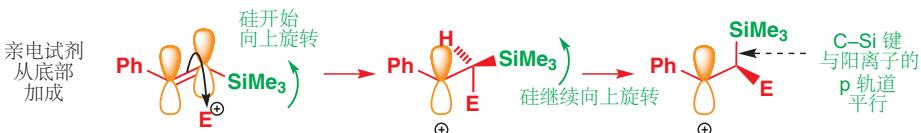
- 三甲基硅基和其他硅基可稳定  $\beta$  碳上的正电荷, 可非常容易地离去。它们可以被想象成非常活泼的质子或“超级质子 (super protons)”。

### 乙烯基硅烷提供了烯烃合成的区域和立体选择性途径

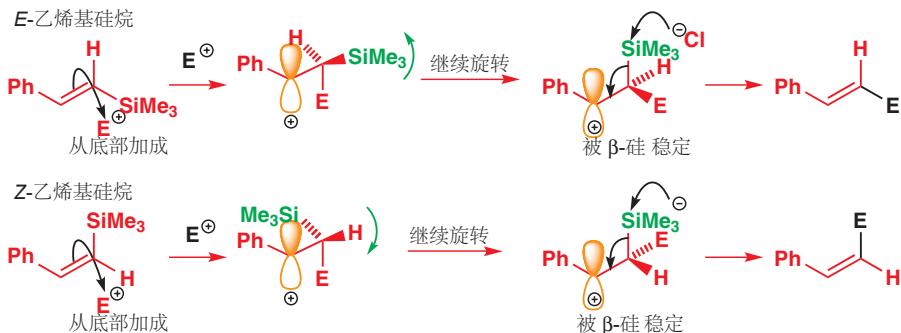
乙烯基硅烷与亲电试剂的反应, 区域选择性与炔基硅烷的类似, 其中硅在本位碳原子被亲电试剂取代。乙烯基硅烷的立体化学是重要的, 因为这个转换中立体化学也会得以保留。



这是一个很吸引人的有趣反应，并应该得到解释。亲电试剂进攻硅旁边，得到在硅  $\beta$  位的较稳定的碳阳离子。在乙烯基硅烷中，C–Si 键与  $\pi$  键的 p 轨道正交，但当亲电试剂进攻  $\pi$  键，比如从底端进攻时（从上端进攻也是类似的）， $\text{Me}_3\text{Si}$  基会开始向上运动。当它旋转时，C–Si 键与剩下的 p 轨道之间的角就会由  $90^\circ$  减小。角度减小，就会使 C–Si 键与阳离子的空 p 轨道的相互作用增大。因此旋转会继续，直到平行，而不会逆向进行。下图显示，最后所得的阳离子中，亲电试剂处于原先  $\text{Me}_3\text{Si}$  基的位置，即与 Ph 处于反式。现在可发生硅基的失去，并给出立体化学保留的产物。



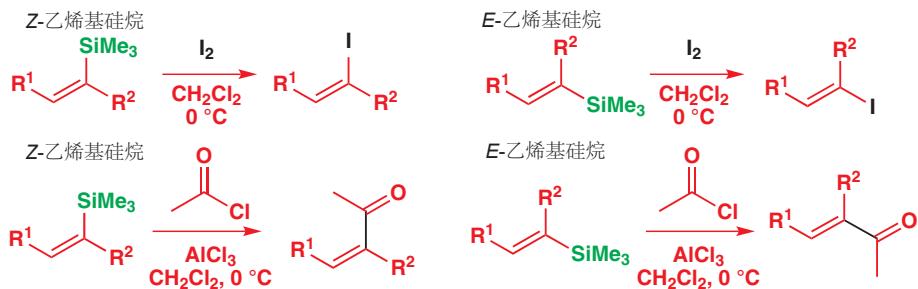
中间体阳离子只有一根单键，因此我们推断，旋转可能会导致几何异构体产物的混合物，但它们并未观察到。 $\text{C–Si}$  键和空 p 轨道之间的相互作用，意味着旋转是受阻的。稳定化作用弱化了  $\text{C–Si}$  键，硅基会在任何后续旋转都未发生时，便迅速被去除。稳定化作用仅在  $\text{C–Si}$  键与空轨道恰当地排列，即在一个平面内时才有效——相当像一根  $\pi$  键。如下是乙烯基硅烷的 E 和 Z 异构体得到的产物。



Interactive mechanism for reaction of vinyl silanes with electrophiles

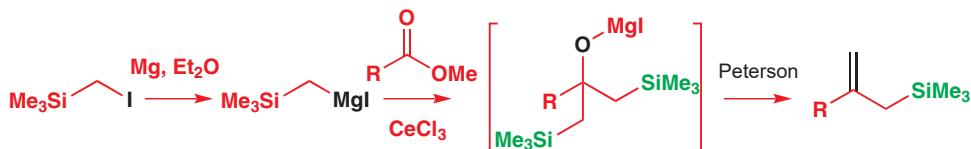
■ 立体构型纯的乙烯基卤是过渡金属催化的烯烃合成反应 (Chapter 40) 中重要的起始原料。

硅通常是不存在于合成流程的最终产物中的，而乙烯基硅烷上硅基的立体专一性移去使它们成为实用的试剂，并可被视作是相当稳定的乙烯基有机金属试剂，与很强的亲电试剂反应时会保留双键位置和几何结构。原去硅基化 (Protodesilylation) 是可将硅替换为质子的过程，是一个很重要的反应。同样好的亲电试剂还有卤素单质，有机卤代物，尤其是 Lewis 酸催化下的酰氯；它们参与这个反应可以形成有确定几何构型的乙烯基卤，或不饱和酮。



## 烯丙基硅烷做亲核试剂

如果硅基沿着碳链移动一个原子，那么将得到一个烯丙基硅烷。烯丙基硅烷可由烯丙基有机金属试剂生产，但通常会出现区域异构体的问题，并得到混合物。较好的方法应包含对双键位置的控制。其中两个实用的例子分别利用了 Wittig 反应和 Peterson 消除反应。试剂由三甲基硅基卤制备，分别形成对应的格氏试剂；或与一个伯 Wittig 试剂发生烷基化，去质子到新的叶立德。格氏试剂，在添加三氯化铈时，对酯加成两次得到对应的叔醇，叔醇在 Peterson 消除反应中失去其中一个  $\text{Me}_3\text{Si}$  基，剩下的  $\text{Me}_3\text{Si}$  基随之变为烯丙基硅烷的一部分。



Wittig 试剂通过最简单的叶立德与相同的硅试剂的烷基化反应制取。注意离去基团（碘）处在与硅相连的碳上，而不是在硅本身上。然后去质子，由于  $\text{Ph}_3\text{P}^+$  是比  $\text{Me}_3\text{Si}$  好得多的阴离子稳定基，因此在磷旁边形成阴离子。新的叶立德可与羧基化合物，例如环己酮以通常的方式反应，产生毫无疑问在烯丙基体系末端硅基化的烯丙基硅烷。



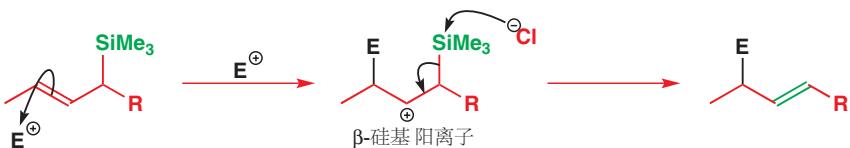
碳–硅键对于相邻的烯烃有两个重要的影响。高能的充满的  $\sigma$  轨道与  $\pi$  体系的几何排列合适，使它们可以相互作用，产生更高能的 HOMO，进而使烯烃对于亲电试剂更加活泼。并且相同的  $\sigma$  轨道也能稳定在烯烃远端发生进攻时，产生的碳阳离子。这降低了亲电加成反应的过渡态，使烯丙基硅烷相较于孤立烯烃活泼得多。

### 烯丙基硅烷比乙烯基硅烷更活泼 但仍可通过 $\beta$ -硅基 阳离子反应

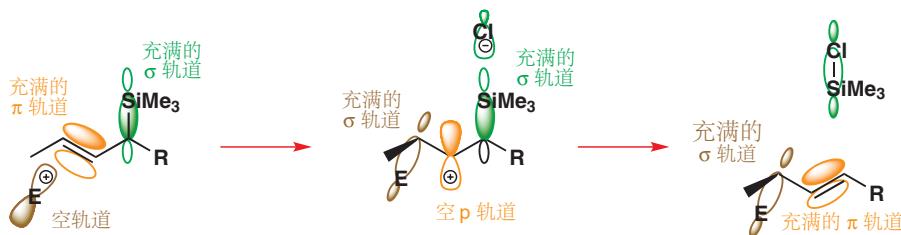
乙烯基硅烷含有与烯烃 p 轨道正交的 C–Si 键——C–Si 键处在  $\pi$  键的节面上——因此在 C–Si 键与  $\pi$  键间无法形成相互作用。与之相比，烯丙基硅烷的 C–Si 键却可以，通常也确实与  $\pi$  键的 p 轨道平行，进而能够产生相互作用。



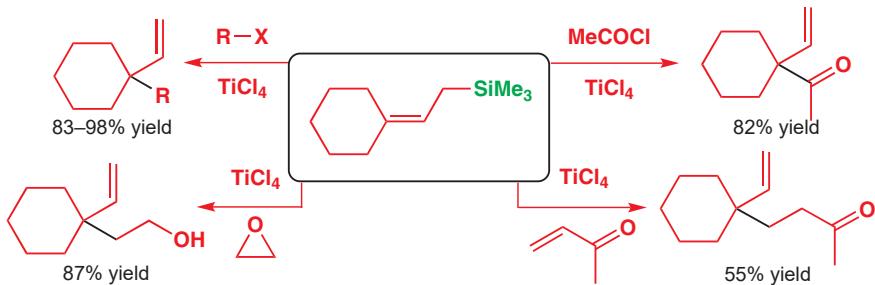
烯丙基硅烷可以与亲电试剂发生比乙烯基硅烷的区域选择性还更好的反应。再次形成处于硅基  $\beta$  位的碳阳离子，此时有两个不同。最明显的，亲电试剂进攻了烯丙基体系的远端，并且因为 C–Si 键已然处在能与中间体阳离子有效重叠的位置上，旋转便不再需要了。过程由通常方式的硅的失去，以重新生成烯烃结束。



分子轨道证实了由含有一根  $\pi$  键和一根 C–Si  $\sigma$  键的烯丙基硅烷，到含有一根新  $\pi$  键以及一根与亲电试剂成的新  $\sigma$  键的烯丙型产物的顺利过渡。中间碳阳离子主要被 C–Si 键对空 p 轨道的  $\sigma$  给体作用所稳定，但也有其他的  $\sigma$ -给电子基 (C–H, C–C, 和 C–E) 的帮助。整个过程是包含烯丙型重排的亲电取代反应。亲电试剂进攻的位点，以及新双键形成的位点，都由硅决定。



烯丙基硅烷相当类似于烯醇硅醚：它们可在被活化，例如被 Lewis 酸活化时与亲电试剂反应。四氯化钛被广泛使用，而其他 Lewis 酸，包括三氟化硼、三氯化铝、三氟甲磺酸三甲硅酯也是成功的。亲电试剂包括由酰氯产生的酰基阳离子，由叔丁基卤或仲苄基卤产生的碳阳离子，被活化的烯基酮，以及环氧；它们都需 Lewis 酸的存在。每个情况中，新键都以黑色标出。



#### ● $\beta$ -硅基阳离子是重要的中间体

乙烯基和芳基硅烷与亲电试剂在硅所处的本位 ( $\alpha$ ) 反应。

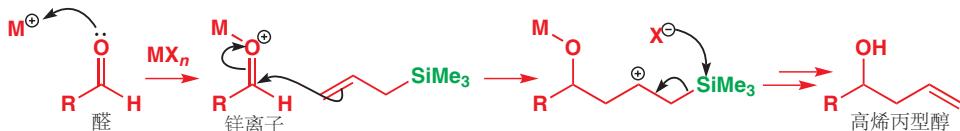
烯丙基硅烷在烯烃离硅的远端 ( $\gamma$ ) 反应。

两种情况下都有  $\beta$ -硅基阳离子中间体。

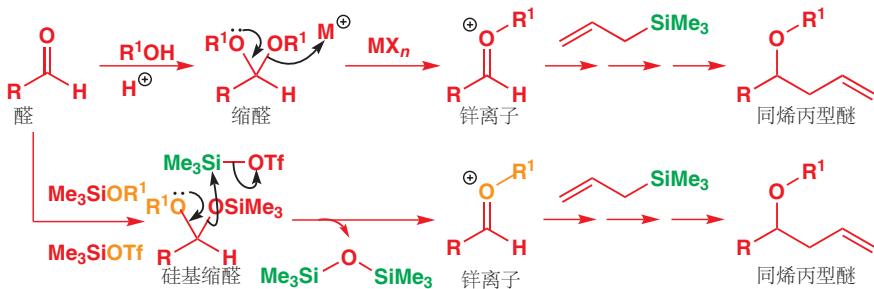
#### Lewis 酸催化经过锌离子的偶联

■ 同烯丙型的意思是烯丙型加一个亚甲基(同系物)。

当羰基化合物通过 Lewis 酸与羰基氧的络合而被活化时，烯丙基硅烷也可与之反应。Lewis 酸，通常是金属卤化物，例如  $\text{TiCl}_4$  或  $\text{ZnCl}_2$ ，它们通过形成含有 金属–O 键的锌离子活化羰基化合物。烯丙基硅烷以通常方式进攻，形成  $\beta$ -硅基阳离子，并被卤离子去硅基化。烷氧基金属的水解给出同烯丙型醇/高烯丙型醇 (homoallylic alcohol)。

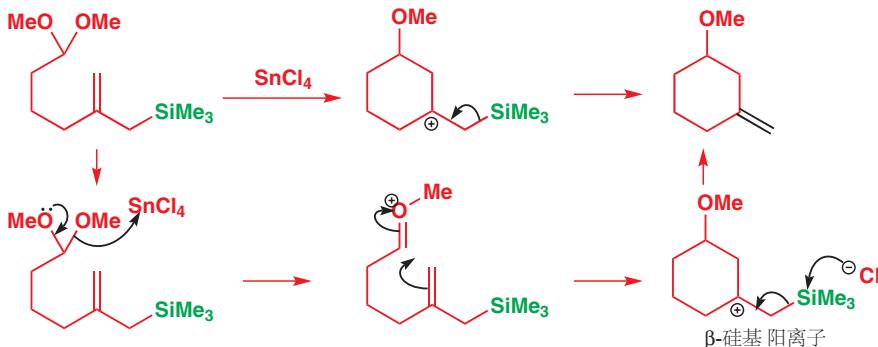


若用 Lewis 酸催化对应缩醛的分解，可得到与前文很接近的活性锌离子。尤其，当缩醛中至少有一部分是硅基时，可用通过添加更多的以 TMSOTf 形式存在的硅，在 Lewis 酸催化的情况下，在反应混合物中产生相同的锌离子。这些中间体  $\text{Zn}^{2+}$  离子都扮演对于烯丙基硅烷的强亲电试剂，以产生同烯丙型醇或醚。



■ 注意观察  $\text{Me}_3\text{Si}$  基是如何模仿质子的行为的，这种模仿直到最终产物  $(\text{Me}_3\text{Si})_2\text{O}$ —水的硅类似物中仍然存在。

最终消除反应的结果的区域控制，可由下面的四氯化锡催化的在缩醛上的分子内反应说明。相同的反应可在没有硅的情况下进行，但中间体阳离子便会有很多可失去的质子，进而产生五种不同的产物！

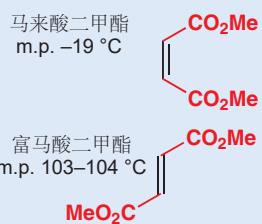


## 烯烃的选择性合成

S, Si, P, 和其他主族元素在有机化学中都有一些重要的功能，其中有一个 S, Si, 和 P 都各自起到明星角色的便是烯烃的合成。您在很多章中都学习了烯烃参与的反应，但目前为止，对于如何制取烯烃我们则谈论得很有限。Chapter 17 是关于消除反应的，您学习了 E1 和 E2 反应。在 Chapter 11 中，您学习了 Wittig 反应，并开始体会磷在烯烃合成中的重要性；而在本章中，您也学习到了 Peterson 消除中硅的参与。而我们现在则将更加细致地研究这些反应，尤其是对于如何控制烯烃形成的几何结构的研究。首先，我们需要说明，这是个很重要的任务，并且，我们还需要回忆一些可被选用的从前学过的反应。

### 不同的物理性质：马来酸酯和富马酸酯

这两个化合物，Z- 和 E-2-丁烯二甲酯，通常被称作马来酸二甲酯和富马酸二甲酯。它们位几何异构体的物理性质的差异提供了生动的例子。马来酸二甲酯是液体，沸点为  $202^\circ\text{C}$  (熔点为  $-19^\circ\text{C}$ )，而富马酸二甲酯则是晶体，熔点在  $103\text{--}104^\circ\text{C}$ 。

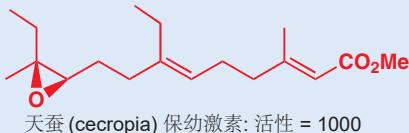


## 取决于几何结构的烯烃性质

烯烃的几何异构体 (geometrical isomers) 是有不同物理、化学、生物性质的不同化合物。它们通常难以通过色谱层析或蒸馏分离，因此拥有以单一异构体制备它们的方法对于化学家是重要的。

### 不同的生物性质：用于害虫防控的保幼激素

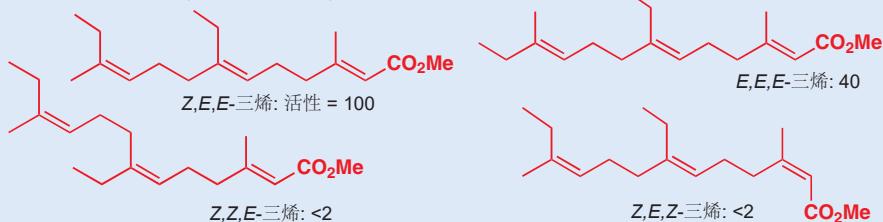
如果害虫可以在成熟前被组织，那么它们就不能再繁殖，因而也就得以控制。昆虫幼体依靠“保幼激素 (juvenile hormone)”控制它们自身的发遇，其中一种是一个三烯的单环氧化物：



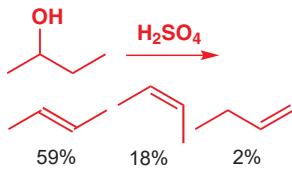
天蚕 (cecropia) 保幼激素: 活性 = 1000

这个化合物的合成类似物，例如如下的三烯，只要双键的几何构型被控制，也是对昆虫发育有组织效果的。三烯的 *Z,E,E* 几何异构体的活性，超过 *E,E,E* 异构体的两倍，超过 *Z,Z,E* 或 *Z,E,Z* 异构体的 50 倍。

保幼激素类似物的活性 (天然激素 = 1000)



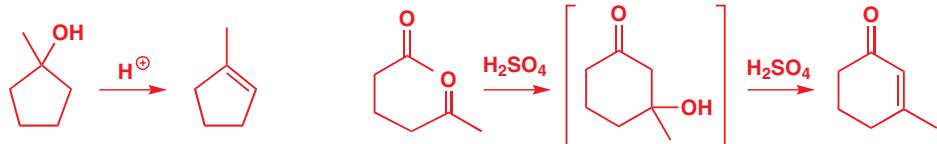
### 消除反应和立体选择性



■ 您应当识别出，第二个反应是 Robinson 增环反应的最后一步 (Chapter 26)。

■ 有些人将几何异构体称为非对映异构体，从某种意义上讲这是对的：它们是立体异构体，但不互为镜像。然而，我们会避免这种用法，因为对于大多数化学家而言，非对映异构体意味着三维立体化学。

不幸的是，大多数消除反应 (Chapter 17) 对产物的几何结构，仅提供很少的控制：在酸中处理仲丁醇，主要给出多取代的 2-丁烯，以几何异构体 3:1 的混合物。但也有一些例外。如果产物包含处于小于八元的环内的双键，那么它就需要是顺式的。例如简单的环戊醇的脱水反应和另一个分子内羟醛反应 (脱水前形成六元环)。



但我们如何用消除反应得到单一几何异构体的开链化合物呢？这些反应分为四个主要类别，我们将依次考察它们，并在章末总结最重要的方法。

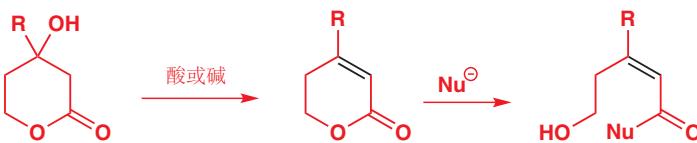
#### ● 制取双键单一几何异构体的方法

1. 仅有一种可行的几何异构体 (例如，六元环中仅能有顺式双键)。
2. 几何异构体处在平衡中，形成较稳定的一个 (通常是 *E*，热力学)。
3. 反应是立体选择性的，通过动力学控制形成 *E* 或 *Z* 烯烃的主要产物。
4. 反应是立体专一性的，烯烃的几何结构取决于起始原料的立体化学和反应机理。

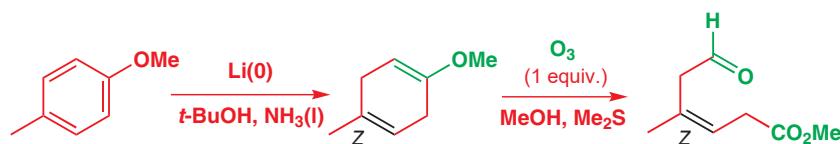
### 利用环状化合物

您可能会认为，这个方法仅适用于环状烯烃的制备，因而太微不足道了，称不上是对双键立体化学的控制方法。然而，化学家要比这更为机敏！保留双键的顺式立体化学，并不需要全碳环。内酯

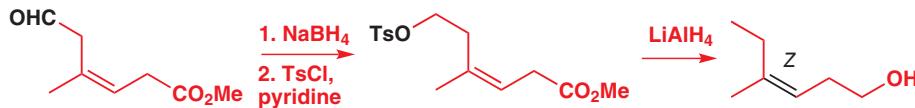
和环状酸酐同样有用。任何在五元或六元环化合物中的双键都必定是顺式构型，像这样的化合物很容易制取。这个羟基内酯的脱水会给出单一的顺式双键，然后与亲核试剂（醇、氢氧根、胺）反应开环即可给出带有顺式双键的开链化合物。



E J Corey 使用相似的思路制备了我们在 p. 678 介绍的昆虫激素。它意识到，若从环状分子开始，则基本的 *Z* 双键会很容易制取（环烯的双键仅可能为顺式），进而通过开环则可得到需要的化合物。下面是它完成的过程。



简单芳香醚的 Birch 还原 (Chapter 23, p. 542) 生成了两个顺式双键。其中较活泼的一个（富电子的一个）会与仅一当量的臭氧反应，给出醛酯并保留 *Z* 立体结构。NaBH<sub>4</sub> 将醛基还原为羟基，羟基还需进一步的去除：一种好的方法是先对甲苯磺酰化，然后用 LiAlH<sub>4</sub> 还原，其中 H 取代了 OTs。LiAlH<sub>4</sub> 也能很好地将酯基还原为醇，并给出 Corey 所需的 *Z*-构型化合物。



## 烯烃的平衡

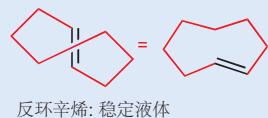
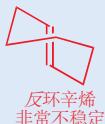
非环状 *E* 烯烃通常比非环状 *Z* 烯烃更稳定，这是由于空阻所指。但 *Z* 烯烃并不能自发地转化为 *E* 烯烃，因为  $\pi$  键的自由旋转是受阻的：断裂  $\pi$  键所需的能量大约为  $260 \text{ kJ mol}^{-1}$ （绕一根  $\sigma$  键旋转仅需大约  $10 \text{ kJ mol}^{-1}$ ）。因而您可能对下面的结果感到惊讶。马来酸二甲酯很容易通过有酸性催化剂存在的马来酸酐与甲醇的回流制取。如果产物被直接分离，获得的是一种在  $199\text{--}202^\circ\text{C}$  下沸腾的液体。这便是马来酸二甲酯。然而，如果产物被搁置，那么会形成富马酸二甲酯（马来酸二甲酯的 *E* 异构体）的结晶。其中的几何构型是如何如此容易地转换的呢？



对于这个过程的一条线索是，它会在痕量胺的存在下被极大地加速。胺或加成或其他亲核试剂的 Michael 加成，为  $\pi$  键的断裂提供了机理。中间体可以自由旋转，亲核试剂的再消去既可以给出 *E* 又可以给出 *Z* 烯烃。*E* 烯烃较好的稳定性和结晶能力使之在平衡中占主导。因此对于不饱和羧基化合物，存在 Michael 加成机理导致的 *Z* 烯烃到 *E* 烯烃的平衡。

## 环内双键

最小的，可以包含反式双键的稳定环是环辛烯（cyclooctene）——反环庚烯（*trans*-cycloheptene）可以存在，但却非常不稳定。



您在 Chapter 19 见到了臭氧作为 C=C 双键氧化分解的试剂。产物在旧的烯烃的两端各有一个羰基。其机理将在 Chapter 34 更详细地讨论。

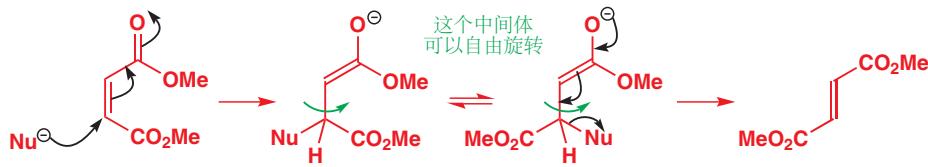
## 有关命名法的警告

当心！顺式、反式并不往往能直接翻译为 *Z* 和 *E*。考虑一个由环己基酮制备的烯胺，您大概会称烯烃中的双键为顺式（处在环内）。但应用为 *E/Z* 命名法制定的严格规则 (p. 405)，它也是 *E*。对于上方提到的 Birch 还原反应的产物中绿色的双键，也同样如此。对于顺式和反式的术语，与另一组有用的术语 *syn* 和 *anti* (Chapter 14) 一样，都没有死板的规则用于确定。因此当您要使用顺式和反式时，请一定附上图示。



这个反应，当然，是我们刚刚讨论过的反应类型的又一简单例子：环状起始原料中形成 *Z* 烯烃。

■ 正是由于这个原因，制备与活泼亲电基团例如醛基共轭的 *Z* 烯烃是非常困难的。



相似的机理可解释羟醛反应后紧跟着的脱水，所给出的  $\alpha,\beta$ -不饱和羰基化合物 所获得的几何结构。任何形成的 *Z* 烯烃都通过反应中可逆的 Michael 加成平衡为 *E*。如下的两个例子说明了这种方法的效果。

### dba

丙酮和苯甲醛发生两次羟醛反应的产物被称作二亚苄基丙酮 dibenzylidene acetone (dba)。它是一些防晒材料的成分，并且在有机金属化学中用作配体 (双键为给体)。

■ 波浪键通常表示立体化学未知或混合。此处，也意味着，此处的立体化学无关紧要！

■ 碘单质的加成-消除既可遵循离子型路径，又可遵循自由基路径。如我们在 Chapter 24 (p. 572) 中阐释的，光照可促进自由基路径。在这个反应中，碘单质吸收光能变为  $\bullet^-$  自由基。烯烃本身也可吸收光以异构化，这是下一节的内容。



### 不共轭烯烃的平衡

碘单质的加成是可逆的，不限于 Michael 受体，对于大多数其他烯烃都是如此。因而碘单质可作为用于使双键的立体异构体处于平衡的实用试剂。



一些日本化学家在它们从箭毒蛙 (poison dart frogs) 中分离的神经毒性化合物的合成中，需要如下的 *E,E* 二烯。但不幸的是，它们的合成方法 (所用的是本章后文会详细描述的 Wittig 反应) 在其中一根双键上仅给出 4:1 的 *E* 选择性。为了生产纯净的 *E,E* 二烯，它们用碘单质处理并用日光灯 (sunlamp) 照射 *E,Z* 二烯，使之平衡为 *E,E*。



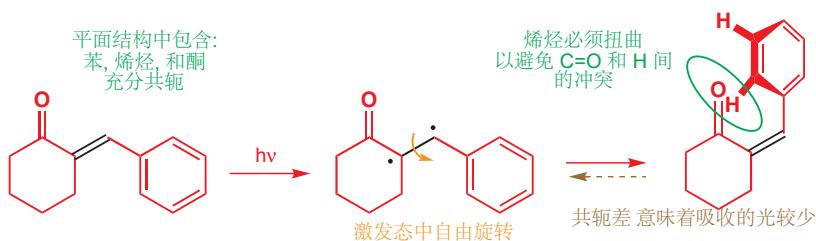
### 用光照由 *E* 烯烃制取 *Z* 烯烃

光照可通过将一个  $\pi$  电子激发进  $\pi^*$  轨道，并短暂地断裂  $\pi$  键，以允许烯烃的两个异构体相互转化。但光照倾向于形成 *Z* 异构体的方式是微妙的。顺式和反式烯烃的一个差异是，反式烯烃通常比顺式烯烃对光的吸收更好——它们吸收的光波长更长，也更多，尤其是当烯烃与羰基共轭时更是如此。空阻迫使顺式烯烃中，用于连接烯烃和羰基的  $\sigma$  键扭曲，进而导致共轭有效程度下降。在 *E* 和 *Z* 烯烃的混合物中，*E* 烯烃较易被光异构化，因此混合物中会逐渐积累 *Z* 异构体。

下面是一个例子。环己酮和苯甲醛的羟醛缩合可给出纯净的 *E* 烯烃 (上一段所述的空阻因素)。用较长波长的 UV 光照射，可以很好的产率将其平衡为 *Z* 烯烃。



对于烯基酮体系末端带有苯环的 *Z*-烯烃(右下)，苯环不可能与烯基酮体系处在同一平面中，因而会有扭曲存在，并使其共轭差于 *E*-烯基酮中的。用仅会被 *E*-烯基酮吸收的较长波长的光照射，可将其不断地平衡回激发态。最终，所有 *E*-烯基酮都转化为了不能被光有效地激发的 *Z*-烯基酮。最终得到的 *E*-和 *Z*-烯基酮的混合物被称作“光稳态(photostationary state)”。

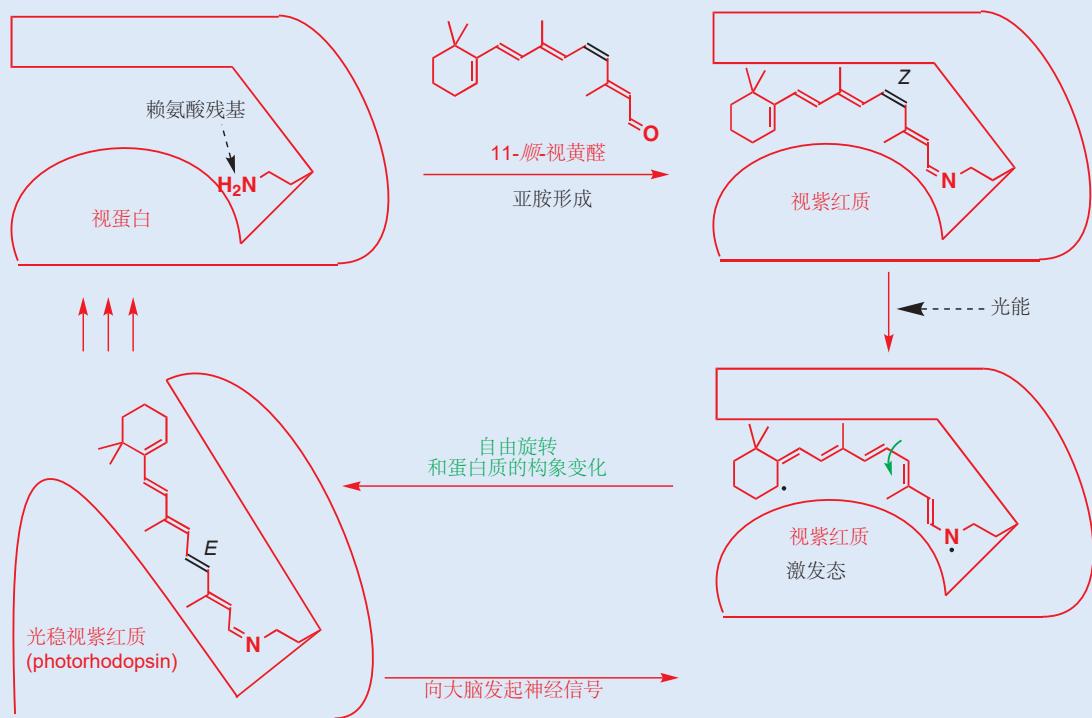


■  $\pi$  轨道上的一个电子被激发到  $\pi^*$  轨道所形成的激发态，可以表示为一个“双自由基(diradical)”— $\pi$  键有效地断裂，形成它的两个电子未成对地分局在两个 C 原子上。

### 视觉中的化学

人眼使用一种顺式烯烃，11-顺-视黄醛(11-cis-retinal)来侦察光，我们看东西的过程的核心是一个顺-反异构化反应。视网膜(retina)的细胞中的感光色素是一个亚胺，由11-顺-视黄醛与视蛋白(opsin)中的赖氨酸残基反应形成。光被视蛋白-视黄醛

化合物(称作视紫红质rhodopsin)吸收时，共轭多烯体系中的一个电子被激发到反键轨道上。激发态允许顺式双键自由旋转，并异构化为反式，这一过程会导致蛋白质分子的构象变化，进而引起一连串的反应发生，并最终导致神经信号被传输到大脑。



### E 和 Z 烯烃可以通过炔烃立体选择性的加成制取

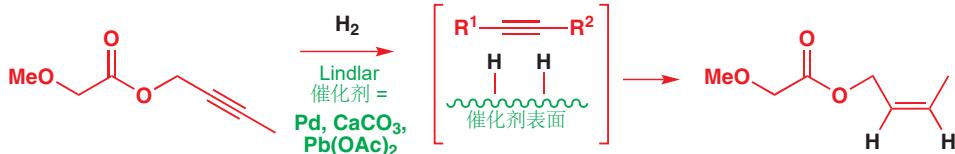
烯烃可以通过炔烃的还原或加成制取，在合适的条件下，这一过程可以立体选择性地形成 *Z* 双键或 *E* 双键。

#### 用 Lindlar 催化剂 *Z*-选择性 地还原炔烃

对于一个重排反应机理的学习中，需要纯净的如下的 *Z* 烯烃。在 Chapter 23 中您学习了由烯烃得

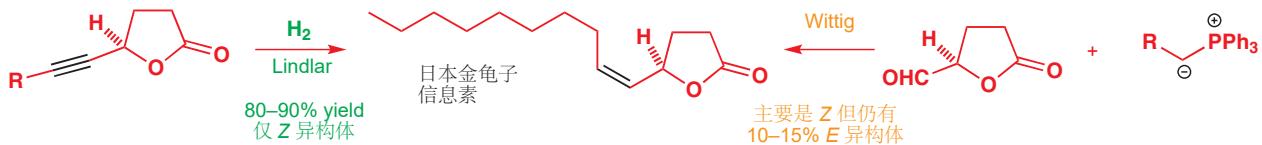
■ 催化氢化通常得到氢 *syn* 加成到烯烃上的产物的原因已于 Chapter 23 中讨论过。

到烷烃的催化氢化反应，也学习了化学选择性控制的可由炔烃得到烯烃的 Lindlar 催化剂（以碳酸钙为载体的钯和醋酸铅）。当时我们没有强调的是，两个氢原子以 *syn* 方式添加到炔烃上，并生成 *Z* 烯烃产物。这个立体选择性的起因，是由于与催化剂成键的两个氢原子，会在同时被送往炔烃上。



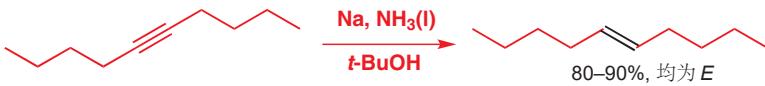
► 我们将在 p. 690 讨论 Wittig 反应的选择性。

下面的化合物是一种破坏性的甲虫的信息素。合成的信息素可用于捕获该甲虫，但它仅在是 *Z* 异构体时有活性。用 Lindlar 催化剂还原对应的炔烃，可给出纯净的 *Z* 异构体；而另一种制备 *Z* 烯烃的反应，Wittig 反应，仍给出可观量的 *E* 异构体。



### 用液氨中的钠 *E*-选择性地还原炔烃

最好的，确保氢 *anti* 加成到三键上的方法，是用液氨中的钠处理炔烃。



钠将电子给予三键的 LUMO（两条正交的  $\pi^*$  轨道中的一条）。所得的自由基阴离子可以从氨溶液中取得一个质子，并给出一个乙烯基自由基。由钠提供的第二个电子，可与之反应给出一个采取更稳定的反式几何结构的阴离子。最终产物被第二分子的氨，或额外添加的质子源 (Birch 还原中常使用叔丁醇) 粹灭，形成 *E* 烯烃。

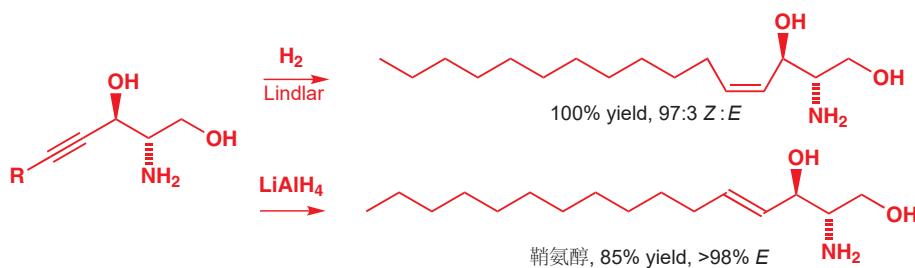


使用得更加广泛的方法，是用  $\text{LiAlH}_4$  或用与之相关的，被称作 RedAl (注：俗称“红铝”，起源于对“Red”缩写的错误理解) 的还原剂还原炔烃。这个反应仅在炔烃附近有一个羟基或一个醚官能团时才可工作，因为这个方法依赖于在还原前铝与氧原子的络合 (配体交换)。

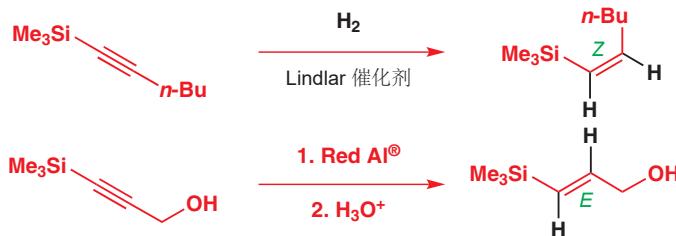


通过对炔烃的加成制取烯烃的方法，有两点很清楚的优势。第一，起始原料通常可以提供炔基阴离子的烷基化直接制取。第二，相同的炔烃可以用两种方法分别制取 *E* 或 *Z* 烯烃。在鞘氨醇 sphingosine (细胞膜的一种成分) 的早期研究中，一些瑞士化学家需要制取天然产物的 *E* 和 *Z* 两种异构

体。当它们制得炔烃时，这便是一个简单的任务了。

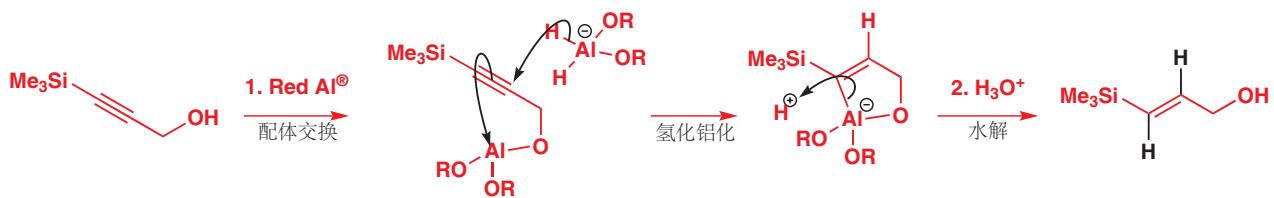


在本章前文中，我们向您介绍了几何纯的乙烯基硅烷的意义，它可作为其他烯烃合成的前体。受控制的炔基硅烷的还原可分别给出这样的乙烯基硅烷，其立体化学由还原方法决定。Lindlar 氢化以顺式方式在炔烃上添加一分子氢，产出 Z-乙稀基硅烷。而对于一个炔丙醇的 RedAl 还原，则相反地产出 E 异构体。



以  $\text{LiAlH}_4$  或 RedAl 进行的氯化铝还原反应的机理，包含一个反式的氯化铝化反应 (hydroalumination)，其中外部的亲核试剂进攻时， $\text{Al}$  与三键的络合。氯化铝化反应的区域选择性再次由硅决定：亲电的  $\text{Al}$  在带有硅基的一端进 (本位碳) 攻炔烃。

■ 在 Chapter 40 中，您会学到更多重要的构建烯烃的方法，它们是乙烯基化合物，尤其是乙烯基卤和乙烯基锡烷的 Pd-催化偶联反应。那些反应的底物中，有很多都可通过与您在此处遇到的相关的反应制取。



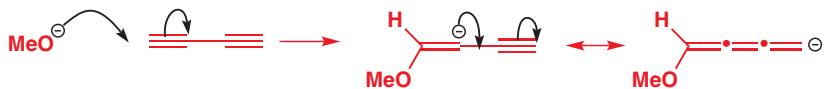
### 亲核试剂对炔烃的加成

这种较稀少，并且相当令人惊讶的得到 Z 烯烃的反应，尤其亲核试剂对丁二烯的加成上，可以得到极好的结果。甲醇的碱催化加成以极好的产率得到 Z-1-甲氧基-1-烯-3-丁炔。这个反应容易使其产物可在市面上购买。注意，甲醇只加成一次：您不应期待亲核试剂能加成到简单炔烃上，正是因为共轭，这种加成才是可能的。

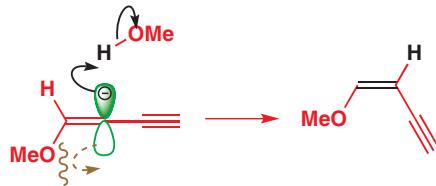


■ 我们在 Chapter 19 (p. 435) 中已用分子轨道向您阐释了，为什么双烯/二烯比普通烯烃更加亲核，也更加亲电。相同的论述也适用于双炔 (diynes)。

甲氧基阴离子对其中一个炔烃的加成可给出共轭的阴离子。这个阴离子是直线型的，其负电荷可离域在第二个炔烃上。因而电荷位于处在分子平面上的 p 轨道中，另一个与之正交的共轭  $\pi$  体系与分子平面成直角。



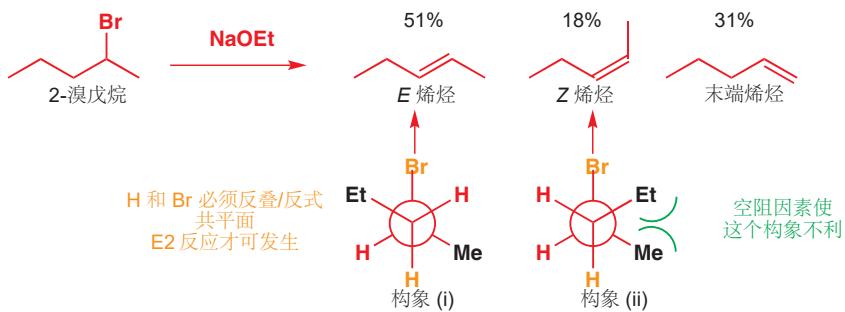
当阴离子与一分子甲醇反应时，质子化发生在远离 MeO 基的 p 轨道的波瓣上，并形成 Z 烯烃。



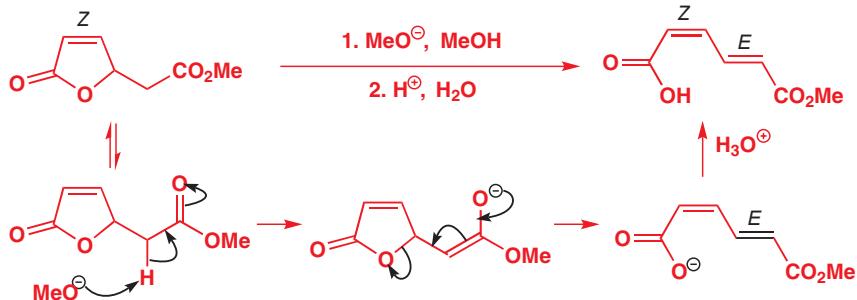
## 通过立体选择性的消除反应得到 E 占主导的烯烃

如果您对于立体选择性和立体专一性反应，动力学和热力学控制不清晰，请重新阅读 Chapters 12 和 17—这些概念对于本章是非常重要的。E2 反应反叠式过渡态的描述在 p. 395.

您在 Chapter 17 中学过，E1 消除反应通常主要给出 E 烯烃（本章的前文也有这样的例子），这是因为导向 E 型双键的过渡态能量低于导向 Z 型双键的过渡态。换句话说就是，E1 反应是立体选择性的，并且它们的立体选择性是动力学控制的。当有多个质子可选时，E2 反应也是如此：有利于形成 E 烯烃，但仍形成混合物。这也是动力学控制。



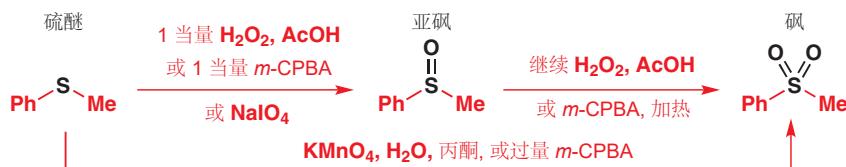
E1cB 反应，例如如下的不饱和内酯在键中的开环反应，通常有更好的区域和立体选择性。双位于环内的双键仍是 Z，而开环所形成的新的一根，则倾向于 E 几何结构。消除步骤的过渡态已经很像产物，并仅由于空间因素，倾向于 E 几何结构。



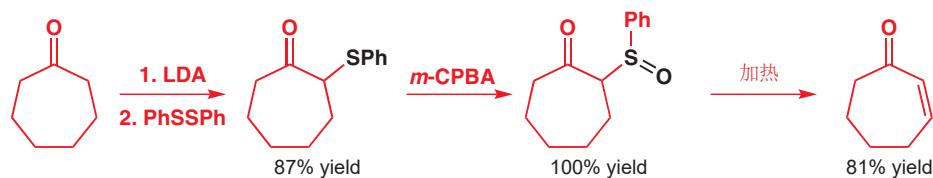
## 亚砜消除反应—氧化制取烯基酮

亚砜处在硫醚和砜之间的，实用而有趣的位置——它们像硫醚一样，是弱的亲核试剂（如 p. 667）。

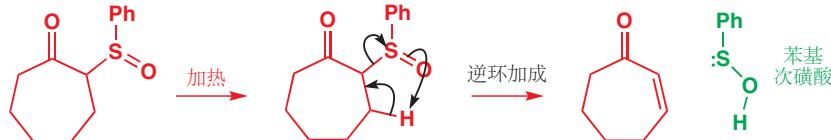
中，砜可以被碘甲烷烷基化以给出亚砜盐；但与此同时，它们可几乎与砜相同地稳定阴离子。它们很容易通过硫醚受控制的氧化反应制取，如下的图表给出了由硫醚得到另两种高氧化态官能团的主要方法。



亚砜可被用于立体选择性地制取烯烃，因为紧挨着共轭基或吸电子基的亚砜在加热条件下很不稳定，会通过消除过程分解。这个过程消去了相当不稳定的苯基次磺酸 phenylsulfenic acid ( $\text{PhSOH}$ )，因此这个反应能发生，部分是由于  $\text{PhSOH}$  可分解为易挥发产物。起始原料可通过环己酮经历其烯醇盐的亚磺酰化，然后再用氧化反应制得。

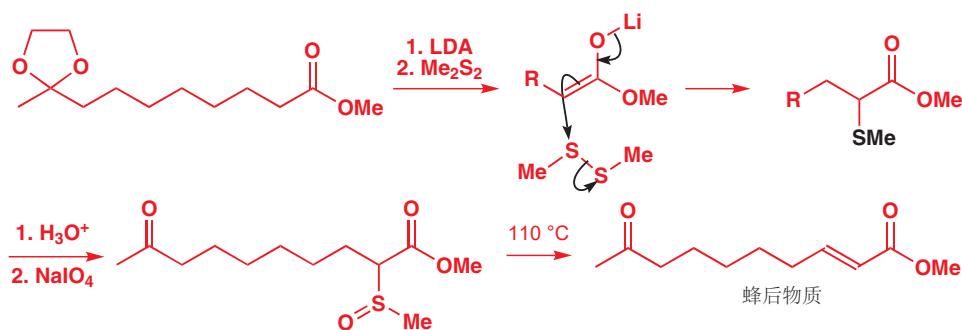


此处的消除反应，遵循一种我们称之为周环反应 (pericyclic reaction) 的机理。当您读到 Chapter 34 时，您就能识别出，它是一个逆环加成反应 (cycloaddition)；但就当下来说，您可以只将其想象为一个质子被离去基团同步移去的反应。此情形中的产物烯烃处于一个七元环中——它需要是顺式的。



Interactive mechanism for sulfoxide elimination

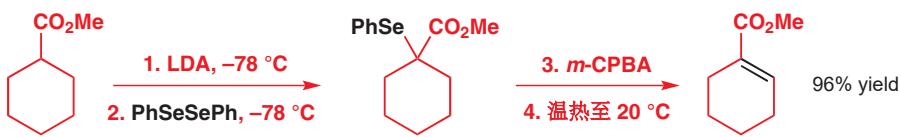
这个反应为在羰基旁边引入双键提供了实用的方法。下面是它在蜂后物质 Queen Bee Substance (工蜂用于喂养那些会成为蜂后的幼虫的化合物) 合成上的使用。蜂后物质同时也是白蚁的一种信息素，可用于捕捉这些破坏性的害虫。硫由酯的烯醇盐与硫亲电试剂  $\text{MeSSMe}$  的反应引入。接着，在酸性下脱去保护基，并用高碘酸钠 ( $\text{NaIO}_4$ ) 将硫醚氧化为亚砜以准备好进行消除反应。在  $110^\circ\text{C}$  下加热即可以 86% 产率给出蜂后物质。



当用硒替换硫时，消除反应还会更容易地发生—— $\text{PhSe}$  基可用相同的方法引入，并用在低温下用  $m\text{-CPBA}$  将其氧化为亚硒砜 (selenoxides)。亚硒砜很少被分离，因为消除反应在室温下也可很迅速

■ 硫和硒有很多共同点，大多数硫化合物都可反映在硒化合物中。通常，有机硒化合物相比对应的硫化合物都倾向于更不稳定，和更活泼。这是由于 C-Se 键比 C-S 键更脆弱。并且它们的气味更难闻。

地发生。

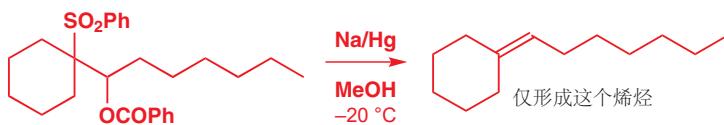


## 区域选择性的 Julia 成烯反应可用于连接

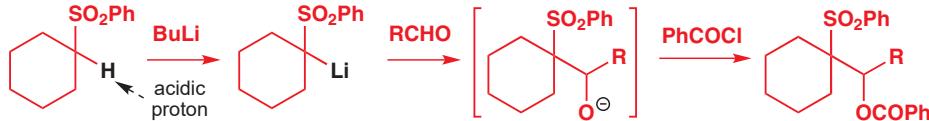
亚砜消除反应向已然完整的碳骨架中，引入双键的有价值的反应。而本节我们将向您展示的一种烯烃合成方法同样基于硫化学，但它是用于连接的(*connective*)——烯烃伴随着两个分开的碎片的结合而形成。它被称作 **Julia 成烯反应/烯基化反应 (Julia olefination)**，并且，大概是本章前文向您介绍的，被砜稳定的阴离子最重要的应用。如下的过程中，仅形成所示出的烯烃，双键处在原先分别带有  $\text{PhSO}_2$  和  $\text{PhCO}_2$  基的两个碳原子间。消除反应被一个还原剂，传统上是钠汞齐 sodium amalgam (金属钠的汞溶液) 推动，它并适用于各种前提是有机物与一个离去基团相连的化合物。

Marc Julia (1922–2010) 出生于巴黎，在伦敦帝国理工学院师从 Sir Derek Barton 获得 PhD 学位，后来在巴黎高等师范学院工作。

■ Olefin 是 alkene (烯烃) 的另一种称呼，**olefination (成烯反应)** 表示的是既包含  $\sigma$  键，又包含  $\pi$  键的烯烃合成反应。

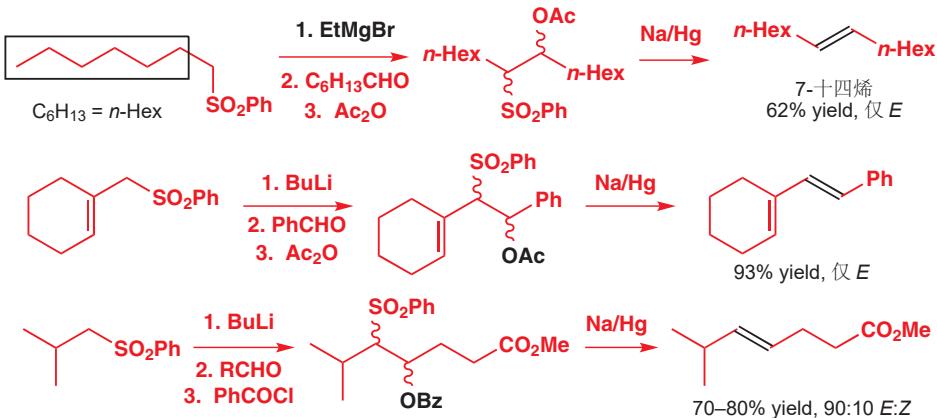


通常，所用的离去基是羧酸根，例如乙酸根、苯甲酸根，起始原料很容易制取。被砜稳定的阴离子加成到醛上，然后通过一个简单的酯化过程引入乙酰基或苯甲酰基。而后便得到了上方的消除反应所用的起始原料。



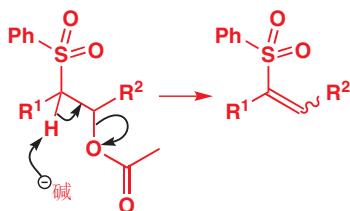
### Julia 成烯反应是立体选择性的

下面是一些简单 Julia 烯基化反应的结果。注意观察，去质子步骤可通过  $\text{BuLi}$  或  $\text{EtMgBr}$  完成，酰基化步骤可通过乙酸酐或苯甲酰氯完成。如您所见，它们高度立体选择性地得到 *E* 异构体，Julia 成烯反应也是制取用于连接的 *E* 双键最重要的方法之一。



E 选择性的原因依赖于消除反应的机理。细节尚不完全清晰，但对于第一步，碱性条件下的还原反应，似乎是对乙酸根或苯甲酸根的消去过程，以给出乙烯基砜。

 Interactive mechanism for Julia olefination



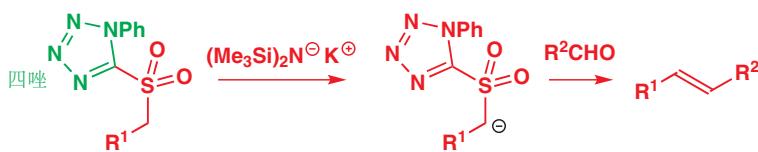
乙烯基砜的立体化学并不构成问题，因为它会立即被钠提供的电子还原，得到乙烯基自由基。与炔烃的 Birch 还原反应一样，乙烯基自由基会采集第二个电子并变为乙烯基阴离子，乙烯基阴离子便会在被质子化前采取更稳定的 *E* 构型，因此最终 *E* 烯烃占主导。



我们知道，由于这个消除反应不是立体专一性的，因此必然存在一个阴离子中间体——换句话说，无论您用哪种非对映体做起始原料（本节中所有的例子都使用的是非对映体的混合物），您都会得到 *E* 烯烃产物。

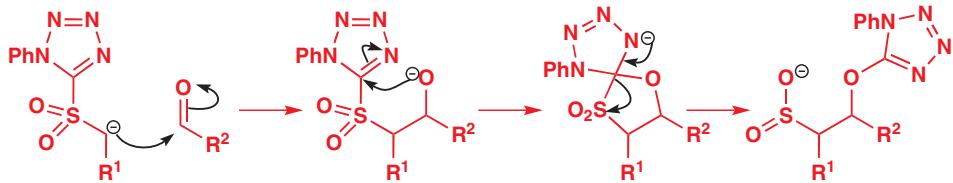
### 一步的 Julia 成烯反应

Julia 反应十分全能，但它需要三步来完成：加成、酰基化，和还原。这个反应的一个更近的版本将其减少到了一步，其中将苯基砜换成了一个带有缺电子杂环，例如四唑（tetrazole）的砜。砜的阴离子通过与强碱（此处是六甲基二硅氨基钾，KHMDS——见 p. 635）反应制取，并直接加成到醛上，给出烯烃。



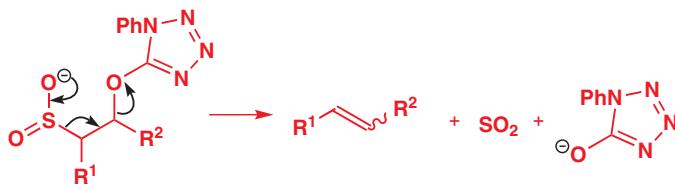
■ 四唑看起来不稳定得吓人，但事实上则常被应用于药物化学中。在学习杂环化学的章节中（29 和 30），您还会再次遇到它们。

加成到醛上后，所形成的烷氧基阴离子通过从硫上攫取杂环，将自己转化为一个离去基。



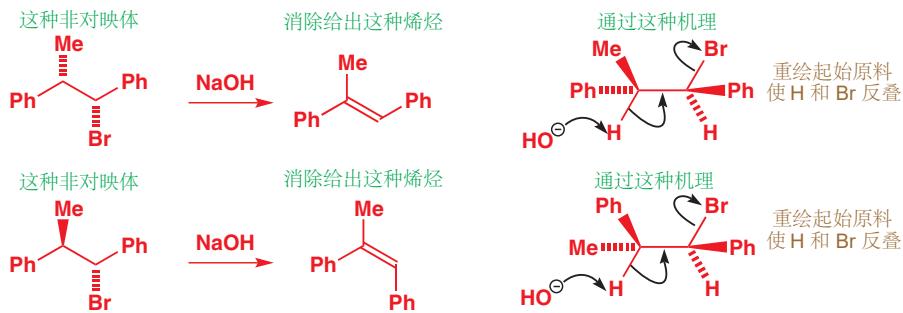
最终的消除由 SO<sub>2</sub> 的离去驱动，通常给出 *E* 烯烃。而仔细地选择碱和溶剂，可将选择性转变为 *Z* 占主导。

Julia 成烯反应能一步完成的“杂环”改进版本由 Marc Julia 的兄弟，同在巴黎高等师范学院工作的 Sylvestre Julia 发现。四唑砜的使用是 Philip Kocieński 的贡献，因此这个反应有时也被称作 Julia–Kocieński 反应 (Julia–Kocieński reaction)。



## 立体专一性的消除反应可以得到烯烃纯净的单一异构体

您在 Chapter 17 中学习过一种立体专一性的消除反应 (E2)。E2 过渡态要求 H 和 Br 处于反叠式构象/反式共平面，这意味着两种如下两种溴代烷非对映体的消除，会得到带有不同双键几何结构的烯烃 (p. 396)。

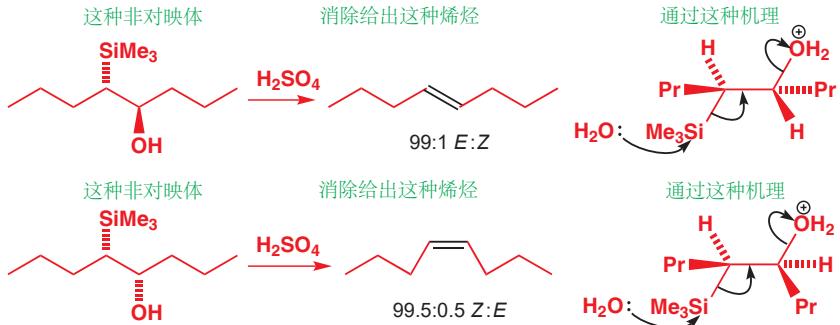


Interactive mechanism for stereospecific E2

然而，这样的反应的使用是受限的——它们的成功依赖于没有其他可被碱进攻的质子选择。逻辑推理表明，这种立体专一性方法仅限于三取代双键的制取：对于氢原子，不能有更多的选择，否则就会立体选择性地得到 E 烯烃 (如 p. 684 中的例子)。解决方法当然是避开涉及到 H 的消除反应，因而您在 p. 671 学习的 Peterson 消除反应是一个好的选择。

## Peterson 反应是立体专一性的

这个消除反应所包含的立体化学，来源于硅，因为它是一个通过反叠式过渡态进行的 E2 消除反应。原则上，它可用于制取烯烃的单一几何异构体，几何结构取决于起始原料的相对 (非对映) 结构。然而，非对应异构纯的起始原料却不容易获得，因而 Peterson 反应的使用是受限的。



Interactive mechanism for stereospecific Peterson elimination

Peterson 消除反应有另一个与上文的版本互补的版本，即碱促的反应。起始原料与酸促 Peterson 反应相同。当加入碱(例如氯化钠或氯化钾)时，羟基会被去质子，氧阴离子会分子内地进攻硅原

子。此时的消除经历顺叠式/顺式共平面过渡态发生——由于氧原子和硅原子成键，它必须如此，并且正是氧原子与硅原子成的强键驱动消除反应的发生。

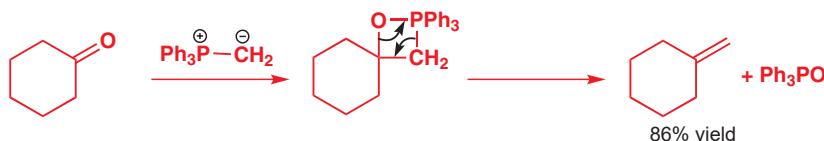


**Peterson** 消除反应的两个版本，由相同的起始原料的对映异构体出发，分别得到相反的几何异构体。因此由任何羟基硅烷的单一非对映体出发，我们都可用通过选择酸或碱，得到自己想要的一种几何异构体的烯烃。而问题仍在于，如何制备单一非对映体的羟基硅烷上！

您已在 Chapter 17 中发现，反叠式过渡态通常有利于消除反应的发生，因为所涉及的轨道排列为直线，这为良好的重叠提供了机会。然而，顺叠式过渡态也可以发生消除反应——碱促的 Peterson 消除应当让您回忆起在 Chapter 11 中首次遇到的 Wittig 反应，包含四元环过中间体。我们将通过对于 Wittig 反应，及对于它的立体选择性的详细讨论完成这一章。

## 也许是烯烃最有用的制取方法—Wittig 反应

Wittig 反应也是我们所讨论的——不涉及 H 的失去的消除反应——这一类别中的一个。您在 Chapter 11 中学习了它，在那里我们简要描述了它的机理。



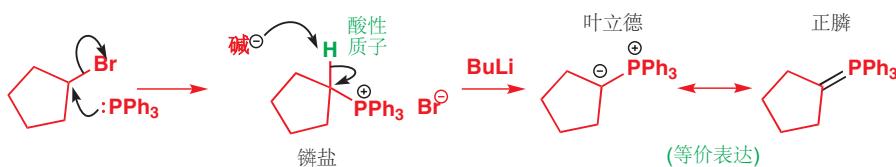
这个 Wittig 反应出现于 p. 237. 我们还曾在 p. 627, Chapter 26 中用 Wittig 反应控制烯醇盐。

Interactive mechanism for the Wittig reaction

概念上讲，Wittig 反应就像是碱促的 Peterson 反应：一个被氧-杂原子强键驱动的 *syn* 消除反应，杂原子换为了膦。但 Wittig 反应中，参与消除的只能是中间体，而不能作为可分离的起始原料。中间体在反应过程中在反应混合物中生成，并自发分解：因而 Wittig 反应是另一个用于连接的烯烃形成反应。而它的易用性使之相比于 Julia 或 Peterson 反应，得到了更广泛的应用。

为了理解反应的细节，我们应当从头开始。磷原子，尤其是那些带正电的，或携带负电性取代基的，可以增加在碳骨架上与之相邻的质子的酸性。因而𬭸盐（以类似于胺形成铵盐的方式，即𬭸于卤代烃反应形成）可被适中强度的碱去质子，给出一个被称作叶立德（ylid，有时也拼为 ylide）的物种，即在相邻的两个原子上分别携带（形式）正电荷和负电荷。叶立德也可表示为双键物种，称为正瞵（phosphoranes）。

■ 在这一点上，磷和硫是类似的：将𬭸叶立德与您之前遇到过的被砜稳定的阴离子对比。



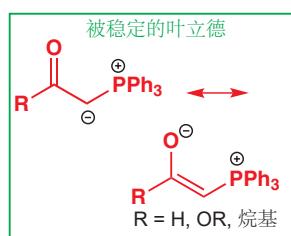
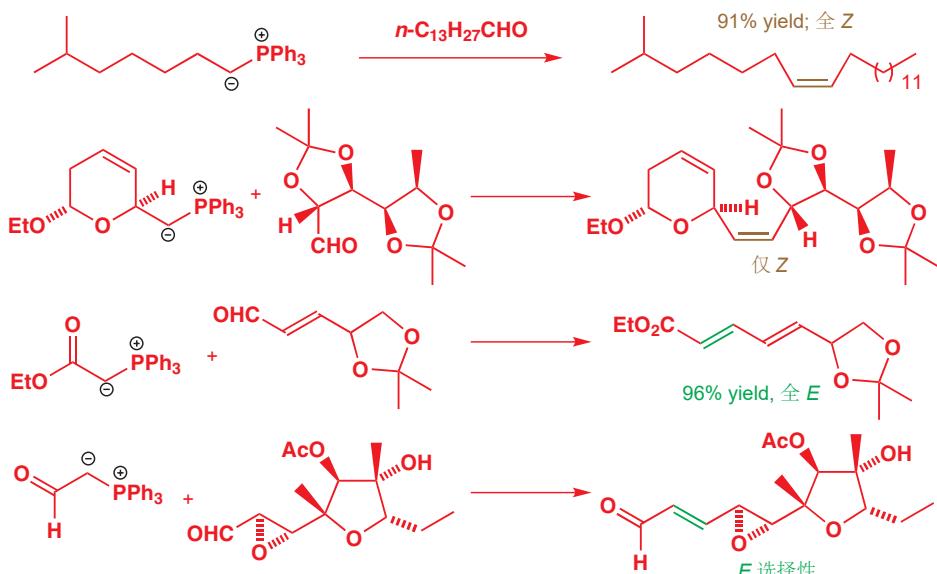
叶立德可以被分离，但通常在它们形成时，便立即被用于反应。它们是对于醛或酮中的羰基的亲核物种，并生成四元环氧磷丁环 (oxaphosphetane) 中间体。氧磷丁环是不稳定的：它们经历消除反应给出烯烃 (如下的例子中产率为 65%)，与副产物氧化膦。极其强的 磷–氧 双键的形成驱动整个反应向前进行。

■ 在 Chapter 11 中，为了帮您理解反应，我们将对羰基加成以形成四元环的过程分显示为两步。这个过程事实上很有可能是协同的 (同时发生)，右侧所示的一步形成四元环的表述是更好的。



### Wittig 反应的区域选择性取决于叶立德

下面是几个应用于天然产物合成的 Wittig 反应。您会注意到，有些反应是 *Z* 选择性的，有些则是 *E* 选择性的。仔细观察，您会发现：区域选择性依赖于叶立德的碳原子上取代基的属性。



我们可以将叶立德分为两类：负电荷邻位有共轭基或阴离子稳定基（例如羰基）的，和没有这类基团的。第一类叶立德中的负电荷不但被磷原子稳定，而且还被邻位官能团稳定，我们称之为**被稳定的叶立德 (stabilized ylids)**——我可以用等价的烯醇盐结构表达这种额外的稳定化作用。剩下的一类则被称为**未被稳定的叶立德 (unstabilized ylids)**。（注：有时可直接称为**稳定型叶立德/不稳定型叶立德**。）

#### ● Wittig 反应的立体化学

一般规则为：

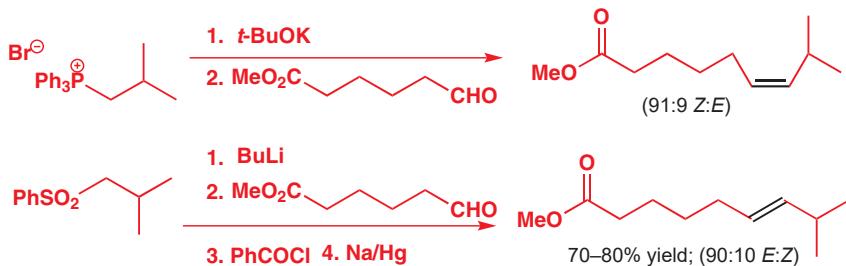
- 被稳定的叶立德的 Wittig 反应是 *E* 选择性的；
- 未被稳定的叶立德的 Wittig 反应是 *Z* 选择性的。



### Z-选择性的 Wittig 反应

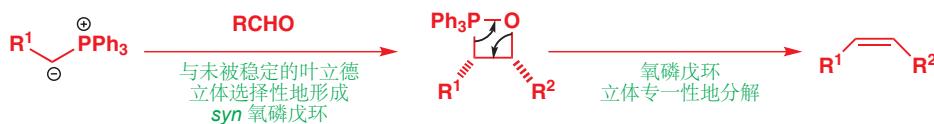
R 基为简单烷基时观测到的 *Z* 选择性与 Julia 成烯反应中观测到的 *E* 选择性很好地互补。这种互补性得到了一些想要制取辣椒素 capsaicin (使得辣椒“辛辣”的化合物) 的两种异构体，以深入研

究辣椒素可能致癌的化学家的利用。*E* 和 *Z* 辣椒素异构体合成中的关键中间体是如下所示的 *E* 和 *Z* 不饱和酯。通过用未被稳定的叶立德的 Wittig 反应，可选择性地得到 *Z* 异构体；同时，用 Julia 成烯反应可得到 *E* 异构体。

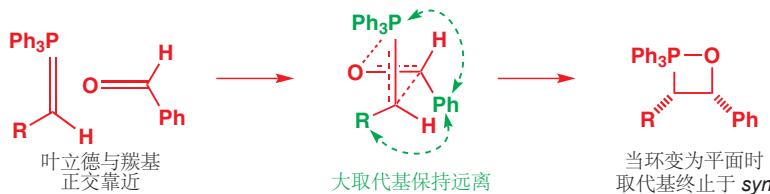


如何解释未被稳定的叶立德的 Wittig 反应的 *Z* 选择性呢？这个反应的情况比我们从前考虑过的其他消除反应更复杂，因为我们需要考虑两个独立的过程：氧磷丁环的形成和氧磷丁环分解为烯烃的过程。消除步骤的解释较简单——它是立体专一性的，在顺叠式过渡态中消去氧和磷。叶立德对炔烃的加成，原则上可以形成中间体氧磷丁环的两种非对映体。由于加成的这一步是不可逆的，并且消除反应也是立体专一性的，这就意味着最终烯烃几何异构体的比例，所反映的是加成这一步的立体选择性。

当 R 不是共轭基或阴离子稳定基时，*syn* 非对映体的氧磷戊环优先形成，结果中占主导的 *Z* 烯烃正反映了这个事实。因而 *Z*-选择性的 Wittig 反应分为：立体选择性的第一步，形成 *syn* 氧磷戊环；紧跟着中间体立体专一性的消除，得到 *Z* 烯烃。



为什么未被稳定的叶立德反应时，倾向于形成 *syn* 氧磷戊环，由于氧磷戊环形成的机理还未被完全理解，这个问题也是争论的焦点。一种可能的解释依赖于轨道对称性的规则，您将在 Chapters 34 和 35 中学到——在这里我们不需要详细地解释，但您有理由相信，叶立德和羰基化合物在一步反应中给出氧磷戊环，而这步反应，是由它们成直角地接近完成的。此处我们将加成到苯甲酸上的叶立德画成了它的正膦形式。更好的过渡态应是大取代基互相远离的，如下所示，如是过渡态的反应结果便是含有 *syn* 立体化学的氧磷戊环。

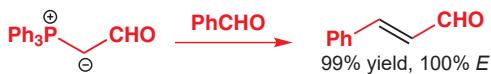


Interactive mechanism of *Z*-selective Wittig reaction

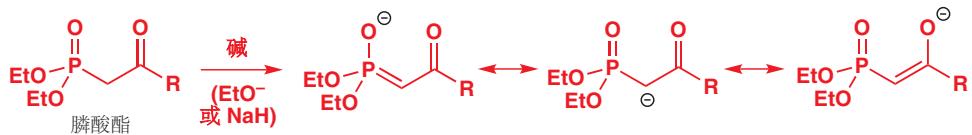
### *E*-选择性的 Wittig 反应

被稳定的叶立德，指的是阴离子被其他共轭所稳定的叶立德，其他共轭通常来源于与一个羰基，它们与醛的反应得到的是 *E* 烯烃。

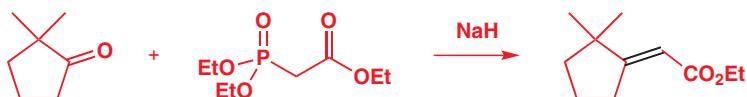
→ 这些叶立德同时也是烯醇盐，我们在 Chapter 26, p. 627 中讨论过。



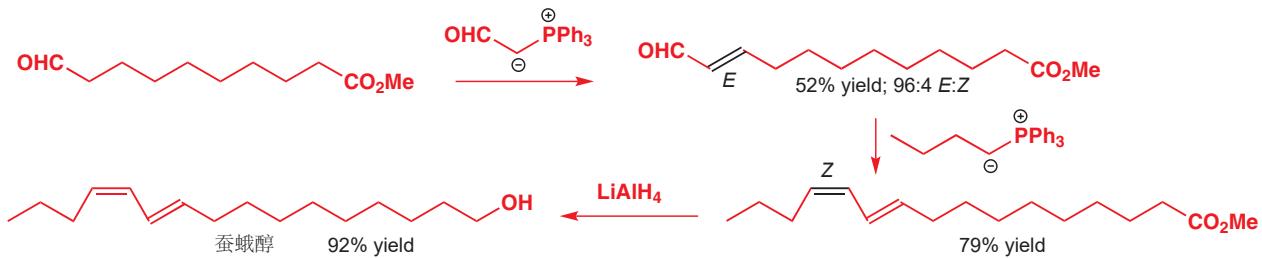
这些被稳定的叶立德确实是稳定的一—例如下方的一个，可以从水中重结晶，并且叶立德比它可能的前体，𬭸盐更稳定。这种稳定性意味着，虽然它们不活泼，但通常使用膦酸酯 (phosphonate ester) 替代𬭸盐是更好的。



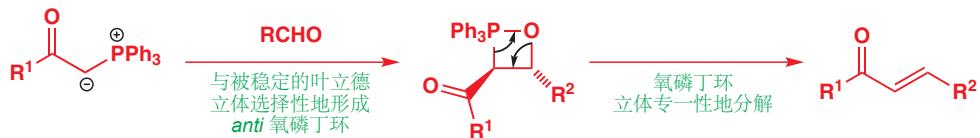
膦酸酯可以被氢化钠或烷氧基阴离子去质子，给出烯醇类型的阴离子，这种阴离子可以与醛或酮很好地反映以给出 *E* 烯烃。用膦酸酯的烯烃形成反应被称为 **Horner-Wadsworth-Emmons 反应** (**Horner-Wadsworth-Emmons reactions**) (Horner-Emmons/Wadsworth-Emmons/Horner-Wittig 均指这个反应)。下面是一些日本化学家在 polyzonimine，由马陆产生的天然驱虫剂的合成中应用的反应例子。



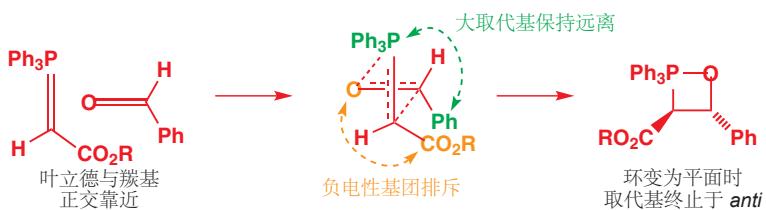
如下的合成为两类 Wittig 试剂选择性的对比提供了一个很好的说明。雌性蚕蛾通过产生一种被称为蚕蛾醇 (bombykol) 的信息素吸引雄性。蚕蛾醇是一种 *E,Z*-二烯，在它的合成中，应用了两次成功的 Wittig 反应，一个使用被稳定的叶立德，一个使用未被稳定的叶立德来控制产物的立体化学。



那么为什么当叶立德被稳定时，反应会变为 *E* 立体选择性的呢？再次说明，细节仍然不清晰，并且存在不少可能的解释。此处我们给出一种越来越被人们接受的解释，基于近期的实验和计算证据得出。看起来，与未被稳定的叶立德一样，烯烃产物的立体化学取决于中间体氧磷丁环的立体化学，因而对于被稳定的叶立德，中间体氧磷丁环是 *anti* 型的。



过去，人们认为 *anti* 氧磷丁环的形成是受动力学控制的，但现在看来，它同样可能是在动力学控制下形成的。与未被稳定的叶立德不同的是，我们原先所关注的，叶立德中与醛上的基团排斥的烷基被换做了负电性的基团，如酯基  $\text{CO}_2\text{R}$ ；于是，于其在乎与烷基的排斥，它更在乎与同样负电性的醛上的极化的  $\text{C}=\text{O}$  键间的排斥 (注：偶极–偶极相互作用)，因而便处在与原先相反的位置上了。当四元环变平时， $\text{CO}_2\text{R}$  基和 Ph 基便会处在四元环相对的两侧。



Interactive mechanism for *E*-selective Wittig reaction

## 小结

本章中，我们首次处理如何制得以单一立体异构体存在的化合物的问题——我们关心的立体异构体，是烯烃的几何异构体。在后面的章节中，我们将更细致地研究立体异构体的制取，并且会由二维跳转到三维，考虑那些展示出非对映选择性和对映选择性的反应。在二维和在三维控制立体化学的方法是相当接近的：单一的非对映体常常通过对双键的单一几何异构体的加成反应制取；而如您在 Peterson 和 Wittig 反应中发现的，单一的非对映体也可立体专一性地变为单一几何异构体。

### ● 立体选择性地制取烯烃的方法总结

#### 制取 顺式 (*Z*) 烯烃

与未被稳定的叶立德的 Wittig 反应  
将烯烃约束在一个环中

炔烃的 *Syn* 加氢  
Peterson 消除反应

#### 制取 反式 (*E*) 烯烃

与被稳定的叶立德的 Wittig 反应通过平衡变为更稳定的异构体  
Julia 成烯反应  
简单消除反应

炔烃的反式选择性还原  
Peterson 消除反应

## 延伸阅读

如果您想阅读更多已被用于探究(被)碘酰基(稳定的)阴离子结构的实验，请见 E. Block, *Reactions of organosulfur compounds*, Academic Press, New York, 1978.

硼和硅化学: S. E. Thomas, *Organic Synthesis: The Roles of Boron and Silicon*, Oxford Primer, OUP, Oxford, 1991.

关于 Wittig 反应机理的一篇近期讨论，见 R. Robiette, J. Richardson, V. K. Aggarwal, and J. N. Harvey, *J. Am. Chem. Soc.*, 2006, 128, 2394.

关于双键几何结构控制的综合描述，见 P. Wyatt and S. Warren, *Organic Synthesis: Strategy and Control*, Wiley, Chichester, 2007 chapters 7–13 以及随附的 *Workbook*, 同样是 Wiley, 2008.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 28 逆合成分析

## 联系

### ► 基础

- 羰基化学 ch6, ch10, & ch11
- S<sub>N</sub>1 和 S<sub>N</sub>2 反应 ch15
- 芳香亲电取代 ch21
- 烯醇和烯醇盐化学 ch20, ch25, & ch26
- 共轭加成 ch22

### 目标

- 合成和逆合成
- 逆向思考
- 如何制取胺和醚
- 合成子是什么?
- 选择制取哪根 C–C 键
- 双官能团切断是最好的
- 烯醇盐化学中的逻辑性规划

### ► 展望

- 非对映选择性 ch32 & ch33
- 周环反应 ch34 & ch35
- 芳杂环的合成 ch30
- 不对称合成 ch41
- 天然产物 ch42

## 创造性的化学

化学首先是一门创造性的学科。目前为止，您在本书中学到的几乎所有知识都有一个隐含的目的：教您如何制造分子。不管出于什么原因，这是大多数化学家终究都会做的。由植物或海洋生物中分离得到的药物是少量的，而由化学家在实验室中制造的药物则可以多得多。从植物中提取的染料范围有限，更多鲜艳而持久的燃料是化学家在实验室中合成的。化学家创造的合成聚合物，已经取代了较贵、较不耐用的替代物，例如橡胶。尽管有负面报道，但 PVC 作为电线的绝缘材料的应用已经阻止了许多次火灾，并挽救了很多生命。精心设计的和控制的杀虫剂为商店货架、市场和超市提供了充裕的无疾病食物，它们更加健康，人们也能活得更长。过去 50 到 100 年间，生活质量的大部分改善都可以追溯到由化学家创造的分子。但，面对制造新化合物的挑战，化学家是如何应付的呢？

合成计划由产品开始，逆向分析直到产物，因为产品是固定、不可改变的。这个过程被称为逆合成 (*retrosynthesis*)，计划合成目标分子的艺术被称为逆合成分析 (*retrosynthetic analysis*)。本章的目标是向您介绍逆合成分析的原则：读完并理解它，是您设计自己的有机合成的道路的开始。

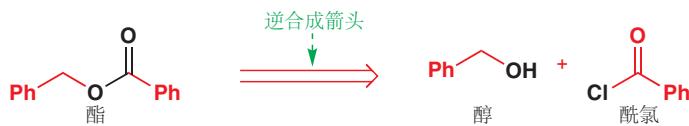
## 逆合成分析：逆向合成

您学过的大多数化学都专注于反应（像“需要向 X 中添加什么可以得到 Y？”这样的问题）或专注于产物（像“X 和 Y 在一起反应时会发生什么？”）。而此时，我们将着眼于起始原料（制取 Z 需要选用什么 X 和 Y？）。我们逆向考察反应，这个过程有一个特别的符号，被称为逆合成箭头（逻辑上的“隐含 (implies)”箭头）。左侧含有逆合成箭头的图表意味着“Z 可以由 X 加 Y 得到”。

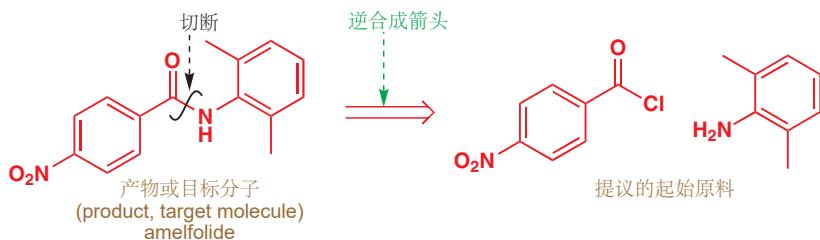


**在线支持** 边栏中出现的  图标表明该位置有对应的在线互动资源可帮助您理解：在您的浏览器中输入 [www.chemtube3d.com/clayden/123](http://www.chemtube3d.com/clayden/123)，将其中的 123 替换为图标出现的页码。对于关联有超过一个资源的页，则输入 123-1, 123-2 等（将 123 替换为页码）来逐一访问这些。

下面是一个非常简单的例子。该化合物是一种驱虫剂。它是一种酯，因而我们知道，它可以由醇加酰氯制取，我们可以用逆合成箭头表示这个过程。



芳香酰胺 amelfolide 是一种抗心律失常药。由于它是一种酰胺，因而我们知道它很容易由对硝基苯甲酰氯和 2,6-二甲基苯胺 制取——我们又可以将其用逆合成箭头表示。像这样的，在思想上将一个分子分解为它的组成部分的过程被称为 **切断(disconnection)**，还可以像下图这样，用一根波浪线 (wiggly line) 表明切断的位点，这也是有帮助的。



## 切断必须符合于已知、可靠的反应

首个制取 amelfolide 的化学家选择由胺和酰氯制取，这是因为它们了解这个反应，这是制取酰胺的标准方法，有很大几率成功。它们选择切断 C–N 键，也是由于这种切断对应的是一个可靠的反应，而其他方式的切断是不可能的。

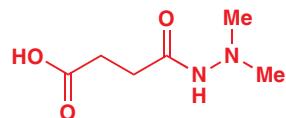
现在您已经看到了逆合成分析工作的原则，您应当能够为侧边栏所示的，被称为丁酰肼 (diaminodiazine) 的化合物给出合理的切断，您可能立即就会发现，这种化合物又是一种酰胺，因此最佳的切断方式仍是 C–N 键，即回到酰氯和二甲基肼上。这一次，我们在逆合成箭头上写下了“C–N 酰胺”，作为切断原因的提醒，我们建议您也遵循这种做法。



### 箭头

您现在已经了解了四种箭头的类型：简单的反应箭头 → 意思是“反应得到”，离域箭头 ↔ 意思是“绘制同一离域结构的两种方式”，平衡箭头 ⇌ 意思是“两个结构会相互转化”，而现在的逆合成箭头 ⇒ 则表示“可以由某物制得”。

■ 本章将很大程度地依赖于您在本书前文所学过的反应，这也为您提供了重温的机会。如果您遇到了一个您不熟悉的反应，请在继续阅读下一个反应前查阅它的相关章节。



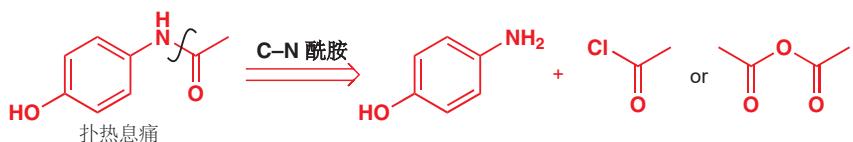
丁酰肼是一种用于抑制菊花生长和矮化果树的人造农药。



## 合成子是被理想化的试剂

丁酰肼的合成使用了酸酐，但酸酐并不是唯一的选择，往往有多种可替代的试剂都对应同一切断

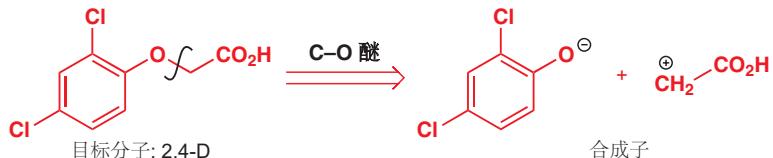
过程。例如同样是酰胺的扑热息痛 (paracetamol), 也既可切断为 胺 + 酰氯, 也可切断为 胺 + 酸酐。



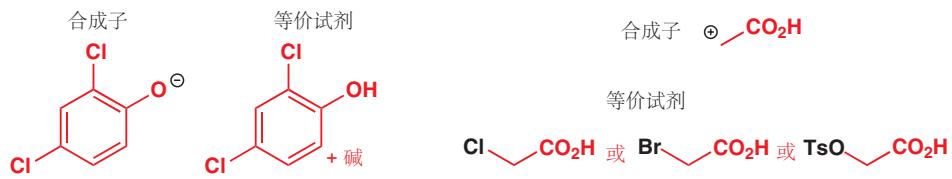
对于哪一个试剂是最好的, 通常只能由实验确定——商业上, 扑热息痛是通过对氨基苯酚和乙酸酐大量制取的, 因为其副产物乙酸, 比 HCl 更容易处理。在逆合成分析中, 我们真的不想被这种应在以后被决定的选择所困扰, 因而最好有一种单一的方法来表示这些可替代的试剂的关键属性。我们可以在方案中, 将酸酐和酰氯都描绘为一种“被理想化的试剂 (idealized reagent)”——一个亲电的酰基  $\text{MeCO}^+$ 。



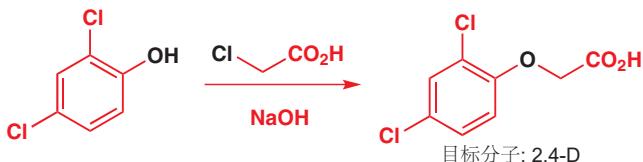
我们称这种被理性化的试剂为合成子 (**synthons**)。合成子是具有有关联的极性 (通过“+”或“-”表示) 的片段, 它们代表我们在正向合成中将要使用的试剂。虽然它们偶尔正是反应经历的中间体, 但它们本身并不是试剂。将切断结果用合成子而非真正的试剂表示, 这可以使我们在无需特别说明试剂的细节的情况下, 表明成键反应的极性。



■ 您会发现, 如果您尝试在阅读我们提出的方案前自行完成逆合成分析, 就会更快地阅读本章, 也能学到更多知识。用一张纸盖住您阅读的页的其余部分, 并在另一张纸写下一下思路。不要仅仅说“哦, 我可以做到”然后就继续——您会错失自学很多化学的机会。不要浪费这个机会! 下一次您阅读本章时, 您就会有记忆作为辅助——而逆合成分析并不是关于记忆的, 它是关于推断的。另一件有关逆合成分析的重要事情是, 很少有单一“正确/合适”的答案, 因此即便您的提议与我们给出的不匹配, 也不要感到失落。请将学习目标置于您的提议与我们的建议不同的地方。



然后, 我们可以将我们提出的合成路线, 从开始到结束地写出。试图预测确切的反应条件是不合理的: 要做到这一点, 您需要对化学文献开展彻底而深入的搜索, 并且做一些实验。然而, 本章中涉及的所有合成路线都是真实的例子, 我们通常会提供给您反应条件的完整细节, 以帮助您熟悉它们。



### ● 合成中所用的一些术语的定义

目标分子(或 TM)	待合成的分子
逆合成分析或逆合成	在思想上将分子分解为起始原料的过程
逆合成箭头	开尾式箭头,
切断	想象的键的断裂过程, 对应于一个真实反应的逆过程
合成子	切断得到的被理想化的碎片(逆合成分析完成后, 需要将合成子替换为试剂以得到合成路线)
试剂	合成中所用的真是化合物, 也许是合成子的等价物

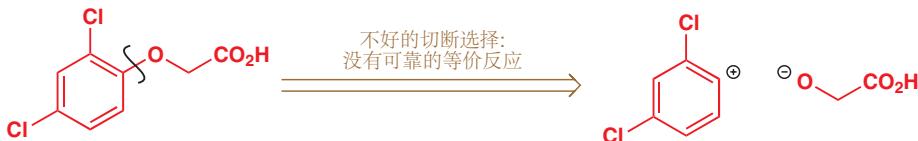
### 选择切断方式

设计一个逆合成分析最难的任务是找出切断的位置。我们将为您提供一些准则, 但最好的学习方法仍是通过实验和练习。逆合成分析的总目标是回到可从化学品供应商购得的起始原料, 并且要尽可能高效。

#### ● 准则 1

切断必须对应于已知、可靠的反应。

我们已经提到, 切断必须对应于已知的、可靠的反应, 这是在进行逆合成时, 需要牢记的最重要的事情。当我们切断醚 2,4-D 时, 由于我们知道醚的合成方式, 我们选择在氧原子旁切断。我们没有选择在氧原子芳基的一侧切断, 因为我们知道没有可靠的, 对应于在未被活化的芳环上的亲核进攻。

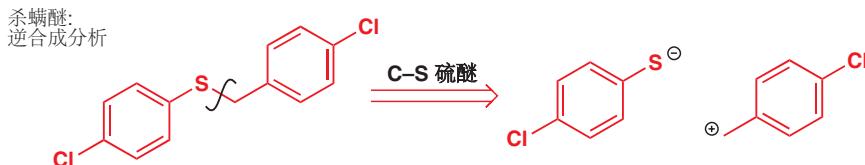


我们在 Chapter 22 讨论了芳香亲核取代可以实现的情境。

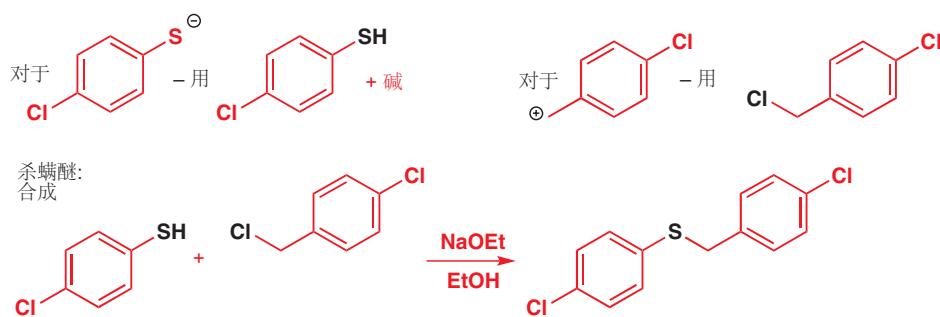
#### ● 准则 2

对于由两个连接在杂原子上的片段构成的化合物, 在杂原子旁切断。

在目前您见到的所有逆合成分析中, 都有将分子的其余部分连接在一起的杂原子(N 或 O), 每种情况下, 我们都在 N 或 O 旁做切断。这一准则适用于酯、酰胺、醚、胺、缩醛、硫醚等, 这些化合物都可以通过取代反应制取。杀螨醚/氯杀螨(Chlorbenside)用于杀虫和杀螨。运用准则 2, 我们可以提出在硫原子旁的切断方法; 运用准则 1, 我们知道我们必须在烷氧基一侧切断, 而不能在芳基一侧切断。(注: 弟啊, 这要如何自己思考啊, 图里已经把切断方式给了啊。)



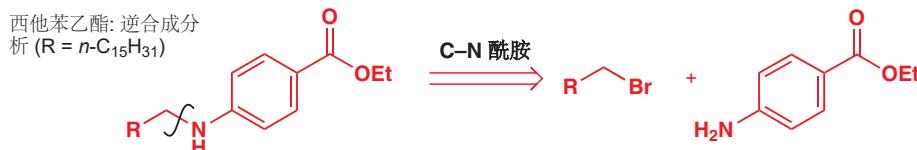
现在, 我们可以提出对应于合成子的试剂, 并给出合成方案了。



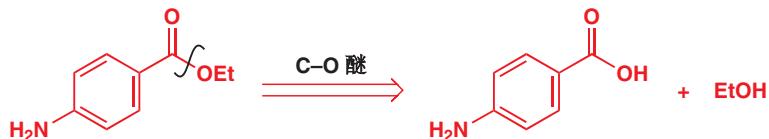
■ 您不应当预测出乙醇钠会作为这个反应的碱，但您应当意识到这个反应是需要碱的，并且应当对用于使硫醇去质子的碱的强度有所想法。

■ 您往往不必首先写出合成子——此处的试剂很简单，我们直接写出它们即可。

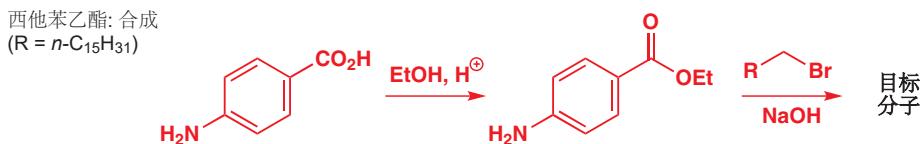
下一个例子是降血脂药物西他苯 (cetaben) 的乙酯，也是它的前体。它是一种胺，因此我们在氮原子旁切断。



溴代烷是可购买的，但我们还需制取芳香氨基酯，对于酯最好的切断方法是羰基和酯化基团 (esteryfying group) 之间的 C-O 键。

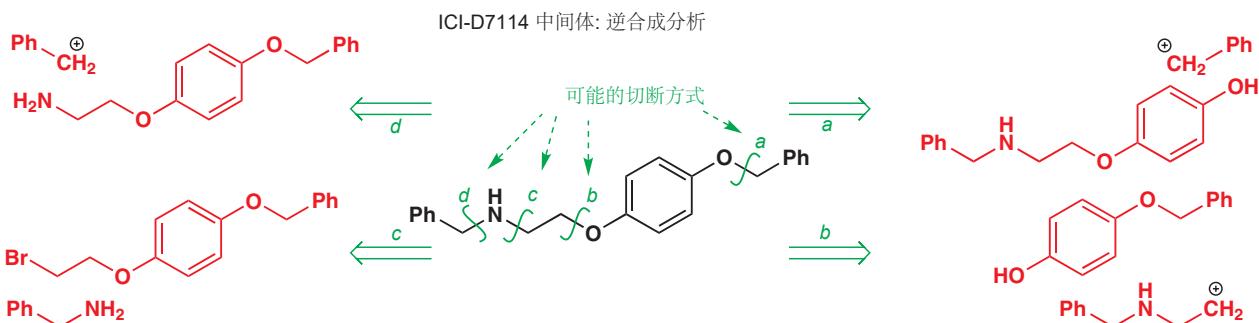


现在，我们设计好了一个我们目标分子的两步合成路线，这是它进行的方式。



## 多步合成: 避免化学选择性问题

下一个化合物是潜在的抗肥胖药物 ICI-D7114 的合成中间体。您可以指出，其中有两个醚官能团和一个胺官能团，它需要数次切断以回到简单化合物。问题在于，我们先做哪个？解决这个问题的一种方式是写出所有可能性，并观察哪一个是最好的。下面有四种合理的切断方法：分别对应两个醚键 (a 和 b) 和胺的两侧 (c 和 d)。



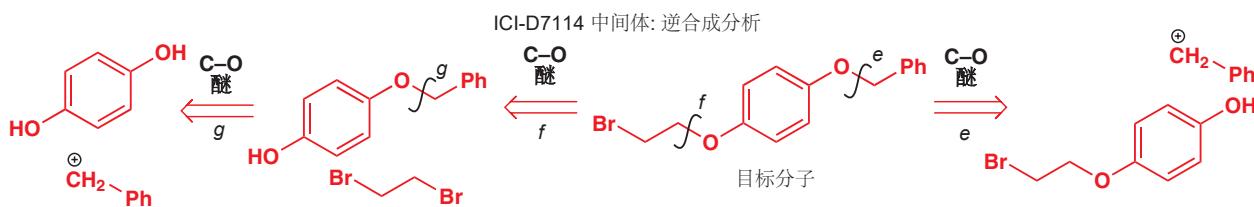
(a) 和 (b) 都会引起化学选择性的问题，因为在碱性氮原子的存在下，使苯酚烷基化会很困难。在(c) 和 (d) 之间，(c) 看似是更好的选择，因为 (d) 之后的下一次切断将会是在  $\text{NH}_2$  基的存在下对 O 的烷基化。为了避免像这样的化学选择性问题，我们会试图将活泼基团的引入放在合成的后期。在逆合成分析方面，可以制定另一条准则。

我们在 Chapter 23 中讨论了这种事。

### ● 准则 3

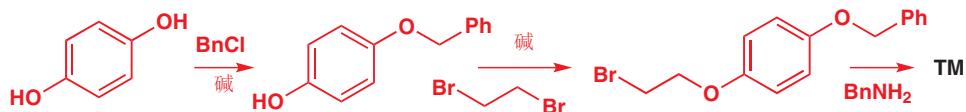
考虑可替代的切断方式，并选择避免化学选择性问题——通常意味着先切断活泼基团——的路线。

这条准则也帮我们思考 ICI-D7114 中间体的下一步逆合成。切断 (c) 使我们得到带有两个醚的化合物，可以继续在 (e) 或 (f) 处切断。



切断 (e) 需要烷基化一种本来就是烷基化试剂的化合物。切断 (f) 则令人满意的多，并得到一种很容易可以继续切断为 4-羟基苯酚的化合物以及 1,2-二溴乙烷。运用准则 3，我们可以说，最好在先切断溴乙基 (f)，然后再切断苄基 (g)，由于溴乙基比苄基活泼，更容易引发化学选择性的问题。

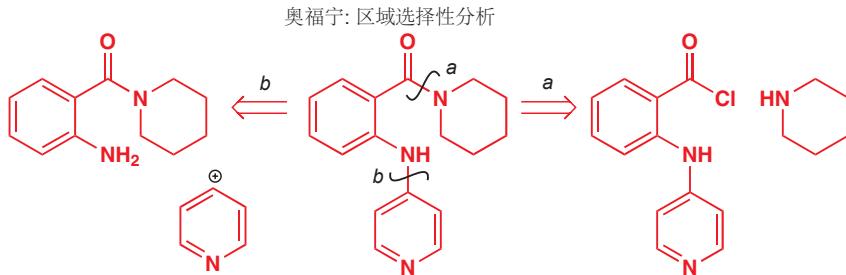
### ICL-D7114 中间体：合成



■ TM 代表目标分子。

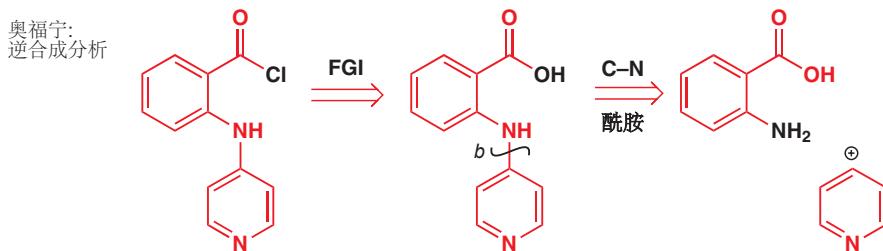
## 官能团相互转化

降压药奥福宁 (ofoxine) 包含一个酰胺和一个胺官能团，我们需要决定先切断哪一个。如果我们先切断仲胺 (b)，就会出现在要在所得的  $\text{NH}_2$  基的存在下构建酰胺的化学选择性问题。

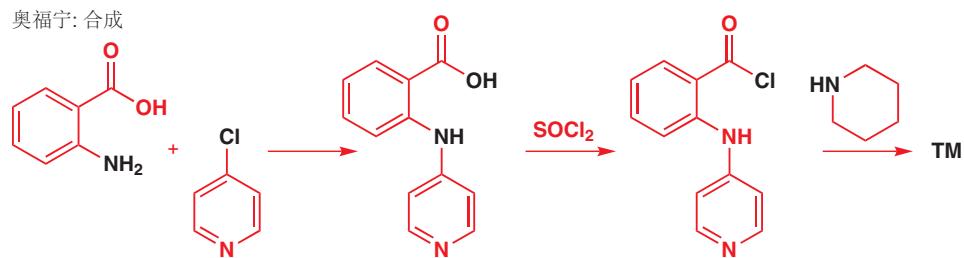


乍一看，切断 (a) 会引发更大的问题，要在酰氯的存在下构筑胺！然而，我们可以从羧酸制取酰氯，羧酸便可以被轻易地切断为 2-氨基苯甲酸 (氨茴酸，anthranilic acid) 和 4-氯吡啶。

我们在 Chapter 22 中讨论了缺电子芳环上的亲核取代反应, Chapter 29 中有更多关于氯代吡啶的细节。



由酰氯到羧酸的逆合成转化并不是真正的切断过程, 因为没有任何东西被切断。相反, 我们称其为官能团相互转化 (functional group interconversion), 或 FGI, 如上方逆合成箭头上所写。官能团相互转化通常辅助着切断过程, 因为下一步反应所需的活泼官能团 (酰氯, 卤原子) 并不一定要在化合物被进一步切断时仍然存在, 它会引发化学选择性问题。同样, 在目标分子含有不容易切断的官能团时, 它们也是有用的。



通过使用合适的试剂, 或合适的一系列试剂, 几乎所有的官能团都可被转化为其他东西。您应该已经对合理的官能团相互转化有了一定得了解。它们主要分为氧化、还原, 和取代三类 (Chapters 10, 11, 15, 和 23).

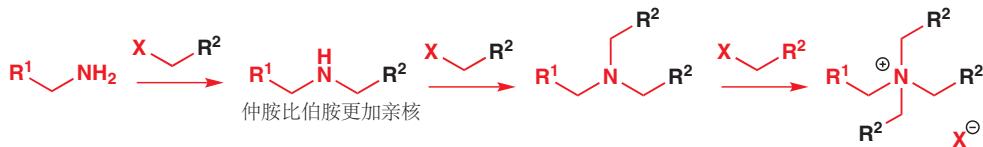
### 使用官能团相互转化的胺合成

胺的合成中会引发一种特别的问题, 对于明显的切断方式, 只有某些特定情境下才是成功的。

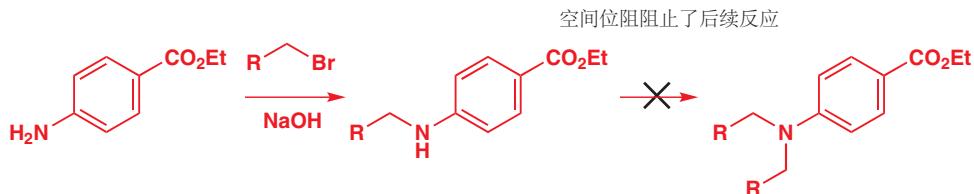


我们在 Chapters 11 和 23 讨论了这一问题。

问题在于, 产物通常比起始原料更加活泼, 并有发生多次烷基化的危险。



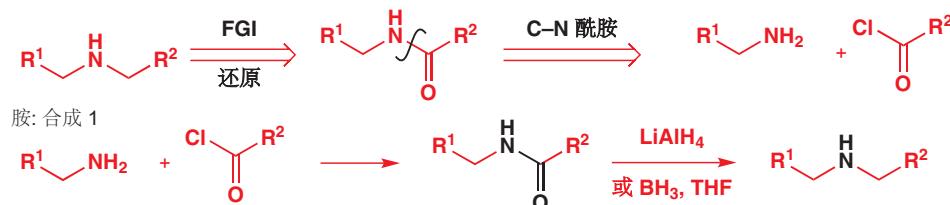
本章的前文提及的几个成功样例, 都或由于空间因素, 或由于电子因素而成为例外, 从现在起, 我们建议您避免按这种方式切断胺。有时, 增加的空间位阻会导致进一步烷基化不利: 这个反应选用西他苯乙酯的原因, 很有可能就是如此。



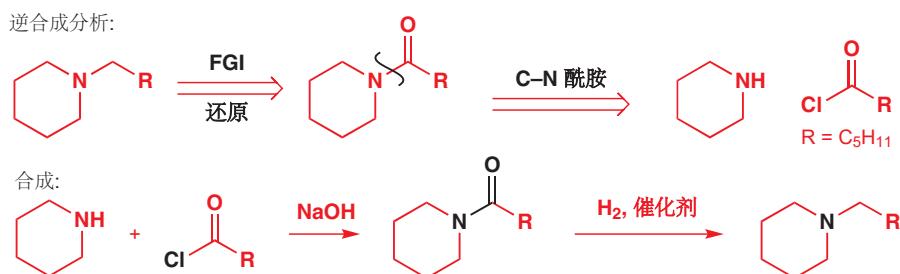
如果烷基化试剂包含诱导吸电子基团，产物则会没有起始原料活泼——在 p. 699 的 ICI-D7114 合成中，苄胺仅被溴代烃烷基化了一次，这是由于芳氧基的吸电子效应所致。

那么有什么替代方法吗？主要有两种，它们都包含官能团相互转化，胺在被切断前都转化为了较不活泼的衍生物。第一种解决办法是将胺转化为酰胺，然后再切断。由酰胺到胺的还原是很可靠的，因此这个 FGI 是合理的。

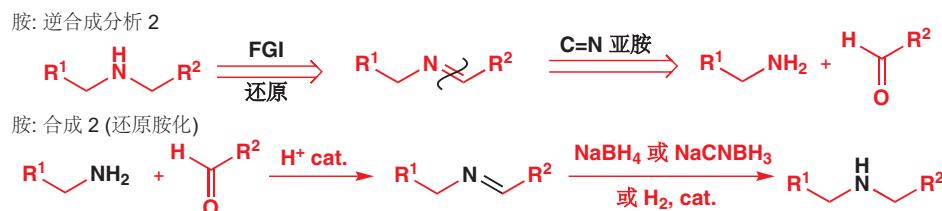
胺：逆合成分析 1



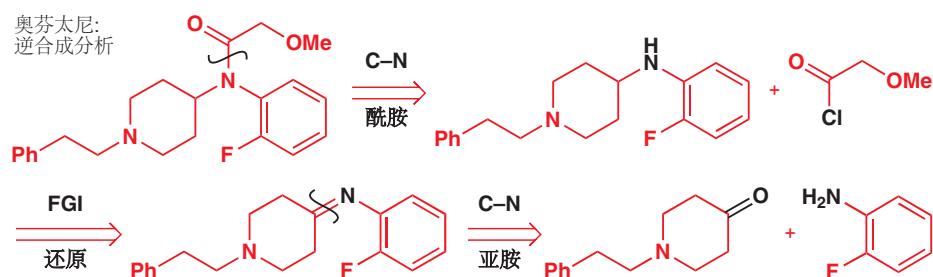
酰胺还原反应法被用于下面这种胺的合成，还原条件为催化氢化。



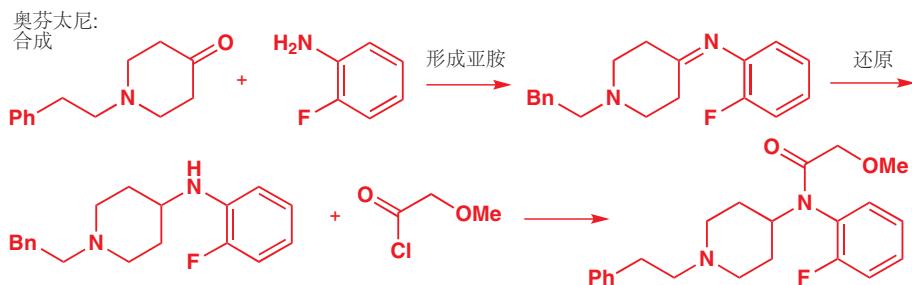
第二种可选的方法是将其转化为亚胺，亚胺可切断为胺加羰基化合物。这种方法被称为还原胺化 (reductive amination) 我们已经在 Chapter 11 中详细地讨论过了。



奥芬太尼 (Ocfentanil) 是一种缺少吗啡的成瘾性的阿片类止痛药。将酰胺切断，可给出一种仲胺，我们可以将仲胺转化为亚胺以切断为一个酮加上 2-氟苯胺。

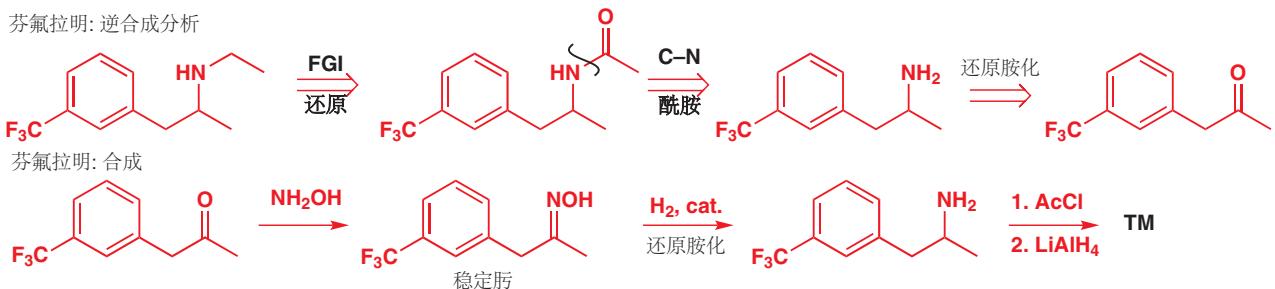


合成过程很明确：还原胺化，然后在仅剩的 NH 基上酰基化。左侧的环中的叔胺不会干扰其中任何一个反应。

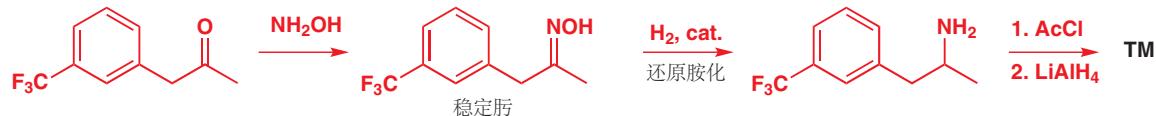


神经活性药物芬氟拉明 (fenfluramine) 有不少种可能的合成路线——如下所示的一种分析，同时使用了酰胺和亚胺的 FGI 方法，也是这种药物制造时使用的路线。注意这种方法中用肟替代了亚胺。N-未取代的亚胺非常不稳定，比具有同样作用的肟不稳定得多，且不易分离。肟通常用  $\text{LiAlH}_4$  还原。

芬氟拉明: 逆合成分析



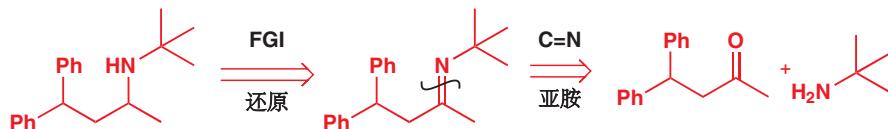
芬氟拉明: 合成



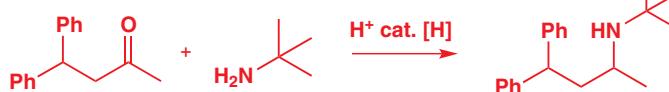
现在，您应当能为仲胺特罗地林 (terodilin) 提出一个合理的分析。其结果位于侧边栏中；请在阅读下文真实的合成过程前，写出逆合成分析，并提出合成路线。

您应当发现，自己可做的选择非常有限：酰胺路线很明显只能在氮旁边有一个  $\text{CH}_2$  基 (由  $\text{C=O}$  还原得到) 时才可以工作，因此我们必须选择用亚胺。

特罗地林: 逆合成分析



特罗地林: 合成

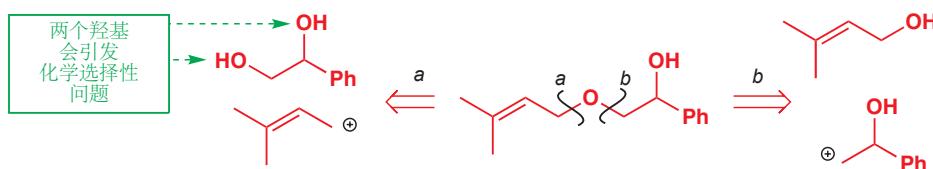


在特罗地林的合成中，亚胺不必被分离——亚胺的还原快于酮的还原（注：碳氧双键键能大），因此在温和的还原剂（通常是  $\text{NaCNBH}_3$  或催化氢化，注：强的氢负型还原剂会先还原极性更大的酮）的存在下形成亚胺，则可直接给出胺。

## 双官能团切断好于单官能团切断

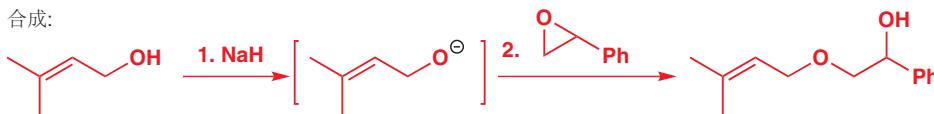
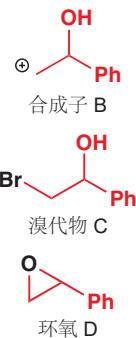
下面是一个在对重排机理的研究中要用到的一个化合物。我们可以在氧原子的任何一边切断，(b) 是更好的选择，因为 (a) 对应的反应不合理：很难在仲羟基的存在下控制烷基化选择性地在伯羟基上发生。

▶ 更多的细节请见 Chapter 23.

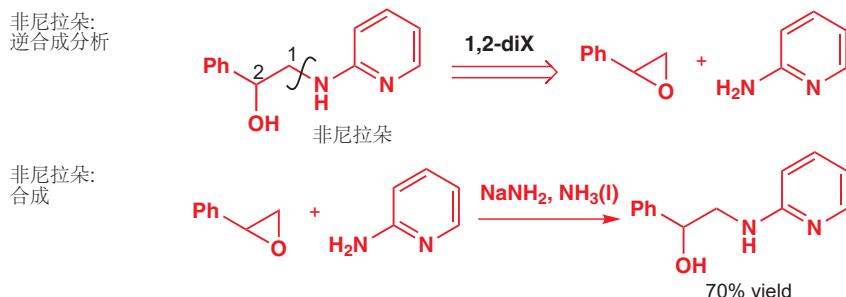


您可能认为，合成子 B 最好的等价物试剂会是溴代物 C。请再机灵一些！一个更好的解决方案是使用环氧 D。在环氧上空阻较小的端基碳原子上的亲核进攻可以为我们提供我们想要的化合物，这也是目标分子的制造中所用的方法。

在使用环氧时，我们已经超越了我们目前为止所讨论过的切断方法，因为我们用一个官能团帮助切断了另一个官能团——换句话说，我们注意到了醇与我们想要切断的醚相邻，并且还设法将它们涵盖在了一步切断中。这类切断过程被称作双官能团切断 (two-group disconnections)，您应当时刻瞭望着使用它们的机会，因为它们是回到简单起始原料的有效方法。我们称这种环氧切断方法为 1,2-切断，因为这种双官能团切断过程中的两个官能团处于 1,2-关系。



药物分子通常都含有 1,2-关系的官能团：2-氨基醇 就是其中重要的一类。例如非尼拉朵 (phenyramidol) 是一种肌肉松弛剂。简单的双官能团切断可使之回到 2-氨基吡啶 和氧化苯乙烯 (styrene oxide)。



■ 您们当中擅长观察的人现在可能会对这个合成能成功的原因提出疑问——总的来说，我们通过伯胺与环氧的烷基化制取了一种仲胺——这正违反了我们在 p. 700 页给出的建议。用环氧进行的烷基化通常在第一步后就停止，因为产物中诱导吸电子的羟基会使之比起始原料更不亲核。在 p. 699 ICID7114 中间体的合成中，同样的效应阻止了胺多次烷基化。

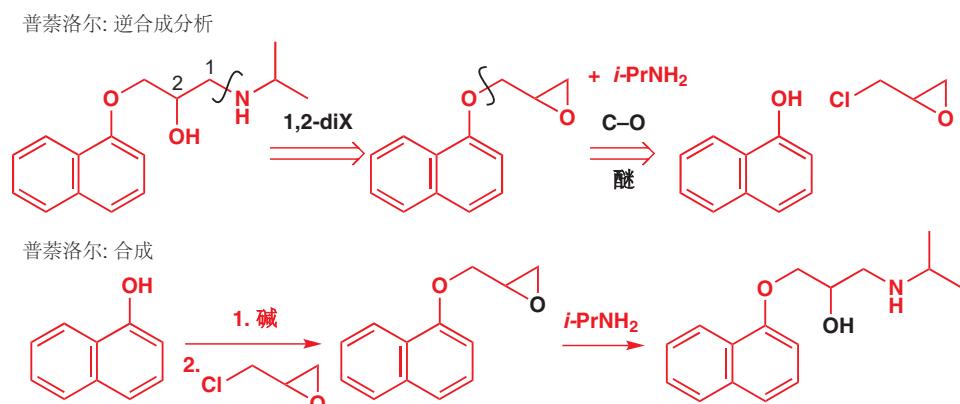
注意我们在箭头上写下的“1,2-diX”代表它是一个双官能团 (“diX”) 切断——我们同样为起始原料标了号，以表明 1,2-关系。在这样的简单的例子中，标号看起来可能微不足道，但它会是您书写逆合成分析的过程中有用的一部分，也能帮助您发现设计双官能团切断的机会。

## 1,2-切断

药普萘洛尔物 (propranolol) 是一种用于降血压的  $\beta$ -受体阻滞药，它曾是世界范围内最畅销的药物之一。它的结构中含有两个 1,2-关系，但最好先切断更活泼的胺。第二步切断不能再利用环氧，但它可以被简单地切断为 1-萘酚 和环氧氯丙烷 (epichlorohydrin)，环氧氯丙烷是这类化合物的一个常用的起始原料。

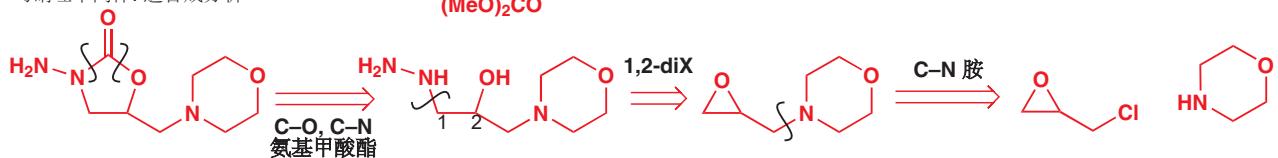
## 环氧氯丙烷

环氧氯丙烷是制造 1,2,3-取代化合物有用的起始原料。环氧比 C–Cl 键更加亲电，合成中第一步的机理是令人震惊的。

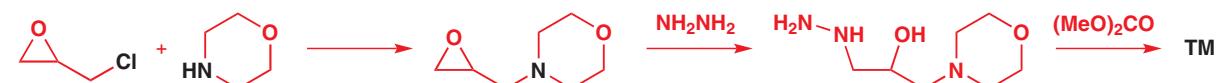


吗硝唑 (Moxnidazole) 是一种抗寄生虫药物，我们的下一个目标分子是这种药物的一个重要的合成中间体。很明显，第一步切断的应是氨基甲酸酯基，随之会得到两个 1,2-关系。其中一种 1,2-diX 切断会给出可以通过吗啉和环氧氯丙烷制取的环氧。

吗硝唑中间体: 逆合成分析



吗硝唑中间体: 合成



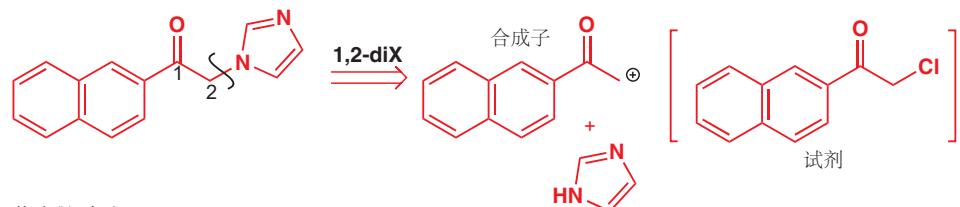
### 有羰基化合物的 1,2-切断



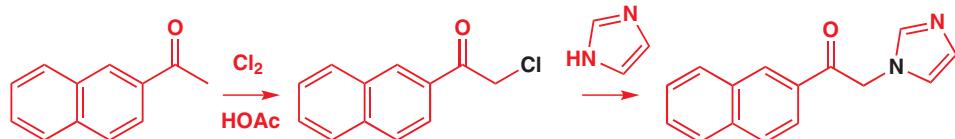
就像环氧是合成子 A 有用的试剂一样， $\alpha$ -卤代羰基化合物 也是该合成子的羰基等价物，合成子 B 有用的试剂。我们可以考虑用双官能团切断得到这个合成子，因为  $\alpha$ -卤代羰基化合物 可以很容易地通过酮、酯，或羧酸的(酸促)卤代反应制取(见 Chapter 20)，并且，卤原子邻位的羰基也使之面对亲电试剂尤为活泼(Chapter 15)。

萘咪酮 (Nafimidone) 是一种抗惊厥药物，明显可以运用这类双官能团切断过程。 $\alpha$ -氯代酮可以简单地通过氯代反应制取，并且即使仅用弱碱(Chapter 8)也能快速而有效地与杂环咪唑发生取代反应。

萘咪酮: 逆合成分析

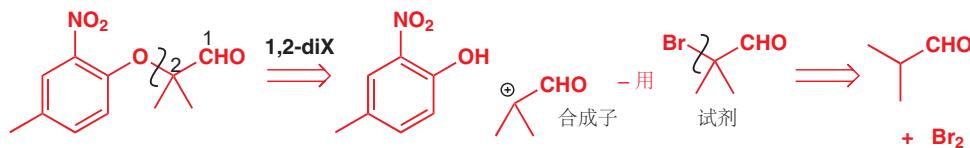


萘咪酮: 合成



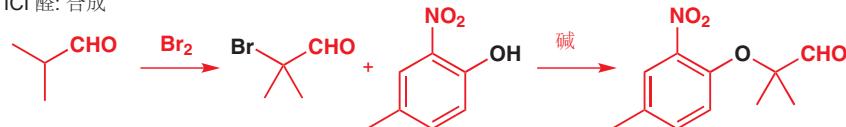
ICI (英国帝国化工集团) 在开发一种血栓素拮抗剂 (thromboxane antagonist) 时需要用到下面的醛。双官能团切断会给出可由异丁醛制取的 2-卤代醛。

ICI 醛: 逆合成分析



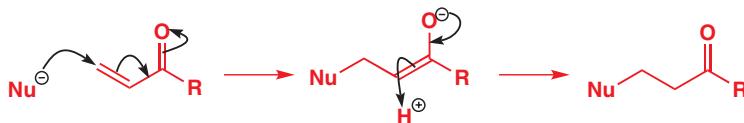
上述合成需要一种羰基化合物在酸性溶液中正常的溴代反应，而下一步则需要一个在叔中心上发生的很不寻常的  $S_N2$  反应。反应能发生是由于醛基的活化作用 (Chapter 15)，这也是在这类合成过程中两个官能团一同工作的进一步证据。

ICI 醛: 合成

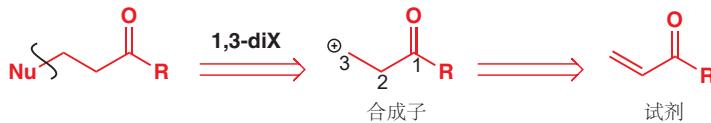


### 1,3-切断

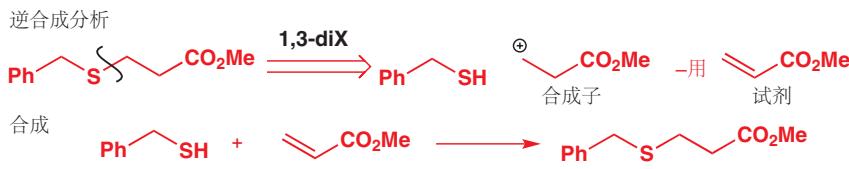
在 Chapter 22 中，您了解了  $\alpha,\beta$ -不饱和羰基化合物发生共轭加成的方式——如下的反应：



因此双官能团 1,3-切断 是可行的，它们对应于这种正向反应。这些 Michael 受体含有与羰基相邻两个原子的亲电位点，因而对应于这个合成子。

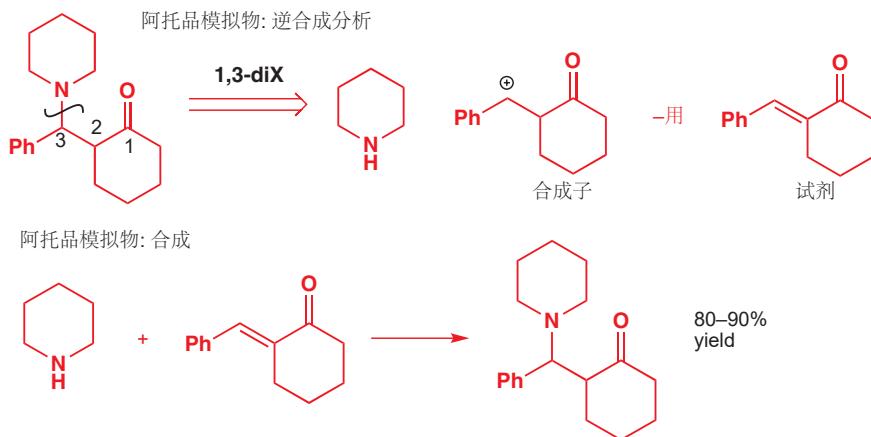


这类反应只有在烯烃与一个吸电子基团共轭时才是可用的——吸电子共轭基通常是羰基，但也可以是硝基、氨基等 (Chapter 22)。这类切断仅在这种氧化程度是可用的。例如我们可以在这种硫醚上使用 1,3-切断。



记住，不是所有的亲核试剂都会成功地经历 Michael 加成——当您设计这种类型的 1,3-切断时，这一点必须牢记在脑海中。大多数可靠的亲核试剂基于氮、硫和氧 (Chapter 22, 注：软)。我们的第二个例子是一种与“致命的茄属植物 (deadly nightshade, 指颠茄)”药物，具有抑制不自主肌肉运动的效果的阿托品 (atropine) 在结构上相似的胺类。胺和酮羰基间存在 1,3-关系，1,3-切断可使之回到哌啶和一个不饱和酮。

不要试图用  $\beta$ -卤代酯作为这种合成子的等价物！它们很难制取，并且不稳定，会经历迅速的 E1cB 消除 (见 Chapter 17, 注：得到不饱和酯)。



► 本章中，我们还将讨论该合成的起始原料，及其他 $\alpha,\beta$ -不饱和羰基化合物的切断方式。

### 总结

在我们离开 C–X 切断，并前去着眼于 C–C 切断前，我们应复习一下前文提到的重要点。我们已经提出了选择切断方式的三条准则。在我们学习了双官能团切断后，我们可以增添第四条：

#### ● 好的切断的准则

- 1 切断必须对应于已知、可靠的反应。
- 2 对于由两个连接在杂原子上的片段构成的化合物，在杂原子旁切断。
- 3 考虑可替代的切断方式，并选择避免化学选择性问题——通常意味着先切断活泼基团——的路线。
- 4 尽可能运用双官能团切断。

双官能团切断相比单官能团切断，更有效地减少了目标分子的复杂性，您应当时刻关注它们。您会在讨论 C–C 键切断方式的下一节中，了解更多双官能团切断。

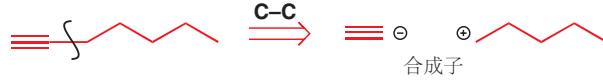
### C–C 切断

到目前为止，我们设计的所有切断均是对于 C–O, C–N, 或 C–S 键的，但当然了，有机合成中最重要的反应是通过形成 C–C 键，构建起碳骨架的反应。我们可以用我们在分析 C–X 切断时几乎相同的方式分析 C–C 切断。例如，请考虑如何制得侧边栏中展示的化合物，它是一种康乃馨香水的合成中间体。

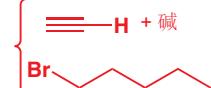


唯一的官能团是三键，我们会运用炔烃的化学考察切断的位置。您知道，炔烃的烷基化是一个可靠的反应，因此明显的切断位置是在三键旁边。

#### 康乃馨香水中间体: 逆合成分析



试剂



► 炔烃阴离子的烷基化已在 Chapter 9 中描述过。

#### 康乃馨香水中间体: 合成



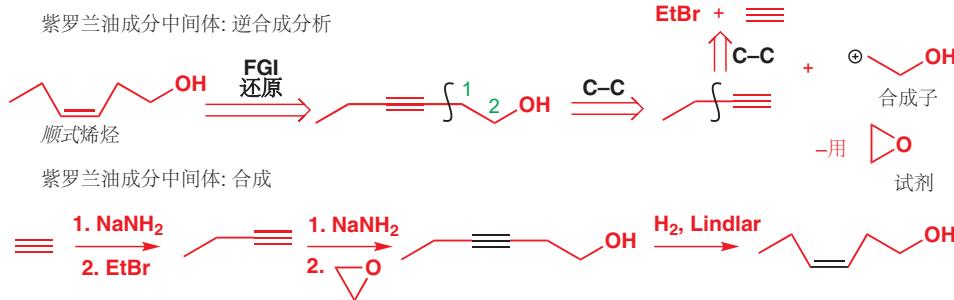
炔烃作为合成中间体尤其有价值，因为它们既可以被还原为顺式双键，又可以被还原为反式双键。



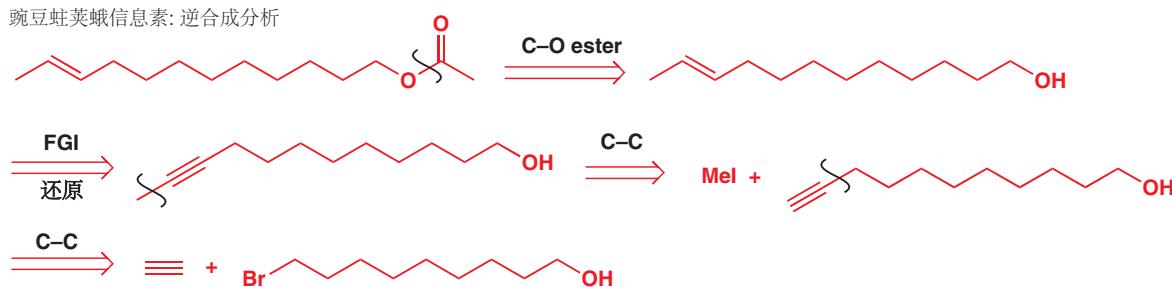
您在 Chapter 27, p.681 中了解了这些还原反应。

对于含有孤立双键的目标分子，将 FGI 为炔烃的考虑作为逆合成分析的开始通常是一个很好的主意，因为这样 C-C 切断就会变得很容易。下面的顺式烯烃是紫罗兰油 (violet oil) 中一种成分的合成中间体。FGI 为炔烃后，可显露出另两个后续的切断方法，利用炔烃的烷基化。其中第一个，是对于有 1,2-关系的 OH 基和炔烃间的切断，因此所用的试剂当然是环氧。

当然，双键的切断还要很多其他方式：待会您便要考察一种切断与羧基共轭的双键的方法。Chapter 27 阐明了制取双键，和控制它们的立体化学的可用方法。



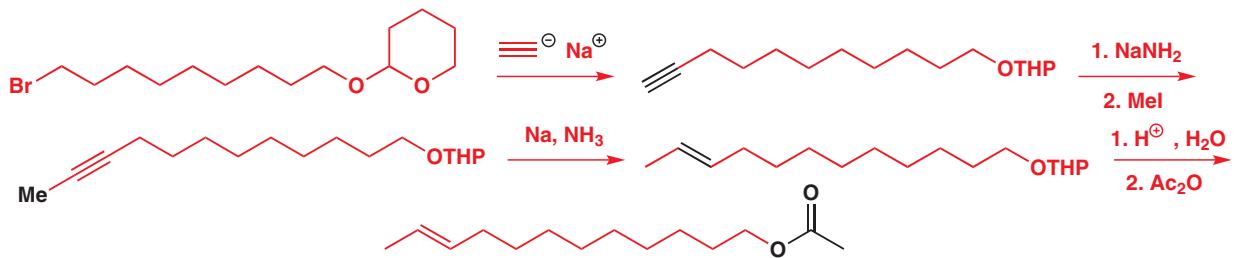
下一个例子是豌豆蛀荚蛾 (pea-moth) 的信息素，可用于捕捉这些昆虫。首先切断酯基，然后将反式双键 FGI 为炔烃。



在炔烃的两边切断，则可得到一个溴代醇的烷基化试剂。在该信息素的合成中，最好将羟基保护为 THP 醚。您应当能想到其他的——进行得可靠，并可为切断提供良好的基础的烷基化类型的反应——例如酯或酮的烯醇盐的烷基化反应 (Chapter 25)。

Chapter 23 中详细地讨论了保护基，THP 位于 p. 551.

豌豆蛀荚蛾信息素：合成



## 1,2 C-C 切断

下一种酯，是镇静剂罗谷亚胺 roglitimiide (待会您会见到完整的合成路线) 的合成中所需的中间体。将乙基切断，因为乙基可以很容易地被酯烯醇盐的烷基化引入。

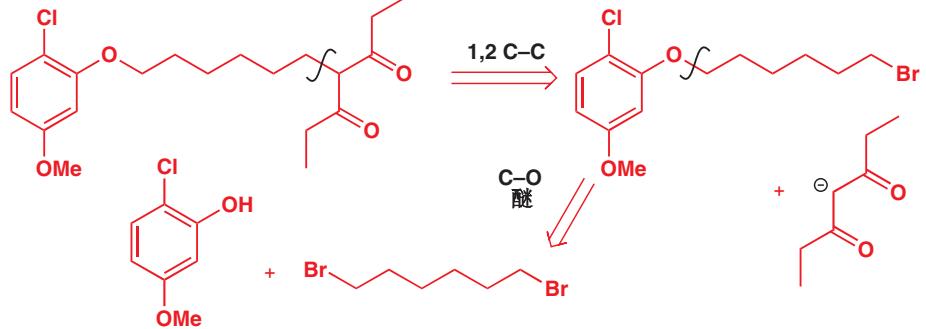
罗谷亚胺中间体: 逆合成分析



我们将这个切断过程标记为“1,2 C–C”，因为在羧基邻位的碳原子上形成了新的 C–C 键。想要发现这种切断方法，您需要寻找在羧基 2-位置的烷基。

阿立酮 (Arildone) 是一种防止小儿麻痹病毒和单纯疱疹病毒“展开”它们的 DNA 的药物，进而使他们变得无害。它的结构特征正是您应当在寻找的：一个与羧基相邻的支链。

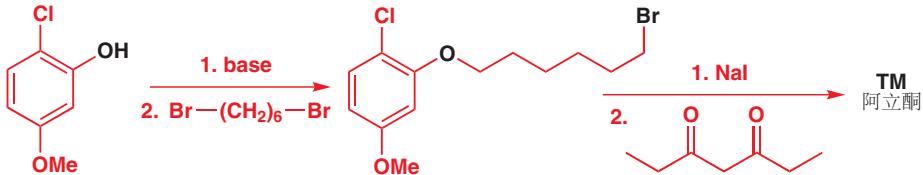
阿立酮: 逆合成分析



如果您不理解为什么，请回顾 Chapter 25。

由于存在两个羰基，烷基化应当非常容易，仅需选用像甲氧基阴离子这样的碱即可。醚的切断很明显。在阿立酮的合成中，烷基化所选用的是碘代烷。

阿立酮: 合成



我们在 Chapters 20 和 25 中介绍了缩苹果酸酯 (即丙二酸酯，malonate esters)，它是控制羧基烯醇化有用的方法。先烷基化再脱羧的流程，意味着我们可以将乙酰乙酸酯和缩苹果酸酯视为下面这些合成子的等价物。

■ 读过 Chapter 26 后，您应当能够说出丙酮本身的烯醇盐不是这一反应好的选择的原因。

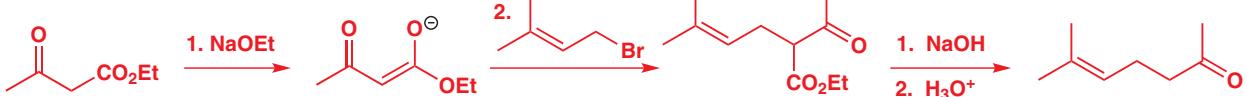


下面的不饱和酮是  $\beta$ -胡萝卜素 ( $\beta$ -carotene)、维生素 A，和其他相似分子重要的工业合成前体。利用羧基的切断方式，可得到可用乙酰乙酸酯作为其好的试剂的合成子。

胡萝卜素前体: 逆合成分析



胡萝卜素前体: 合成



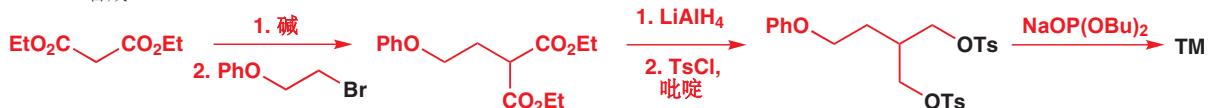
下面的有机磷化合物，belfosil，是一种  $\text{Ca}^{2+}$  通道阻滞剂。您还没见过太多有机磷化合物，但您应当通过类比本章前文提到的硫醚，推断出 C-P 键会是好的切断位点。我们可选溴离子作为离去基团，但溴代烃不方便进一步切断，因此我们回到更通用的二醇上——在正向合成中，我们会需要一个额外的步骤将 OH 基转化为离去基团。二醇仍然没有明显的切断方式，但将其 FGI 为酯氧化程度，则会显露出一个缩苹果酸酯衍生物。

#### belfosil: 逆合成分析



在合成中，二醇被转化为双对甲苯磺酸酯 bis-tosylate (如果您忘记了对甲苯磺酸酯和甲磺酸酯，请回顾 Chapter 15)，并与一个磷亲核试剂结合。

#### belfosil: 合成



注意，在逆合成分析中，我们将基于磷的官能团切断为了醇，而没有切断为比如说卤代烃。氧基官能团 (醇、醛、酮、酯和酸) 有一个普遍的性质——通用性。它们很容易在彼此间通过氧化还原，或取代反应相互转化。此外，您将要遇到的 C-C 切断中，很多都对应于氧基官能团的反应，尤其是羰基的反应。面对目标分子中一个不寻常的官能团，最好的选择便是将其转化为相同氧化程度的氧基官能团——这通常会使得随后的 C-C 切断更简单。因此我们增添一条新的准则。

#### ● 准则 5

转化为氧基官能团以方便 C-C 切断。

到目前为止，您遇到的每个情况中，我们都利用了分子中存在的官能团，来帮助我们用 1,2 C-C 切断方式切断 C-C 键。您可以在炔烃、羰基化合物，和烷基化的芳环中寻找 1,2 C-C 切断方式。并且，如果目标分子不是一个羰基化合物，那么请思考，是否有官能团，例如羟基，可以转化为羰基 (如我们在 belfosil 的合成中所做的)。



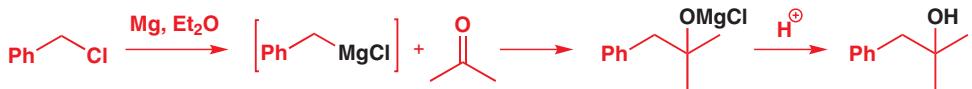
## 1.1 C-C 切断

所有的这些切断方式，都依赖于一种碳亲电试剂和一种亲核的官能团的反应。而另一种选择，用碳亲核试剂 (例如格氏试剂) 与亲电的官能团的反应，则会允许我们在醇上实施 C-C 切断。例如下一页的，具有令人回忆起丁香的香味的化合物，它 (不像许多其他的，是醛或酮的香水) 对碱 (alkali) 稳定，因而是肥皂中有用的香水。



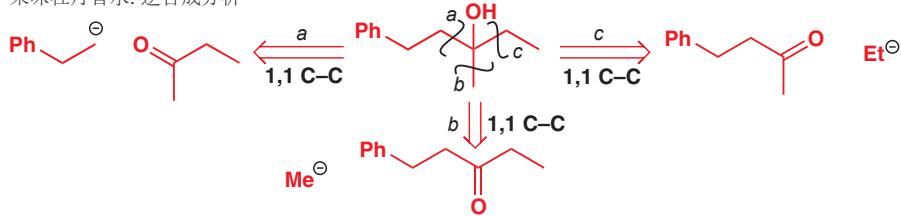
让我们着眼于唯一的官能团，羟基，它可以在那里切断呢。在羟基旁边切断得到的合成子，所对应的明智的试剂分别是格氏试剂和丙酮。该香水便是由苯氯和丙酮依这种方式制造的。注意我们将这种切断方式标记为 1,1 C-C，因为所切断的键与羟基官能团处在同一碳原子上。

丁香香水: 合成



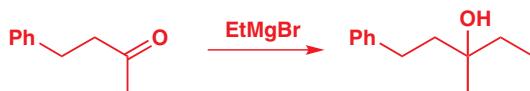
而下面这种类似的醇含有“类似牡丹的水果气味”，可以通过三种方式切断。

果味牡丹香水: 逆合成分析



切断 (c) 可使之回到一种酮，这种酮又可以很便宜地由丙酮和苯甲醛开始得到，这是它的合成所选用的路线。

果味牡丹香水:  
合成



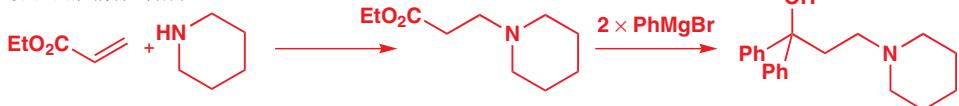
### 双键的切断可能是一条捷径

在连接羟基的碳上有两个完全相同的基团的叔醇，通常通过两当量的格氏试剂与酯制取。抗组胺剂化合物芬哌丙烷 (fenpiprane) 的一个叔醇前体的合成就为此提供了一个例子：由于含有两个 Ph 基，该叔醇可被切断为 酯 + 格氏试剂。所需的酯包含 1,3 官能团关系，因而可以切断为胺加 Michael 受体。

芬哌丙烷前体: 逆合成分析

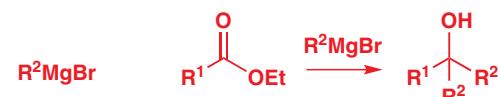


芬哌丙烷前体: 合成



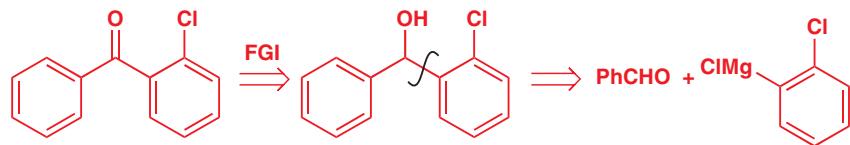
► 我们在 Chapter 10 中介绍了几种完成这类反应的方法。

格氏试剂对酯加成两次的事实告诉我们，**酮**以这种方式切断通常是不可靠的，因为格氏试剂还会继续加成到酮上。

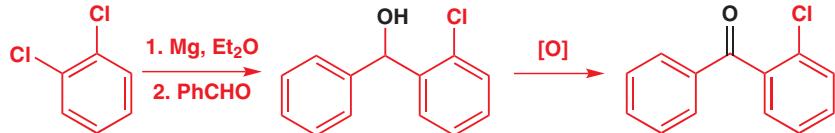


对于酮来说，可选的切断方法是先转化为醇氧化程度，然后再切断。这是氯苯胺丙醇 (chlorophenol) 的合成的起始原料所选用的制取方法。

氯苯胺丙醇起始原料：逆合成分析

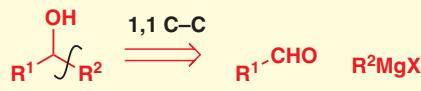


氯苯胺丙醇起始原料：合成

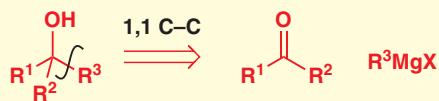


### ● 总结：利用格氏试剂的 1,1-切断

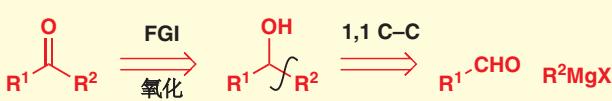
仲醇



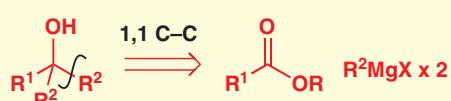
叔醇



酮



$R^2 = R^3$  的叔醇

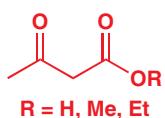


## 可用的起始原料

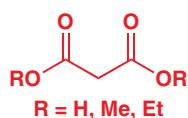
对于 p. 710 的“果味牡丹香水”，三种路线中的任意一种都可得到可接受的合成，最终选择 (c) 的关键在于由可用化合物/可购买的化合物 (available compounds) 合成起始原料的容易性。但您该如何知道哪些化合物会是可用的呢？本章的前文中，我们一直在回避这个问题，我们所做的逆合成分析常常也是不完整的，因为所提出的起始原料本身仍需在实验室中合成。然而，从现在起，我们会将每个分子一直分析到可用的起始原料，来帮助您对什么是可用的，什么是不可用的有所感觉。

绝对确定你能买到某种化合物的唯一方法是在供应商目录中查找它，这也是化学家在评估评估几条可能的合成路线时会去做的事。一条很好的经验法则是：**至多包含六个碳原子和一个官能团**（醇、醛、酮、酸、胺、双键，或卤代烃）**的化合物**通常是可用的。对于有较重支链的化合物，这不一定正确，但对于大多数含有这些官能团的直链化合物，可以买到的则至多含有八个左右碳原子。当然，还要很多其他可用的化合物，包括一些双官能团化合物。下面是它们中的一些例子。

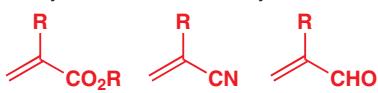
乙酰乙酸乙酯



缩苹果酸酯



丙烯酸酯 ( $R = H$ )；甲基丙烯酸酯 ( $R = Me$ )  
acrylates // methacrylates



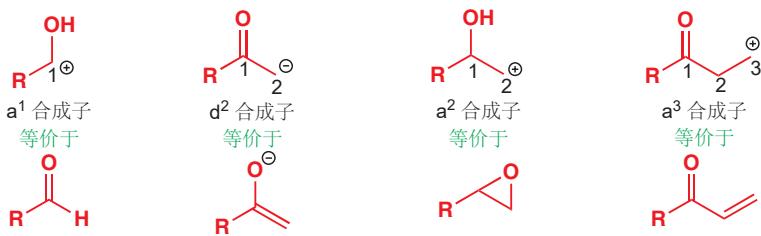
随着您对我们使用了哪些化合物做起始原料的观察，您很快就会开始明白哪些化合物是可用的。

供应商目录可以免费得到，并且也是非常有用的工具书。您应当考虑获取一本。另外，大多数化学部门都提供可通过结构搜索的在线和 CD 目录。

## 供体和受体合成子

现在，您已经遇到过形形色色的合成子，将它们分类为给体 (*donor*) 和受体 (*acceptor*) 合成子对我们是有帮助的。我们称被负电性极化的合成子为给体合成子，符号为 “d”；被正电性极化的合成子为受体合成子，符号为 “a”。

我们还可以根据官能团与反应位点的相对位置，对合成子进一步分类。下面图表所示的第一种合成子，对应于醛，由于它是一个受体，并且在与活性中心相同的碳上携带官能团，因而被称为一个  $a^1$  合成子。第二种给体合成子的反应位点在羰基的 2-位置，因而被称为  $d^2$  合成子。前文中您还遇到了另两类合成子，对应于环氧化与 Michael 受体，我们可以将其分类为  $a^2$  和  $a^3$  合成子。



这种术语是有用的，它将合成子还原为了裸露而基本的物件：仅表达它们的极性，和极性所处的位置。它们实际携带的官能团，如您所知，没有那么重要，因为 FGI 常常能使我们将一种官能团转化为另一种。

### ● 合成子被划分为 a (受体) 或 d (给体)

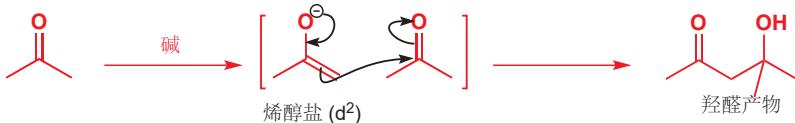
数字表明给体或受体位点与官能团的相对位置。

$a^1$  合成子的一个例子是羰基化合物， $d^2$  合成子的一个例子是烯醇盐或烯醇盐等价物。

## 双官能团 C–C 切断

### 1,3-双官能团化化合物

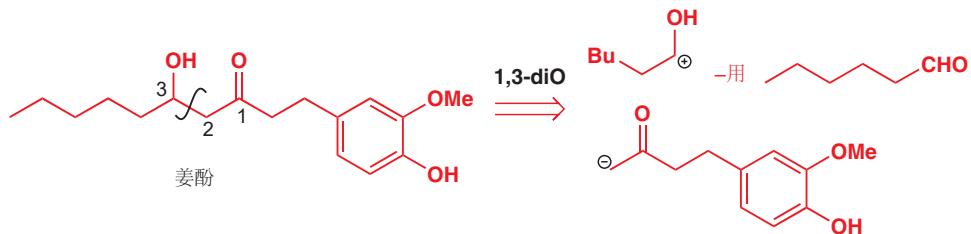
不止格氏试剂能和醛或酮反应，制造醇：烯醇盐也可以做到——我们用 Chapter 26 讨论了这种反应，羟醛反应，和它的变种，以及控制它的方法。



羟醛反应在有机合成中极其重要，因为它可以制得带有处于 1,3-关系的两个官能团的化合物。每当您在目标分子中发现了这种 1,3-关系——请想想羟醛反应！切断过程可以如是表达。

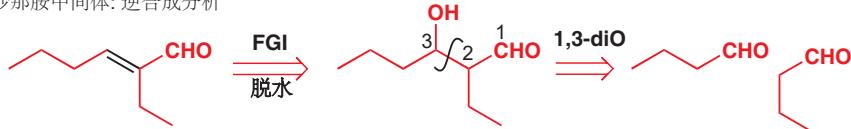


我们将这种切断方法称为双官能团 C–C 切断，因为我们结合利用了 OH 基和 C=O 基指导我们切断。切断过程会得到一个我们会用烯醇盐等价物作为试剂的  $\alpha^1$  合成子，和一种我们会用醛或酮作为试剂的  $\alpha^2$  合成子。Chapter 26 中有很多例子，我们选用了姜酚 (gingerol)。一旦您观察到了 1,3-关系，切断方法就会很明显。



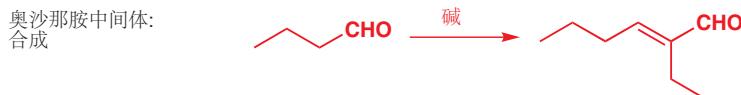
羟醛反应的  $\beta$ -羟基羰基化合物产物通常容易脱水为  $\alpha,\beta$ -不饱和羰基化合物；因此如果您在分子中发现了  $\alpha,\beta$ -不饱和羰基化合物，也应当打算用羟醛反应制取。您首先需要实施一步 FGI，得到  $\beta$ -羟基羰基化合物，然后再切断。

奥沙那胺中间体：逆合成分析

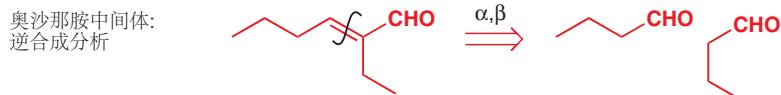


下面的醛是镇静剂奥沙那胺 (oxanamide) 合成的中间体。由于羟醛反应的两个化合物是相同的，并不需要采取特殊的预防措施以阻止副反应发生。在合成中，脱水是自发发生的。

■ 消除通过 E1cB 机理进行，因而很容易——见 Chapters 17 和 26.

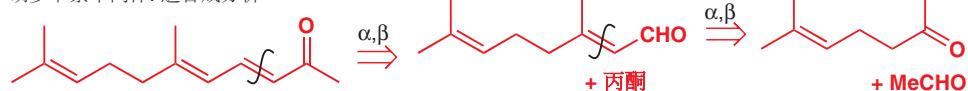


不饱和羰基化合物的切断十分常见，因而通常可用简写表达。



下一个化合物是胡萝卜素的早期合成所需的。它又是一种  $\alpha,\beta$ -不饱和酮，因此我们可以用同样的“ $\alpha,\beta$ ”切断方式。第一部切断所生成的醛仍是  $\alpha,\beta$ -不饱和的，因此我们可以进行另一次  $\alpha,\beta$  切断，得到我们已经讨论过合成路线的酮 (p. 708)。

胡萝卜素中间体：逆合成分析



要求乙醛的烯醇盐与酮发生羟醛反应注定会失败：乙醛本身是非常好的亲电试剂。因此，正向合成中选用酯来发生第一步反应，然后再通过我们在 Chapter 23 中讨论的多种还原方法中的一种，将酯转化回醛。

► 酯通过烯醇锌完成的羟醛反应是 Reformatsky 反应, p. 631 的一个例子。

胡萝卜素中间体：合成



如果您不能理解我们在说什么，那么您必须返回 Chapter 26 并阅读有关羟醛反应的选择性的内容。

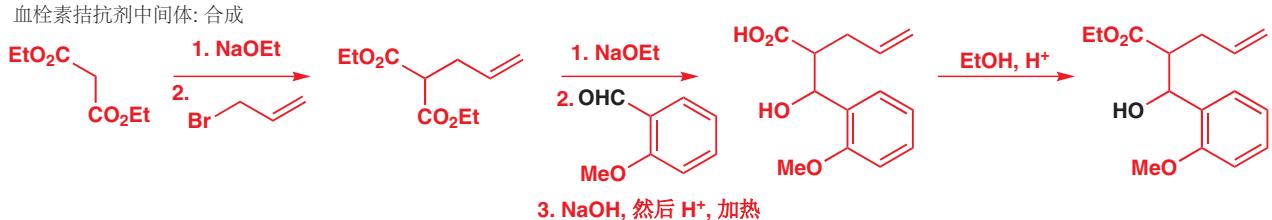
第二个羟醛反应没有选择性的问题，因为醛不能被烯醇化。这个流程中的 Reformatsky 反应说明了一个事实，那就是如您在 Chapter 26 中了解的，酯氧化程度的化合物也可以很好地进行羟醛类型的反应，您同样可以指望以这种方式切断  $\beta$ -羟基或  $\alpha,\beta$ -不饱和的酯、酸、腈。只要记住去寻找 1,3-关系，将官能团转化为氧基形态，然后将其切断为  $d^2$  加  $a^1$  合成子。

下面，是一个化学家在研究用于抑制血栓块形成的血栓素拮抗剂时，所需的化合物。您会立刻发现，酯和羟基间存在 1,3-关系，因此我们需要 1,3-diO 切断。



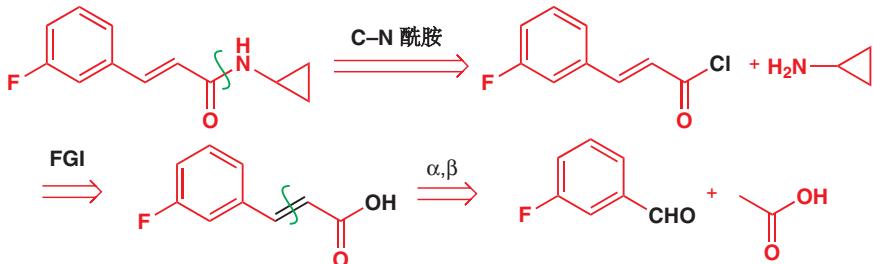
► 缩苹果酸酯的烷基化已在 Chapter 25, p. 596 讨论。

“酯烯醇盐”  $d^2$  合成子的一个很好的等价物是  $\beta$ -二羰基化合物，因为它们可以很容易地切断为缩苹果酸二乙酯和一种烷基化试剂。



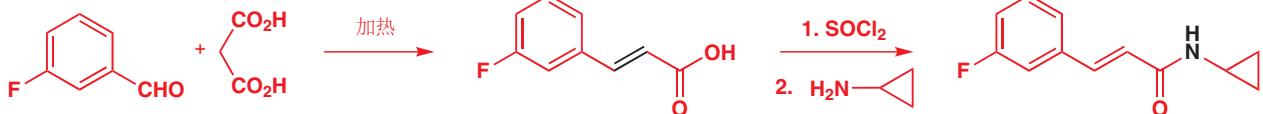
下面的不饱和酰胺被称为环桂氟胺 (cinflumide)，是一种肌肉松弛剂。对酰胺的切断，会得到可通过酸的 FGI 获得的酰氯。然后您会发现有  $\alpha,\beta$ -不饱和羧基，它的切断不过是一种隐蔽的 1,3-diO 切断，继而得到间氟苯甲醛。

#### 环桂氟胺：逆合成分析



用缩苹果酸化学 (缩苹果酸酯路径的变体，脱羧自发进行，p. 630) 完成正向反应还是最好的选择。环丙胺单元 (此处是酰胺) 存在于很多生物活性化合物中，游离胺是可获得的。

#### 环桂氟胺：合成

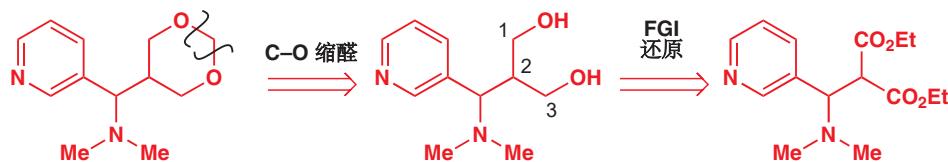


#### 留心隐蔽的官能团关系

镇静剂多匹可明 (doxpicomine) 是一个比先前的目标分子更加困难的问题。乍一看，并没有什么

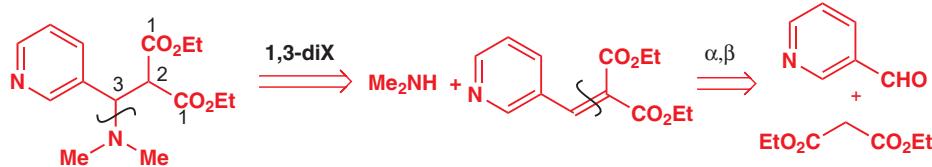
有用的切断方式，尤其是由于分子中不含羰基。然而，若将缩醛去除，就会显露出一个 1,3-二醇，它可由很有前途的二酯通过还原获得。

多匹可明：逆合成分析 I



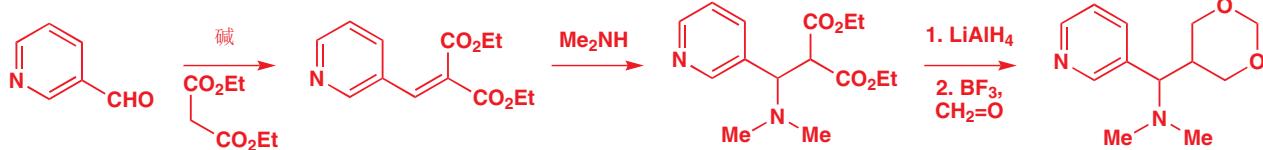
二酯含有 1,3-diCO 关系，可以被切断，但我们要将缩苹果酸的使用先放在心里，并转而去通过 1,3-diX 切断法切断 3-氨基羰基化合物 ( $\text{Me}_2\text{N}$  基于两个酯基都有 1,3-关系) 以得到不饱和酯。这种  $\alpha,\beta$ -不饱和酯便可以很好地切断为杂环醛和缩苹果酸二乙酯。

多匹可明：逆合成分析 II



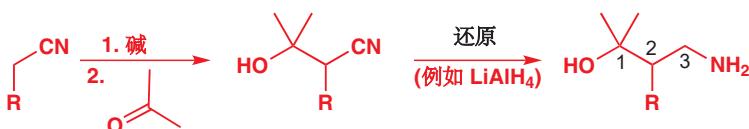
合成路线仅包含四步。使用了双官能团切断的，好的逆合成分析，往往会得到很短的合成路线。

多匹可明：合成

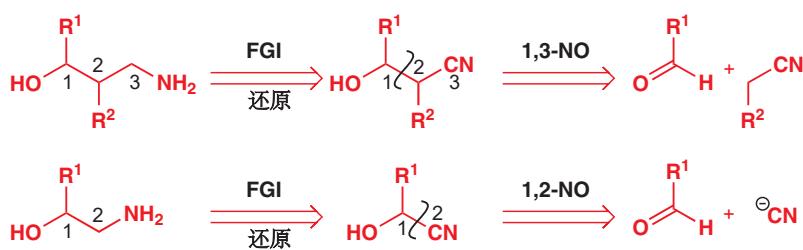


### 1,3-关系的 N 和 O 的羟醛方式的切断过程：I

腈可形成另一类，与醛和酮经历羟醛类型的加成的重要的化合物。因为腈可以被还原为胺，这个反应也是另一类合成 3-氨基醇的有用途径。



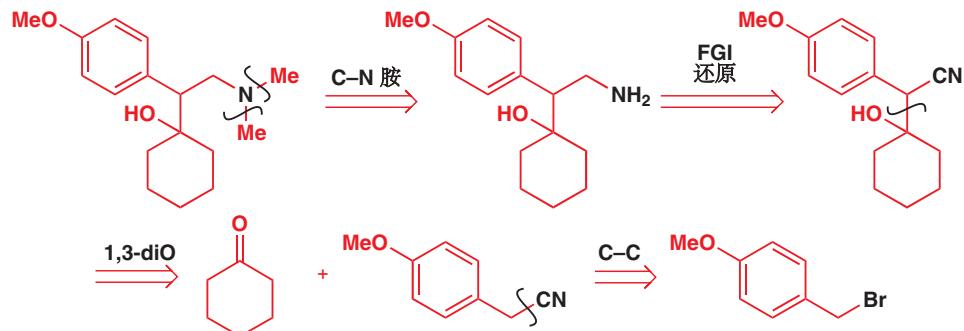
这个反应，与氰醇的还原反应 (Chapter 6) 相结合，意味着不管是 1,3- 还是 1,2-关系的 N 和 O，都可以由腈获得。



文拉法辛 (Venlafaxine) 是一种抗抑郁药，像很多神经活性剂一样，也是一种氨基醇。其中，两个官能团处于 1,3-关系，因此我们打算用 1,3-diO 切断方法。通常，您会需要将胺转化为醇，但

若能发现使用腈的机会，您就可以避免这种额外的步骤。首先要去除两个 N-Me 基。

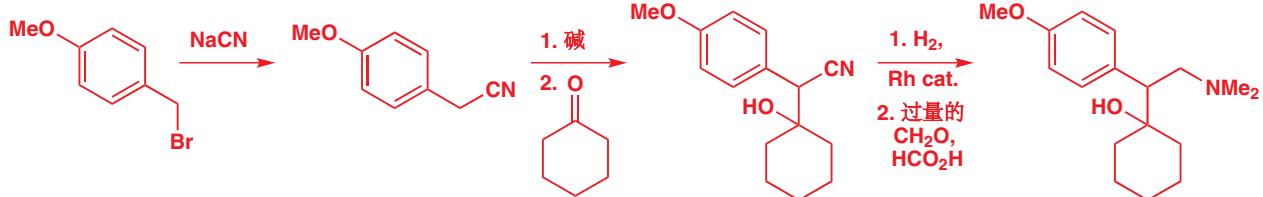
文拉法辛: 逆合成分析



■ 这种通过还原胺化在伯胺上添加两个甲基的有用方式有时被称作 Eschweiler—Clarke 反应 (Eschweiler—Clarke reaction)。更多甲酸做还原剂的内容，见 Chapter 41, p. 1116.

在正向合成中，腈的还原最好用氢气和一种金属 (Rh) 催化剂完成。最后伯胺的甲基化通过亚胺和亚铵离子完成 (见 Chapter 23)，这可以阻止其他不想要的烷基化反应。试剂为过量的甲醛 ( $\text{CH}_2=\text{O}$ ) 和做还原剂的甲酸 ( $\text{HCO}_2\text{H}$ )。

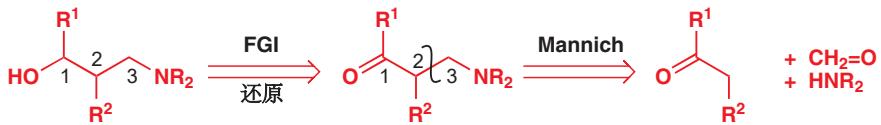
文拉法辛: 合成



### 1,3-关系的 N 和 O 的羟醛方式的切断过程: II——Mannich 反应

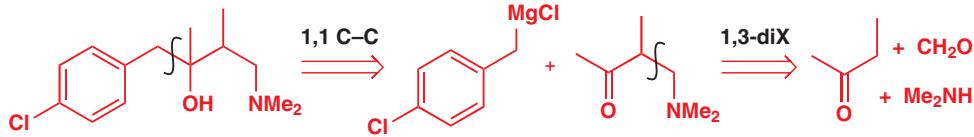
另一种用于制取与羰基有 1,3-关系的胺的重要方法是 Mannich 反应。您在 Chapter 26 中了解了这个反应，它为甲醛的羟醛反应提供了可靠的方式。由于胺是被直接引入，而非由腈还原得到的，因而两个烷基在开始时便可以存在。您可以将其与上文的方案进行对比。

Mannich 切断方式

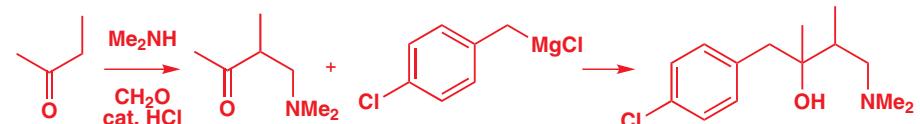


我们的例子是氯丁替诺 (clobutinol)——一种止咳药。先用 1,1 C-C 切断方法切断叔醇，这一步提供了可用 Mannich 反应制取的 3-氨基酮。产物是非对映体的混合物。

氯丁替诺: 逆合成分析

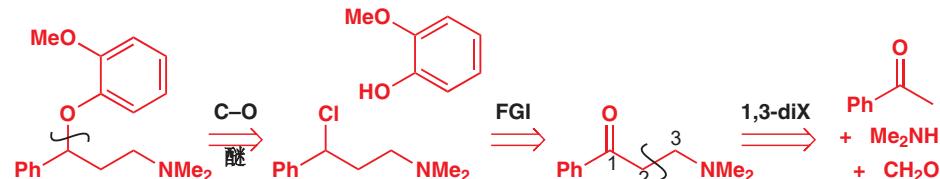


氯丁替诺: 合成



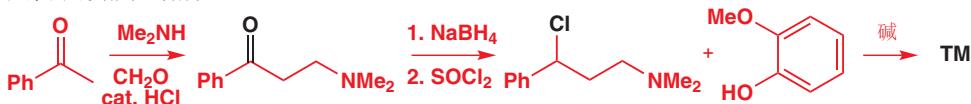
您会立刻发现，下面的抗抑郁药尼索西汀 (nisoxetine) 的类似物含有 1,3 关系，但不幸的是，我们不能将它直接切断为氨基醇，这样做会需要在富电子芳环上发生亲核取代反应。我们需要在另一侧切断醚，得到氯代烷。

尼索西汀类似物：逆合成分析



运用准则 5 (p. 709)，我们想将卤原子转化为氧基官能团，明智的方法是选择酮。这个化合物的 1,3-切断 对应于一个 Mannich 反应。由于 Mannich 反应直接生成胺，这也是另一个不需要将胺 FGI 为醇的例子。

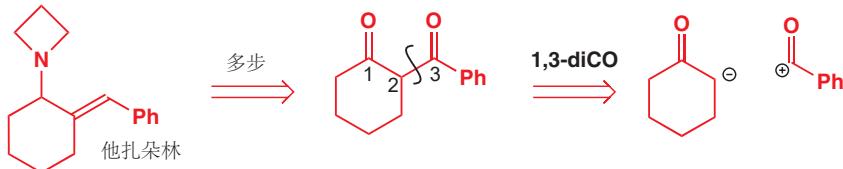
尼索西汀类似物：合成



### Claisen 酯切断: 1,3-diO 关系的两个羰基

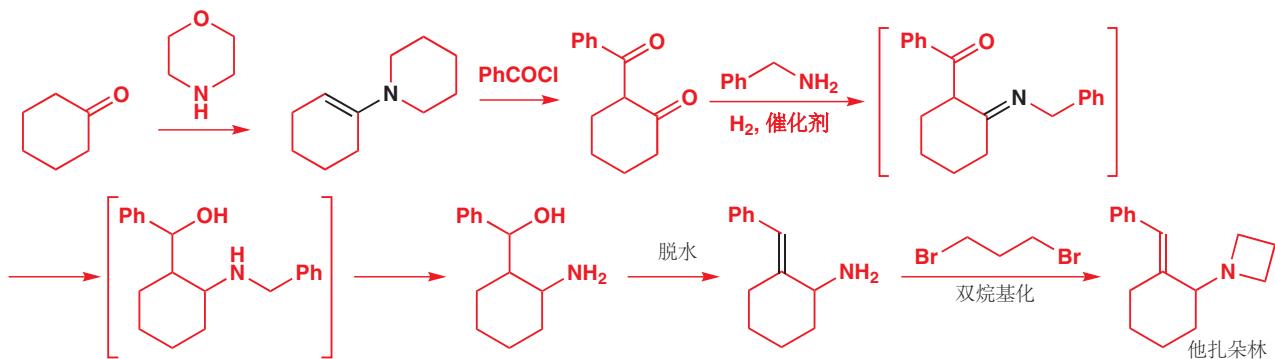
1,3-二酮可用以相似的方式被切断：这时切断过程对应于一个 Claisen 缩合反应，结果仍是 1,3-diO，您需要寻找的也是 1,3 关系。合成子仍是 d<sup>2</sup> 加 a<sup>1</sup>，但其中 a<sup>1</sup> 合成子上升到了酯氧化程度。二酮是抗抑郁药他扎朵林 (tazadolene) 合成中的起始原料。1,3-二酮结构的切断往往需要对位置的选择，您应当根据准则——(a) 对应最可靠的反应，(b) 得到最简单的起始原料——做出选择。本情况下，切断为环己酮是更好的选择。

他扎朵林起始原料：逆合成分析



合成路线是有趣的，烯胺酰基化后，再由与苄胺 (PhCH<sub>2</sub>NH<sub>2</sub>) 的还原胺化形成 C–N 键，灵巧地引入氨基，而后在氢解的作用下同时还原酮和亚胺，形成 N-苄基键 (Chapter 23)。脱水和两次烷基化即可给出他扎朵林 (tazadolene)。步骤 3, 苄胺对二酮的进攻有有趣的化学选择性。其中一个与苯基共轭，因此活性较弱，未受影响，只有在六元环上的酮被进攻了。

烯胺的酰基化已在 Chapter 26 中讨论。



1,3-二羰基关系可能不会在目标分子中存在，1,3-diO C–C 切断前可能需要先进行 C–杂原子切断或 FGIs。溴匹立明 (Bropirimine) 是一种含溴的抗病毒和抗癌药物。溴原子可以在最后，通过亲电溴代反应引入。

#### 溴匹立明: 逆合成分析

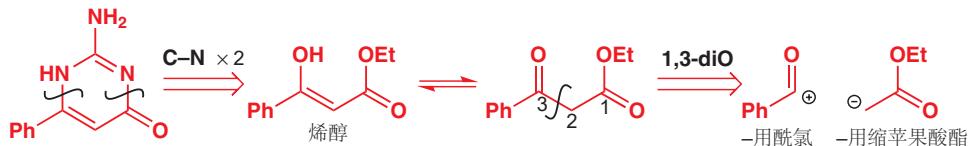


两根 C–N 键的切断可以移去一分子的胍 (guanidine) 并且显露出很容易切断的 1,3-二羰基关系。

▶ 脰是离域的强有机碱, p.

175.

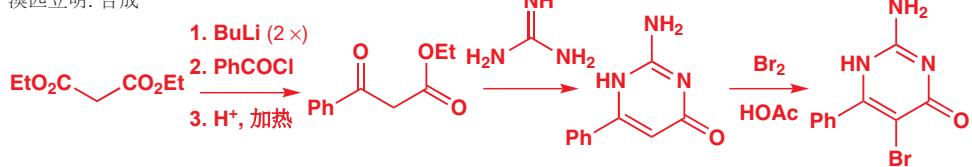
#### 溴匹立明: 逆合成分析



1,3-二羰基由带有一点不寻常的变化的缩苹果酸酯化学得到：锂衍生物使 C–酰基化以很好的产率进行。产物和胍仅需简单的回流，即可消除杂环，然后溴代则可得到溴匹立明。

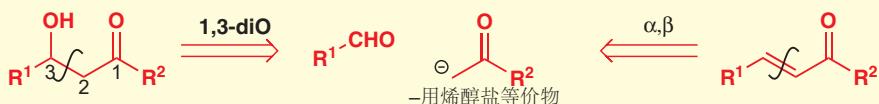
■ 这个例子是使用羧基化制造芳杂环的一个提前示范。芳杂环是下两章，29 和 30 的主题。

#### 溴匹立明: 合成

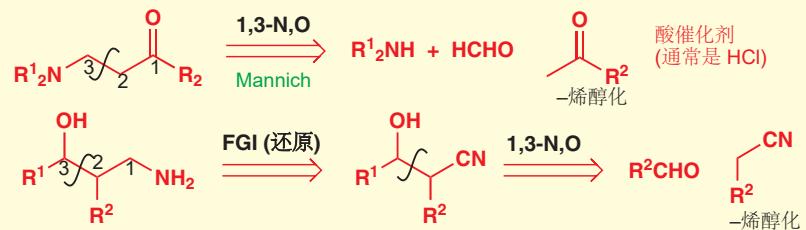


#### ● 总结: 1,3-diO 切断

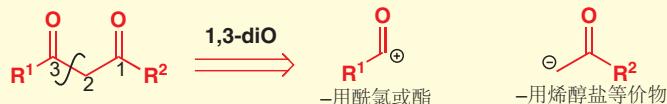
3-羟基羰基 和  $\alpha,\beta$ -不饱和羰基: 用羟醛反应



3-氨基酮 和 醇: 用 Mannich 或腈的羟醛反应



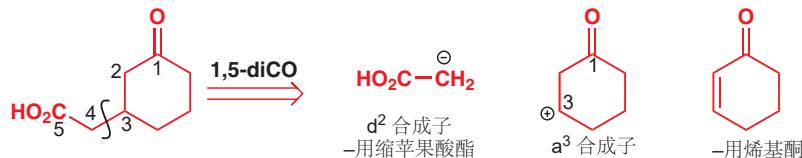
1,3-二酮: 用 Claisen 缩合



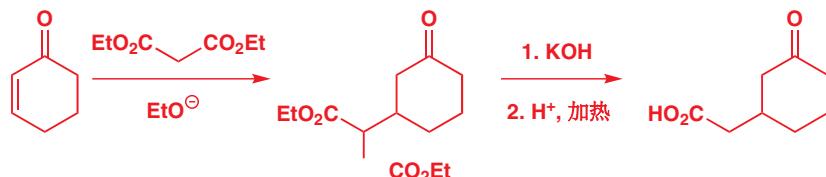
## 1,5-关系的官能团

下面的化合物含有处于 1,5 而非 1,3 关系的两个羰基。如果想让切断给出烯醇盐的话，所需的另一合成子便是  $a^3$  而非  $a^1$ ：换句话说，一个 Michael 受体。

1,5-二羰基化合物：逆合成分析

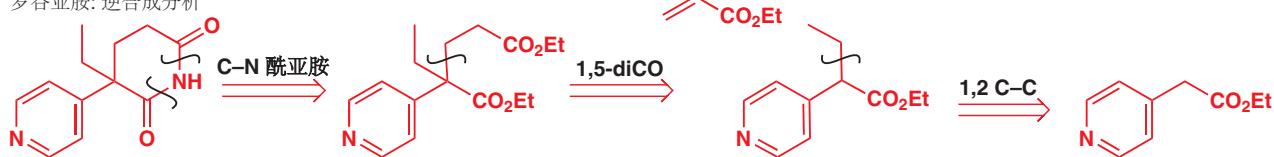


如在 Chapter 25 中所讨论的，合成仅在 (a) 正确的试剂烯醇化，(b) 亲核试剂对不饱和羰基化合物，经历共轭（而不是直接的 1,2-）加成。缩苹果酸酯衍生物很容易地烯醇化，并且发生 Michael 加成，因而是这类反应好的选择。



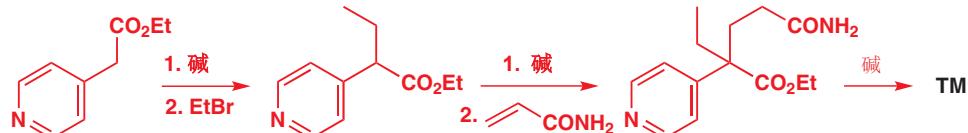
烯醇盐对  $\alpha,\beta$ -不饱和羰基化合物的 Michael 加成是获取 1,5-双官能化化合物很好的方法，您应当在目标分子中寻找 1,5-关系以便用这种方法来合成。我们的例子是镇静剂罗谷亚胺 (rogletimidine)，它可以被切割为 1,5-二酯。后续通过 1,5-diCO 切断可给出我们之前通过酯烯醇盐的乙基化得到的化合物。

罗谷亚胺：逆合成分析



这个合成中，用不饱和酰胺做 Michael 受体会更加有效。

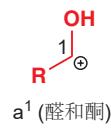
罗谷亚胺：合成



在 Chapter 26 中有很多烯醇盐发生共轭加成的例子。

## “自然反应性”和“极性反转”

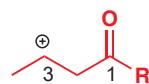
回想一下下面的这些，我们在双官能团 C–C 切断中用过的合成子。



$a^1$  (醛和酮)



$d^2$  (酯或酮的烯醇盐)



$a^3$  ( $\alpha,\beta$ -不饱和羰基化合物)

您会注意到，受体合成子数字都为奇数；给体合成子则为偶数：沿着碳链逐渐远离羰基，给体和受体的属性会在其中交替变化。这种羰基化合物的“自然反应性”解释了为什么我们容易讨论 1,3- 和 1,5-双官能化化合物 的制造方式——它们分别由  $a^1 + d^2$  和  $a^3 + d^2$  得到。对于  $d^1$  或  $a^2$  合成子的试剂是稀少的，因而有 1,2- 或 1,4-关系的官能团的化合物，需要特别的逆合成考虑。

对于有  $a^2$  和  $d^1$  反应性的“非天然”合成子，您都已经分别遇到过一个例子了。这样的合成子被用德文命名为极性反转的 (*umpolung*, 意为“*inverse polarity*”), 由于它们的天然反应性是颠倒的，极性反转的试剂便成为了 1,2- 和 1,4-双官能化化合物合成的关键。

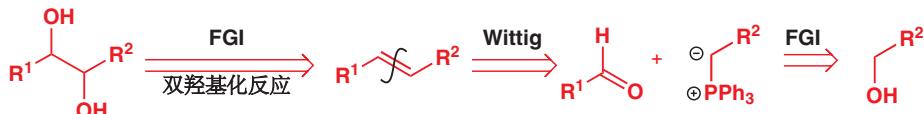
#### 两种极性反转的合成子和等价试剂



我们将以对 1,2- 和 1,4-双官能化化合物 的切断的考察结束这一章，它们需要我们使用  $d^1$ ,  $d^3$ ,  $a^2$ , 和  $a^4$  合成子的极性反转的试剂。这些合成子有许多对应的试剂——如果您对了解更多内容感兴趣，请查阅专业书籍。

### 1,2-双官能化化合物

我们谈论双官能团切断法的第一个内容便是制取 1,2-双官能化化合物 的方法，我们使用环氧作为  $a^2$  合成子。环氧，当然也是 1,2-双官能化的，并且事实上这常常是制取 1,2-双官能化化合物的关键：用已经包含 1,2 关系的事物。在本章的前文中，您已经了解过了许多这种类型的策略。也许最简单的方法是对烯烃的亲电加成。如果烯烃由 Wittig 反应制取，那么目标分子中（最后的）切断便应是处在两个官能化的碳原子之间。下面的例子用双羟基化反应完成了亲电加成步骤，不过，环氧化、溴化和水中的溴化（加成的官能团为 Br 和 OH）同样是可行的。

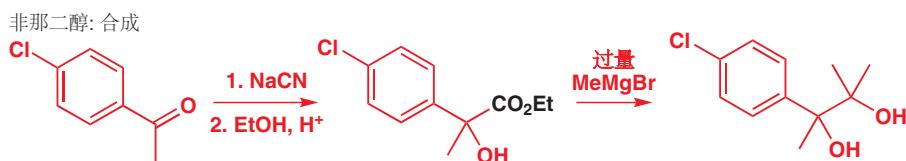


正常的 C–C 切断也是可行的，需要切断为“自然的”  $a^1$  合成子以及极性反转的  $d^1$  合成子。一种很有用的极性反转的试剂是氰根，从下面的镇静剂非那二醇（phenaglycodol）的合成中便可见一斑。带有两个 R 基的叔丁基，应当促使您想到对酯的两次格氏加成。需要 FGI 为腈官能团，便可进行 1,2-diX 切断得到氰根和酮。

#### 非那二醇：逆合成分析



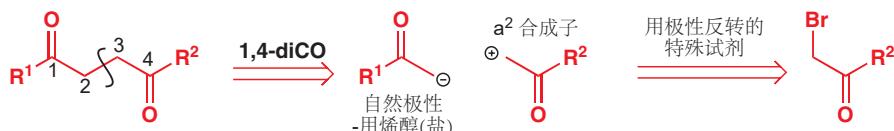
起始原料很明显可通过氯苯的 Friedel–Crafts 酰基化反应获得，合成的其余部分如下所示。注意，腈在酸性乙醇的作用下，可以直接转化为酯，由于还有游离的 OH 存在，格氏试剂需要过量。



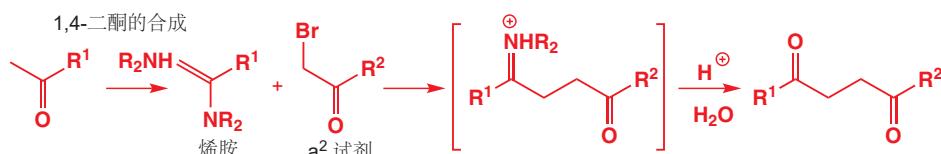
### 1,4-双官能化化合物

这个情境的可行性更多，我们会以对它们的简要分析结束这一章，也将向您展示，这一主题在本书的讨论范围外还要多多。

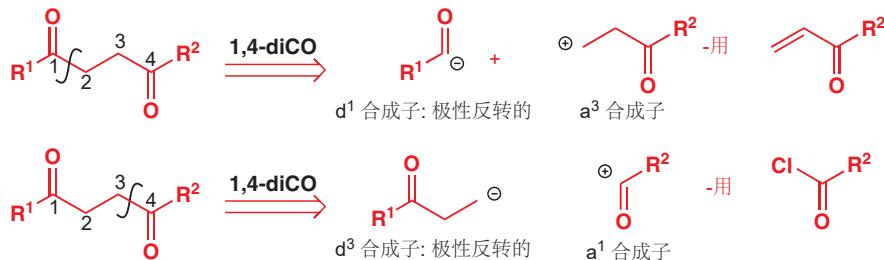
如果我们以 1,4-二羰基化合物 开始，我们会首先考虑从中心键切断。



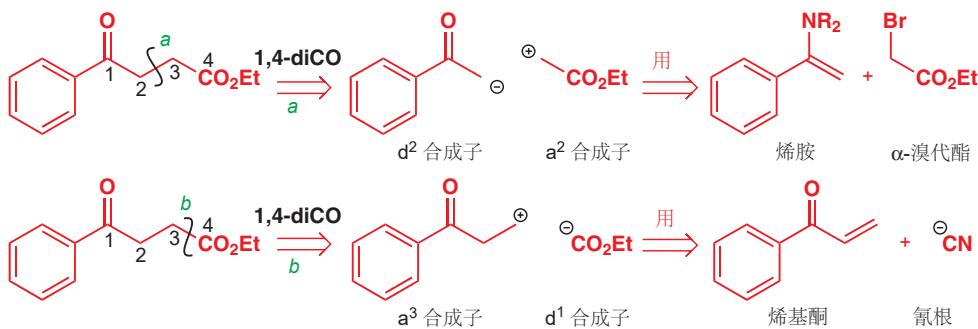
我们可以用烯醇盐作为其中一个试剂，但我们还需要另一个极性反转的试剂。这并不是非常困难的一类极性反转试剂，如果我们小心地选择烯醇(盐)等价物， $\alpha$ -溴代羰基化合物 就可以很好地完成任务。在 Chapter 25 中，我们建议您用烯胺完成这个反应。合成路线如下：



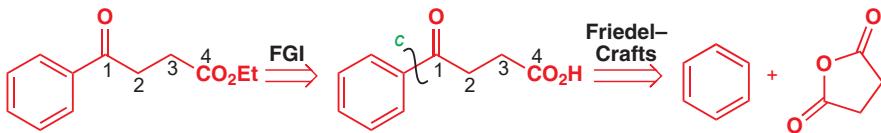
如果我们试图切断另一根键，那么就会有两种可能性，因为两个片段是不同的。我们可以既可以用  $d^1 + a^3$  策略，也可以用  $a^1 + d^3$  策略。每种情况都包含一个自然的合成子和一个极性反转的合成子。



用您到目前为止见过的试剂，这些策略会很难实现，但氰离子对不饱和羰基化合物的共轭加成会是  $d^1 + a^3$  策略的一个例子（注：上一章还讨论过用二噻烷实现的方法）。我们包含这些例子，是为了向您证实，在 1,4-二羰基化合物 的合成中，极性反转是难以逃脱的宿命。如果您要合成这种酮酯，那么您必须认真考虑上面的两种策略。



还有一种避免极性反转的制取方法，那就是要在 1,4 关系的外部切断。凑巧，我们已经遇到过这种策略的实际应用 (p. 568)。它包含苯环与一个环状酸酐的 Friedel–Crafts 酰基化反应 (Chapter 21)，通过很短的路线，便直接得到了这个产物。这种策略仅在一些特殊情境下可用。



## 小结

一个分子最好的合成路线不能被精确地预测。逆合成分析使您可以提出多种得到目标分子的策略，通过彻底的文献搜索和实验，您便能逐个削减这些可能的方法，并得到最容易成功的一个。这样的思考支撑着分子合成的设计，从相对简单的分子，到新一代药物、农药，以及已知的最复杂的分子都是如此。逆合成思考同样强化了理解有机反应的关键——亲电试剂和亲核试剂的结合。合成和反应是同一硬币的两面。从现在起，我们将开始使用本章中介绍的方法和术语，我们认为它们能开发您的理解。

## 延伸阅读

S. Warren and P. Wyatt, *Organic Synthesis: the Disconnection Approach*, Wiley, Chichester, 2008 (译本：有机合成：切断法，科学出版社，2010); S. Warren and P. Wyatt, *Workbook for Organic Synthesis: the Disconnection Approach*, Wiley, Chichester, 2009.

大多数药物化合物的例子和数据都来源于专利文献。我们建议您不要尝试使用它们，但如果您对原始工作感兴趣，可用查阅这些论文：

非尼拉朵：A. P. Gray, D. E. Heitmeyer, and E. E. Spinner, *J. Am. Chem. Soc.*, 1959, **81**, 4351.

普萘洛尔：R. Howe and R. G. Shanks, *Nature*, 1966, **210**, 1336; A. F. Crowther and L. H. Smith, *J. Med. Chem.*, 1968, **11**, 1009.

吗硝唑：C. Rufer, H.-J. Kessler, and E. Schröder, *J. Med. Chem.*, 1971, **14**, 94.

阿立酮：G. D. Diana, *et al.*, *J. Med. Chem.*, 1977, **20**, 757.

罗谷亚胺：A. M. Boss, D. W. Clissold, J. Mann, A. J. Markson, and C. P. Thickitt, *Tetrahedron*, 1989, **45**, 6011.

多匹可明：R. N. Booher, S. E. Smits, W. W. Turner, and A. Pohland, *J. Med. Chem.*, 1977, **20**, 885.

文拉法辛：J. P. Yardley *et al.*, *J. Med. Chem.*, 1990, **33**, 2899.

奥沙那胺：K. W. Wheeler, M. G. van Campen, and R. S. Shelton, *J. Org. Chem.*, 1960, **25**, 1021.

溴匹立明：H. I. Skulnik, S. D. Weed, E. E. Eidson, H. E. Renis, W. Wierenga, and D. A. Stringfellow, *J. Med. Chem.*, 1985, **28**, 1864.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 芳杂环 1: 反应

## 联系

### 基础

- 芳香性 ch7
- 烯醇和烯醇盐 ch20
- 芳香亲电取代 ch21
- 芳环上的亲核进攻 ch22
- 烯醇和烯醇盐的反应 ch25 & ch26

### 目标

- 在概念上由苯衍生的芳香体系：将一个 CH 替换为 N 会得到吡啶
- 将 CH=CH w 替换为 N 会得到吡咯
- 吡啶如何反应
- 吡啶衍生物如何拓宽吡啶的反应性
- 吡咯如何反应
- 呋喃和噻吩与吡咯的对比
- 将更多氮原子放入五元或六元环中
- 稠环：吲哚、喹啉、异喹啉和中氮茚/吲哚
- 既包含氮还包含其他杂原子——氧或硫——的环

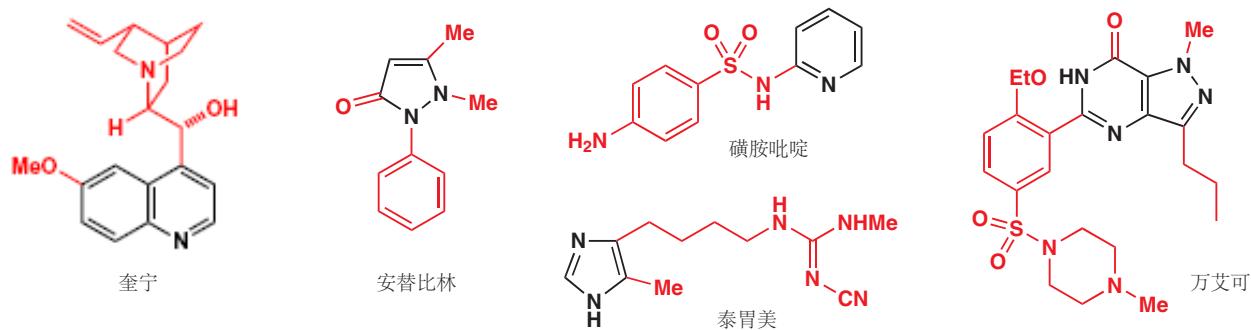
### 展望

- 芳杂环的合成 ch30
- 饱和杂环 ch31
- 生物化学 ch42

## 引入

苯在其环状共轭体系中含有六个电子，因而是芳香的。我们由它例外的稳定性得知它的芳香性，它与亲电试剂作用的性质特殊，是取代而不是加成，并且环电流使它在质子 NMR 光谱中拥有较大的化学位移。本章和下一章的内容，是将苯中的一个或多个原子换位例如 N, O, 和 S 的杂原子后，所得的其他芳香体系。包含五、六元环的这些体系有成千上万种，我们只会考察其中一小部分。

对于“芳香”相对准确的定义，我们在 Chapter 7 中已经阐释过。苯和它的芳香衍生物的反应已在 Chapters 21 和 22 中描述：这两章是您处理本章之前必须阅读的。



我们的主题是芳杂环(芳香杂环, aromatic heterocycles), 我们必须认真地对待这一主题, 因为大多数——很有可能是三分之二的——有机化合物都属于这一类别, 这包括对于人类最重要的化合物中的一些。如果我们只考虑药物, 我们可以用杂环定义医学史。即使在十六世纪, 奎宁(quinine)的结构还未知, 它就被用于预防和治疗疟疾。第一种合成药物是用于退烧的安替比林(antipyrine, 1887). 第一种有效的抗生素是磺胺吡啶(sulfapyridine, 1938). 第一种价值数百万英镑的药物(1970s)是抗溃疡药物泰胃美(Tagamet), 而目前最受关注的药物是治疗男性阳痿的常用的万艾可(俗称伟哥, Viagra, 1997).

这些化合物都含有芳杂环结构, 以黑色标出。其中三种含有的是五、六元单环, 剩下的两种则含有稠合(fuse)在一起的两个五、六元环。环中氮原子的数目由一个至四个不等。我们将首先着眼于简单的, 带有一个氮原子的六元环: 吡啶(pyridine).

## 当苯环的一部分被氮原子替代时芳香性仍会存在

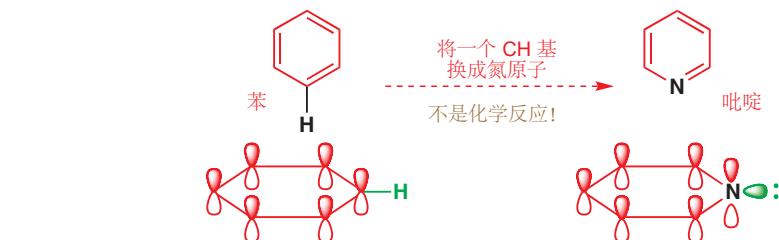
苯是芳香的, 是毋庸置疑的。但现在我们必须提问——如何将一个杂原子嵌入环中并保留芳香性? 需要什么种类的原子? 如果我们想用杂原子替换苯中的一个碳原子, 我们需要可以形成三角形构型的杂原子, 以保留环的平面六边形形状; 并且还要求这个杂原子具有 p 轨道, 以保留六个离域电子。氮符合这些要求。当我们把苯中的一个 CH 基换成氮原子时, 会发生如下的变化。

Interactive structure of pyridine



### 命名法

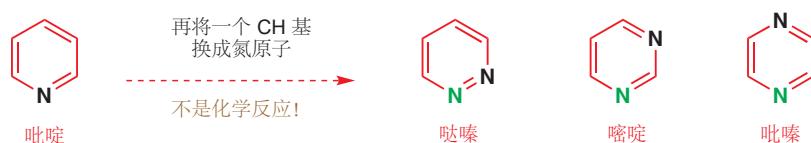
杂环化学最烦人的事情之一便是处理一堆看似不合乎逻辑的名称。当然, 您没必要尝试记住所有名称, 但它们基本的制定思路会帮助您。我们很快就会提供一个指南, 说明哪些名称应当记住。请暂时接受, “amine(胺)”以“-ine(啶、嗪)”结尾, 因而任何名称以“-ine(啶、嗪)”结尾的杂环化合物都是氮杂环。音节“azo-(氮杂)”也指氮, “pyr-(吡)”(通常)指六元环(除了吡咯pyrrole!).



环中的轨道, 在位置、形状上都没有改变, 我们仍有来源于三根双键的六个电子。一个明显的区别是, 氮是三价的, 因而没有 NH 键。相反, 一堆孤对电子占据了苯中 C-H 键的空间。

在理论上, 吡啶是芳香的。那么在现实中呢? 最重要的证据来源于质子 NMR 光谱。苯的六个电子在 7.27 ppm 处共振, 比烯烃区域低场 2 ppm, 这清楚地证明了环电流(ring current, Chapter 13). 吡啶并不像苯一样是对称的, 它有三种落在同一区域内的质子。如我们将要了解的, 吡啶同样很稳定, 并且, 根据合理的评估, 吡啶是芳香的。

我们会继续在纸上进行, 将更多 CH 基换为氮原子的过程, 并将发现三种新的芳杂环: 吲哚(pyridazine), 嘧啶(pyrimidine), 和吡嗪(pyrazine):



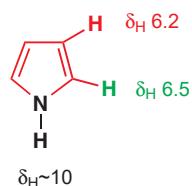
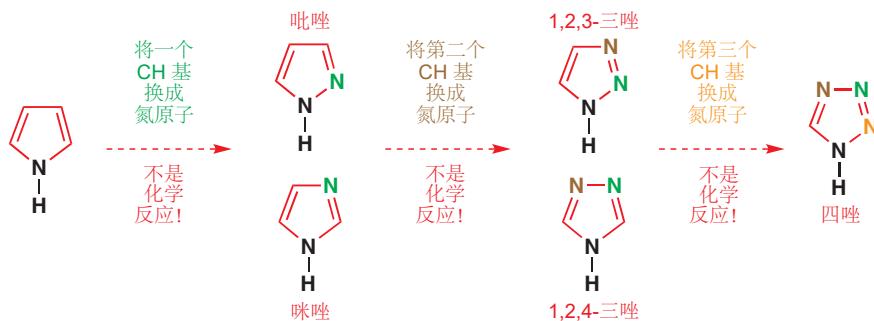
有另一种将苯转化为杂环的方式。除了仅仅用来自 N 的一个电子替换  $\pi$  体系中原有的一个电子, 我们还可以用氮的孤对电子直接替换  $\pi$  体系中的两个电子。也就是说, 我们可以用一个氮原子取代苯中的一个 CH=CH 单元。这样做的条件是将孤对电子放入离域体系, 这将意味着将其放入

一个 p 轨道。我们仍有来自余下的双键的四个电子，再加上氮的两个孤对电子，总体上便有了六个电子。氮原子必须仍是三角型的，包含一对处在 p 轨道上的孤对电子，因而 N–H 键在五元环平面内。



吡咯 (Pyrrole) 的  $^1\text{H}$  NMR 光谱稍稍不令人信服，因而环上有两种类型的质子，在比苯、吡啶的质子更高场区 (6.5 和 6.2 ppm) 共振，但它仍在芳香区域，而非烯烃区域内。吡咯同样比苯和吡啶面对亲电试剂更加活泼，但它仍然通常发生芳香取代反应 (Friedel–Crafts、硝化、卤代) 而不是加成反应：吡咯是芳香的。

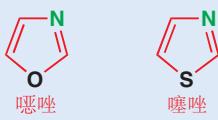
将吡咯中更多的 CH 基换为氮原子，可以得到另两种杂环化合物，吡唑 (pyrazole) 和咪唑 (imidazole)；再经历一次替换，得到两种三唑 (triazoles)；经历两次替换 (共经历三次)，则可得到单一的一种四唑 (tetrazole)。



所有这些化合物都被普遍接受为芳香化合物，因为它们广泛地具有芳香化合物所应具有的的 NMR 光谱特征和反应性。如您所料，在芳环中引入杂原子，除了会改变环的大小，事实上更会对化学性质产生很大影响。影响化学性质。现在，我们需要回到吡啶，并慢慢地研究这些重要杂环的化学性质，并建立起支配它们行为的一套原则。

### 更多的命名法

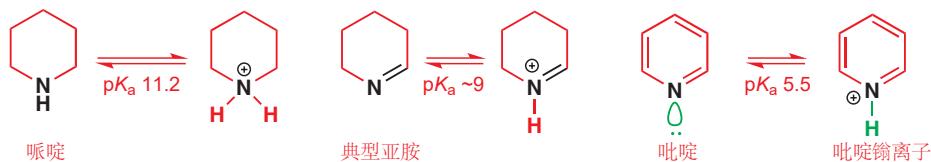
结尾 “-ole (唑)” 是系统的，并指代五元杂环。含氮的五元杂环，有时还被统称为 “azoles (唑类/吖唑)”。噁唑 (Oxazole) 和噻唑 (thiazole) 用于指咪唑的氧和硫类似物。



## 吡啶是一种非常不活泼的芳香亚胺

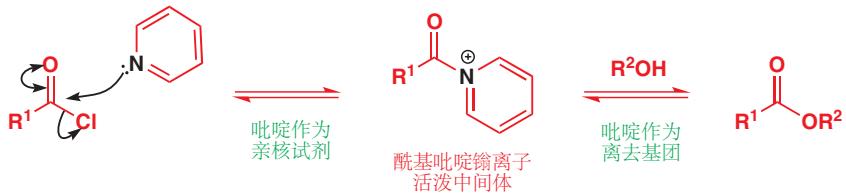
吡啶环中的氮原子是平面三角型的，有一对孤独电子在环平面中。这使其成为一个亚胺。您曾遇到过的大多数亚胺 (例如，在 Chapter 11 中) 都是羰基反应的不稳定中间体，而吡啶则是一个稳定的亚胺——稳定性来源于芳香性。所有的亚胺的碱性都比饱和胺弱，吡啶而是一种弱碱，(共轭酸的)  $\text{pK}_a$  为 5.5. 这意味着吡啶𬭩离子 (pyridinium ion) 和羧酸的酸性相像。

■ 吡啶同样有毒，并含有恶臭——这是用吡啶作溶剂的缺点。但它便宜，并仍然是受欢迎的溶剂。



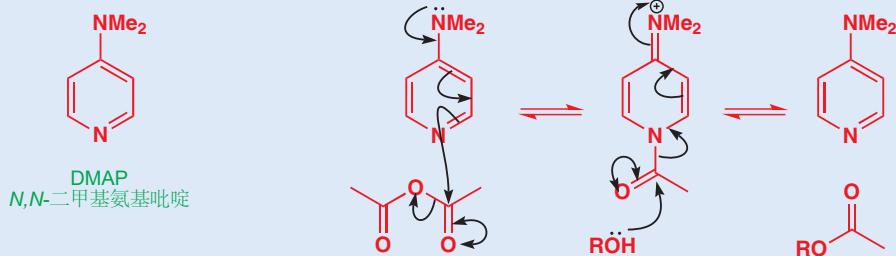
吡啶是对于羰基合理的亲核试剂，因而常被用作酰基化反应的亲核催化剂 (nucleophilic catalyst). 酯的制取，通常是用酰氯和醇在吡啶溶液中完成的 (完整机理在 Chapter 10, p. 199).

Interactive mechanism for pyridine nucleophilic catalysis



### DMAP

有一种氨基吡啶，是比吡啶本身更有效的酰基化催化剂，因而在催化领域有独特的角色。它是 DMAP (*N,N*-二甲基氨基吡啶)，其中的氨基被用于增强吡啶氮原子的亲核特性。鉴于吡啶“催化”的酰基化反应需要在吡啶溶液中进行，DMAP 的催化仅需要在其他溶剂中少量地加入便可达到同样的效果。



吡啶氮原子的亲核性，是由于氮上的孤对电子不能离域到环中。它们处在与环  $p$  轨道正交的  $sp^2$  轨道中，正交的轨道间不会有相互作用。用画箭头的方式试一试。任何使电子离域的企图都会导致不可能的结果！



$sp^2$  轨道中的孤对电子与环中的  $p$  轨道成直角：  
正交轨道间没有相互作用



试图离域孤对电子  
得到荒谬的结果

### ● 吡啶氮原子的孤对电子不是离域的。

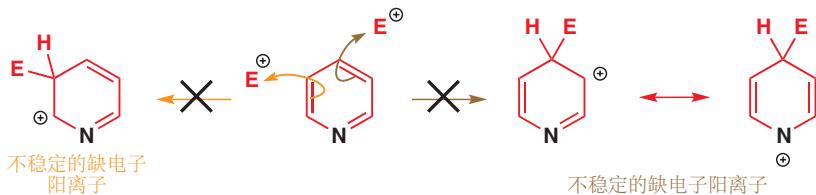
对于吡啶的反应性，我们的主要问题应该是：氮原子对环的余下部分产生了什么影响？重要的轨道——芳香体系的  $p$  轨道——从表面上看与苯中的一样，但更加负电性的氮原子会降低所有轨道的能量。充满轨道较低能，就意味着亲核性较弱；LUMO 较低能，则意味着亲电性较强。这是对吡啶

的化学性质很好的指导。它在芳香亲电取代中不如苯活泼；但对于苯很困难的亲核取代，对于吡啶则较容易。

▶ 苯上的亲电取代反应  
在 Chapter 21 中讨论过。

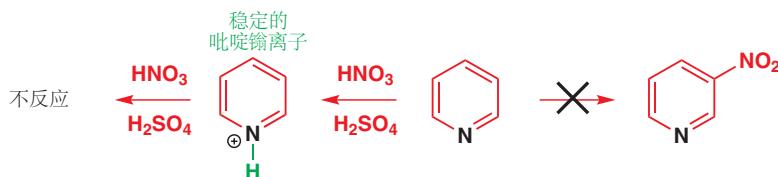
### 吡啶在芳香亲电取代中表现得差

吡啶  $\pi$  体系轨道较低的能量，意味着发生在环上的亲电进攻是困难的。对此的另一种看法是，氮原子会使这个反应将要形成的阳离子不稳定（由于是缺电子阳离子），尤其是当阳离子中的正电荷可以离域在氮原子上时。

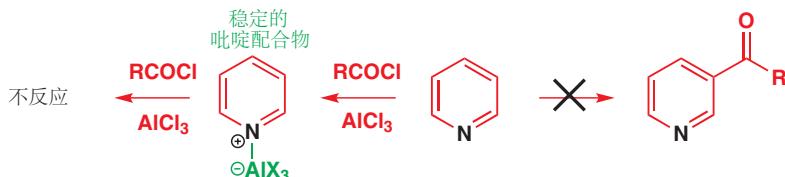


■ 将不稳定的缺电子阳离子中间体与稳定的吡啶𬭩离子对比。吡啶𬭩离子的形成使用氮的孤对电子，但不稳定中间体中却不涉及。注意观察，这个反应最佳的选择是在 3 号位，但即便如此仍然不发生。在 2 号位和 4 号位的反应更糟糕。

一个同样严重的问题是，氮的孤对电子是碱性的，并且也合理地是好的亲核试剂——这是它在酰基化反应中扮演亲核催化剂的角色的基础。一般的亲电取代反应，例如硝化反应的试剂，都是酸性的。用通常的  $HNO_3$  和  $H_2SO_4$  混酸处理吡啶，则只会使氮原子质子化。吡啶本身面对亲电试剂是非常不活泼的，吡啶𬭩离子则完全不反应。



其他反应，例如 Friedel–Crafts 酰基化反应，需要 Lewis 酸催化，它们也会在氮上反应。吡啶是对于 Al(III) 或 Sn(IV) 等金属很好的配体，同样，配合物中的氮带正电，它也完全不会与亲电试剂反应。



#### ● 吡啶不发生亲电取代反应

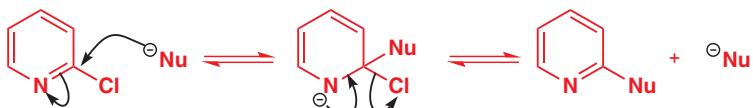
在吡啶上的芳香亲电取代反应不是一个有用的研究。环本身就是不活泼的，并且亲电试剂还会进攻氮，使环更加不活泼。请避免使用简单吡啶上的硝化、磺化、卤代，及 Friedel–Crafts 反应。

### 吡啶的亲核取代反应容易进行

与之相比，氮原子通过降低  $\pi$  体系 LUMO 的能量，使吡啶面对亲核取代反应更加活泼，尤其是在其 2 号和 4 号位。在这两个位置上的卤素很容易被亲核试剂取代。

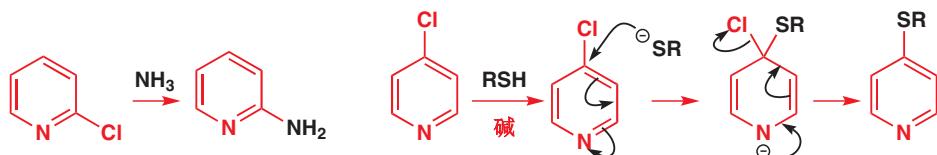
▶ 苯上的亲核取代反应在 Chapter 22 讨论过。

 Interactive mechanism for nucleophilic substitution on pyridines



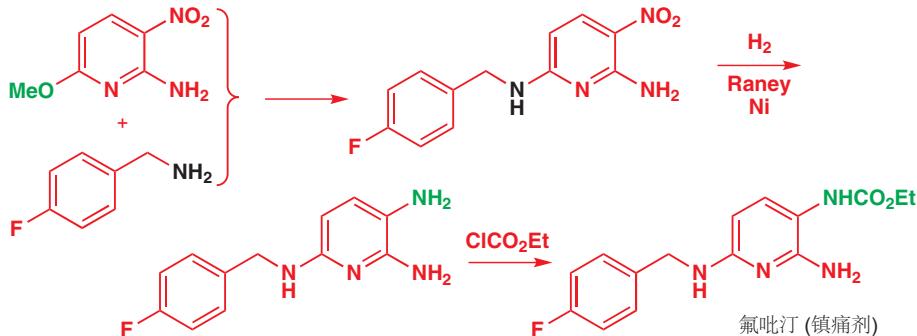
阴离子中间体被负电性的氮原子，及在环上的离域所稳定。这些反应与芳香亲核取代反应 (Chapter 22) 有一些相似之处，但更像是羰基的反应。阴离子中间体是一个四面体中间体，会失去最好的离去基团以重新生成稳定芳香体系。胺、烷硫基阴离子等亲核试剂在这些反应上工作良好。

► 注意观察它与羰基上的亲核取代反应 (Chapter 10) 的相似性。



这些反应中不必包含像氯一样好的离去基团。继续与羰基反应进行类比，2- 和 4-氯代吡啶相当像酰氯，但在我们只需要使用活性较弱的吡啶基醚 (pyridyl ethers)，这类似于用酯制取酰胺的过程。2-甲氧基吡啶的取代反应可用于合成氟吡汀 (flupirtine)。

► 您会在本章的后文中继续了解这个合成。



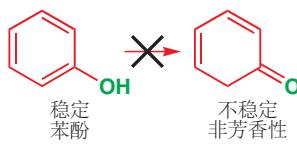
第一步是一个芳香亲核取代反应。第二步中，硝基被还原为氨基，这对吡啶环没有造成任何影响——芳香性的另一证据。最后，孤对电子无法离域到吡啶 N 上的那个氨基，在其他两个氨基 (胺基) 的存在下被酰基化。

### 吡啶酮是良好的亲核取代底物

这些亲核取代反应的起始原料 (2- 和 4-氯代- 或 甲氧基吡啶) 本身，是由吡啶酮 (pyridones) 的亲核取代反应制取的。如果您被问到，2-甲氧基吡啶 可能是如何制取的，您很有可能会类比对应的苯化合物，提出，是通过酚的烷基化制取的。让我们考察其细节。

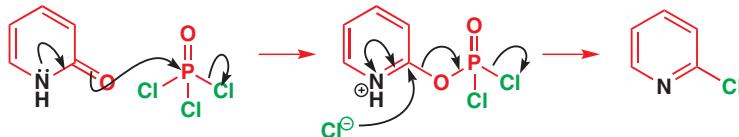


这个反应的起始原料是一种 2-羟基吡啶，它可以通过将氧上的酸性质子转移到氮上，互变异构为类似酰胺的结构，被称为吡啶酮。在苯酚体系中，由于酮式不是芳香的，哪个结构稳定是毋庸置疑的；而对于吡啶来说，两个结构都是芳香的。



事实上，2-羟基吡啶 倾向于以“酰胺”的形式存在，因为在芳香性保留的情况下，它还利用了 C=O 强键提供的稳定性。每根 C=C 双键中都有两个电子，酰胺的三角型氮上还有一对孤电子。典型酰胺结构中孤对电子的离域使这一点表现得更清楚。

吡啶酮很容易制备（见 Chapter 30）并且从其结构上预测，它可在氧上烷基化。一个更重要的反应，是与  $\text{POCl}_3$  反应直接转化为氯代吡啶。这个反应开始于氧原子对磷的进攻，这一过程创造了一个离去基团，随后是芳香亲核取代反应。整体效果与由羧酸形成酰氯（Chapter 10）很相似。



同样的反应也可在 4-吡啶酮上发生，这种化合物以相同的方式离域，并且以“酰胺”式存在；但该反应不能发生在以“酚”式存在的 3-羟基吡啶。它唯一的互变体是其两性离子，但吡啶氮的碱性太弱，不足以从羟基上移去质子。

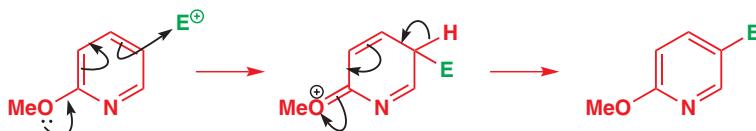


### ● 吡啶可发生亲核取代反应

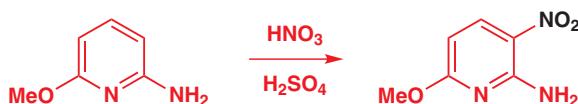
吡啶，只有在被给电子取代基活化后，才可以发生亲电取代反应（见下一节）；但即便除了环上的氮原子，没有其他活化，它们也很容易发生亲核取代反应。

### 被活化的吡啶可发生芳香亲电取代反应

只有当吡啶中含有给电子取代基，例如  $\text{NH}_2$  或  $\text{OMe}$  时，才能发生有用的亲电取代反应。对于苯环，它们起活化作用（Chapter 21），而对于吡啶，它们则是必不可少的。它们提供一对可以提高 HOMO 能量的非键电子，并使反应发生。简单的氨基或甲氧基吡啶，合理地在活化基的邻位和对位很好地反映。这些反应，能在尽管分子是吡啶的情况下发生，而不是因为分子是吡啶。



一个实践性的例子发生于镇痛剂氟吡汀的批量生产中，一个同时包含  $\text{MeO}$  和  $\text{NH}_2$  基，被双重活化的吡啶，就像是苯环一样被硝化。硝基在氨基的邻位和甲氧基的对位出现。活化作用足够弥补在反应条件下几乎完全被质子化的分子。



→ 这是 p. 728 中氟吡汀合成的起始原料。

Interactive tautomerism between 2-hydroxypyridine and pyridone

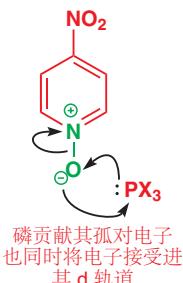
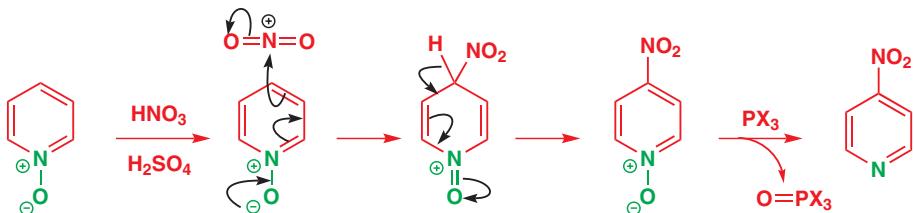
### 吡啶 N-氧化物 面对亲电试剂和亲核试剂都活泼



当分子含有这样的活化基时，当然很好，但如果沒有呢？我们如何硝化吡啶本身？答案涉及一个精妙的技巧。我们需要一个可以活化环，并且稍后可以去除的富电子取代基，并且还需要阻止氮原子与亲电试剂反应。所有这些，都可以用单一的一个原子做到！

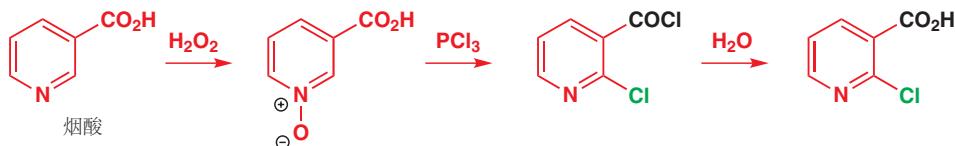
因为氮原子具有亲核性，吡啶可以被例如 *m*-CPBA 或乙酸中的  $H_2O_2$  氧化为 吡啶 N-氧化物 (pyridine N-oxide). 这些 N-氧化物 是稳定的偶极物种，氧上的电子离域在吡啶环中，并升高分子的 HOMO. 与亲电试剂的反应发生在 2 (邻位) 和 4 (对应) 号位，为了远离带正电的氮，主要在 4 号位。

Interactive structure of pyridine N-oxide

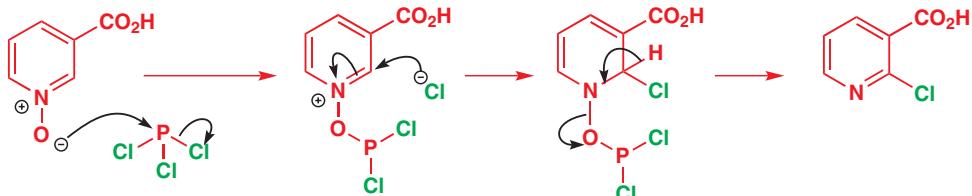


现在，需要将氧移除，最好的方式是用三价磷化合物，例如  $(MeO)_3P$  或  $PCl_3$ . 磷原子会在一步中拆除氧原子，形成非常稳定的 P=O 双键。在这个反应中，磷原子既做亲核试剂，又做亲电试剂，但主要还是亲电试剂，因为在这里  $PCl_3$  比  $(MeO)_3P$  更活泼。

与使简单亲电取代反应发生的相同的活化作用——氧化为 N-氧化物——也能使一种有用的亲核取代反应发生。氮原子上的正电荷促进亲核进攻，氧原子还可以与  $PCl_3$  转化为离去基团。我们的例子是烟酸 (nicotinic acid)，我们将在 Chapter 42 讨论它在生物学上的重要性。

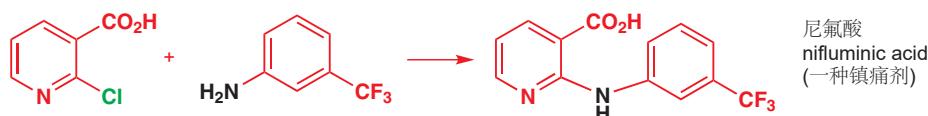


N-氧化物 与  $PCl_3$  在氧上反应，反应释放的氯离子加成到最亲电的位点，即两个吸电子基之间的位置。现在，简单的消除即可恢复芳香性，并得到一种看似是通过氯代，而非亲核进攻得到的产物。



试剂  $PCl_3$  同时会将羧酸转化为酰氯，而酰氯会在最后一步中被水解回去。这是一个实用的流程，因为氯原子被引入到 2 号位，这便使它可以继续被取代，例如被胺取代。

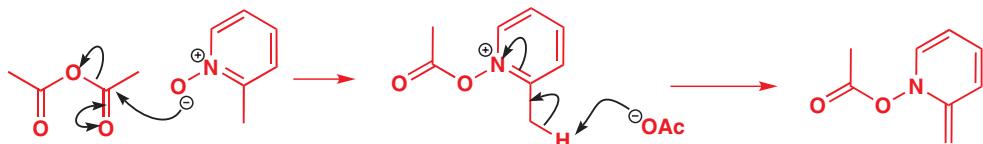
Interactive mechanism for nucleophilic substitution on pyridine N-oxide



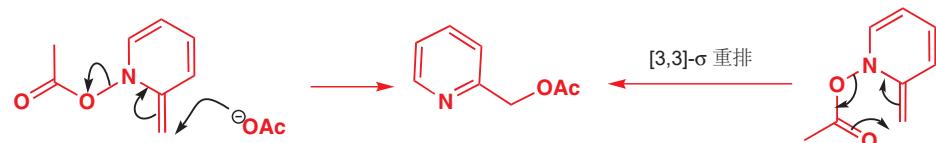
### ● 吡啶 N-氧化物

吡啶 N-氧化物对于环中相同的几个碳原子(2-, 4-, 和 6-)的亲电和亲核取代都是有用的。

如果 2 号位有一个烷基，那么在更远距离处的亲核取代反应，将会在与酸酐反应时发生。如上一个反应一样，酰基化发生在氧上，但此后，会在侧链上失去一个质子，得到一个不带电的中间体。



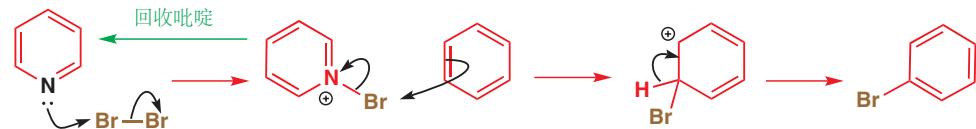
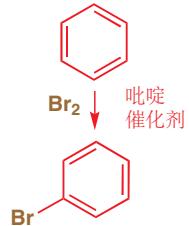
这个化合物会发生重排，乙酰基迁移到侧链上，并恢复芳香性。这也许是一个离子型反应，也许属于您今后会学习的一种重排反应，被称为 [3,3]-σ 重排 (Chapter 35)。



### 吡啶作为催化剂和试剂

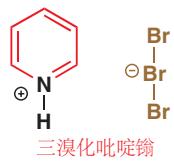
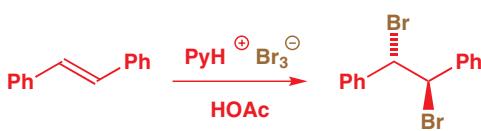
由于吡啶充裕且低廉，以及化学性质极其丰富，它便得到很多应用。使苯溴化最简单的方式，不是我们在 Chapter 21 中推荐的，用 Lewis 酸催化剂，而是仅仅将液溴滴入少量吡啶存在的芳香化合物中。只需要大约一摩尔百分数的吡啶，并且还需要被冷却，以防止反应失控。

如我们已经了解到的，吡啶通过其氮原子进攻亲电试剂。这会产生活泼物种，N-溴代吡啶𬭩离子，继而被苯进攻。吡啶是比苯好的亲核试剂，也是比溴离子好的离去基团。这是亲核催化剂的另一个例子。



亲核催化剂在 p. 200  
讨论过。

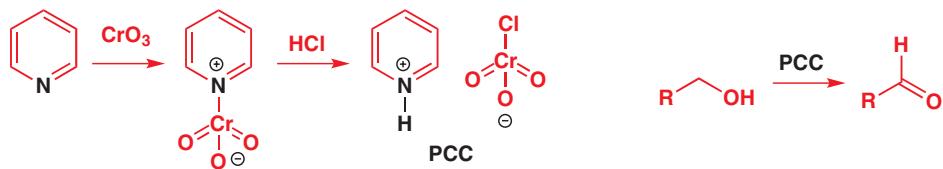
另一种在溴化反应中使用吡啶的方式，是用稳定的晶体化合物替代危险的液溴。这个化合物，被称作三溴化吡啶𬭩 (pyridinium tribromide)，是吡啶与  $\text{Br}_3^-$  阴离子的盐。它可被用于溴化烯烃等活泼的化合物 (Chapter 19)。



这些方法都基于吡啶  $\pi$  体系面对溴等亲电试剂反应性的缺失。注意，第一种情形中，苯和吡啶同时存在。吡啶仅会通过氮原子(可逆地)进攻溴，绝不会通过碳原子。

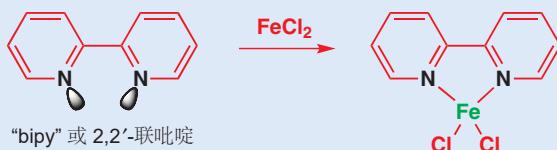
醇的氧化反应一般用 Cr(VI) 试剂完成 (Chapter 23)，但这些试剂，如 Jones 试剂 (硫酸中的

$\text{Na}_2\text{Cr}_2\text{O}_7$ ), 通常是酸性的。一些 Cr(VI) 化合物的吡啶配合物可以解决这个问题, 它们中, 唯一的酸是吡啶𬭩离子 ( $\text{pK}_a$  5) 作为酸。两种最著名的是 PDC (重铬酸吡啶𬭩盐) 和 PCC (氯铬酸吡啶𬭩). 吡啶与  $\text{CrO}_3$  反应, 会形成配合物, 但它很容易着火。用 HCl 处理可得到 PCC, 它的危险性小得多。PCC 在由伯醇到醛的氧化反应中很有用, 稍稍酸性的条件可以避免过度氧化 (Chapter 23).

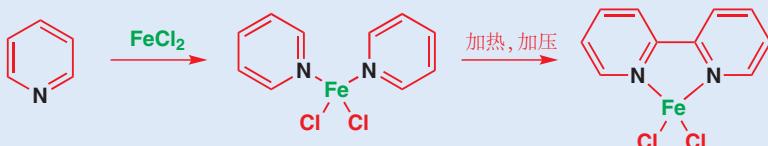


### 联吡啶 (bipy)

吡啶与金属形成配合物的能力在其二聚体——著名的配体 “bipy” 或 2,2'-联吡啶 (2,2'-bipyridyl)——中得以增强。它是对于很多过渡金属很好的双齿配体, 尤其偏爱 Fe(II)。

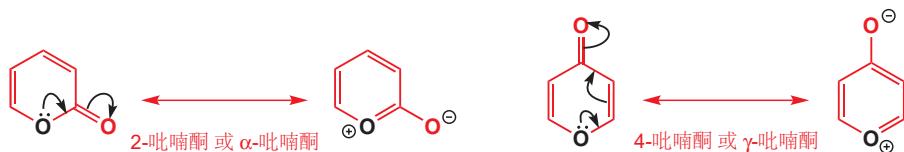


让两个吡啶环以这种形成 bipy 的方式结合, 看起来相当困难。它确实非常困难, 除非您通过使用一种有利于产物的试剂使反应容易进行。还有什么比  $\text{Fe}(\text{II})$  更适合这一角色呢? Bipy 通过用  $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$  在高温高压下处理吡啶来批量生产。只有一少部分的吡啶被转化为  $\text{Fe}(\text{II})$  络合的 bipy (大约 5%), 而余下的吡啶还可进行下一次反应。这可能是一个在  $\text{Fe}(\text{II})$  配位层内的自由基过程 (Chapter 37).

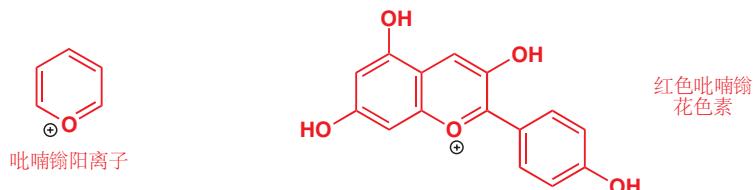


## 六元芳杂环可以包含氧

虽然吡啶压倒性地是六元芳杂环中最重要的一个, 但仍有氧杂的六元芳环, 吡喃酮 (pyrones) 存在, 它看起来像吡啶酮。虽然  $\alpha$ -吡喃酮相当不稳定, 但吡喃酮是芳香的。

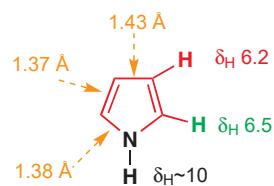


吡喃𬭩 (pyrylium) 盐是稳定的芳香阳离子, 以金属配合物的形式为很多花提供了颜色。基于其他元素 (例如 P) 的六元芳杂环确实存在, 但它们超出本书的范围。



## 五元芳杂环在亲电取代上表现良好

对于吡咯，几乎一切上述情况都是相反的。它比苯环容易得多地发生亲电取代反应——几乎太容易了——但亲核取代反应则更加困难。吡咯不是碱，也不能转化为  $N$ -氧化物。我们需要搞清楚其中的原因。最大的区别在于，氮孤对电子离域在环中了。<sup>1</sup> NMR 光谱提出，环中的所有位点，都几乎同样地富电子，化学位移比苯低大约 1 ppm. 环是平面型的，键长都非常相似，氮原子对面的键比其他的稍长一点。



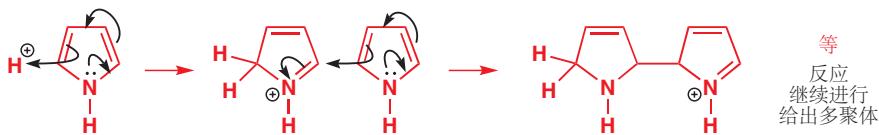
Interactive structure of pyrrole

您很快就会了解到，由于五元环，孤对电子的离域可以同样好地画在每个原子上。所有的离域都将电子由氮原子推向环，因此我们料到，以氮原子为代价，环上是富电子的。HOMO 能量应当更高，而环也将更加亲核。

离域造成的一个明显的结果，是氮原子碱性的减弱，和 NH 基酸性的增强。事实上，吡咯充当碱的  $pK_a$  大约为 -4，低于 pH -4 时会在碳上发生质子化。与之相比，NH 质子 ( $pK_a$  16.5) 可以被相比于移去一般仲胺的质子弱得多的碱移去。环的亲核特征意味着吡咯很容易被亲电试剂进攻。与溴单质的反应不需要 Lewis 酸，并且全部四个空位都会被取代 (验证吡咯的芳香性)。与吡啶和溴的反应性 (p. 731) 对比：仅在氮上发生一次反应。



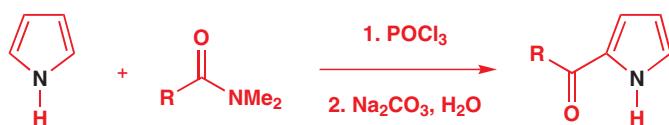
从某种角度，这是一个良好的反应，但通常，我们并不需要同一分子中含有四个溴原子，因此对吡咯的一个问题在于，如何控制反应仅给出单取代物。另一个问题在于，不能使用强酸。虽然质子化并不发生在氮上，但却会发生在碳上，质子化的吡咯会加成另一个分子。



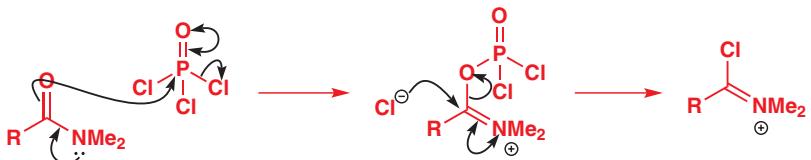
### ● 吡咯聚合物！

$pK_a$  低于 -4 的强酸，例如  $H_2SO_4$ ，若不想使吡啶聚合，则不能选用。

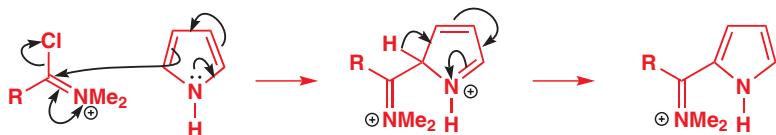
一些反应可以得到控制，以很好地产率给出单取代产物。其中一种是 Vilsmeier 反应，(Vilsmeier reaction)，反应中， $N,N$ -二甲基酰胺与  $POCl_3$  结合，在没有强酸或 Lewis 酸的存在下制得一个碳亲电试剂。这是 Friedel–Crafts 酰基化反应的替代方法，可与芳香化合物排序中较活泼的一端的化合物 (吡咯) 反应。



在第一步中，酰胺与将要带着羰基氧离开的  $\text{POCl}_3$  反应，羰基氧被替换为氯。这会是个很不利的过程，但 P–O 强键的形成提供了帮助，这很像您之前了解过的氯代吡啶形成反应。



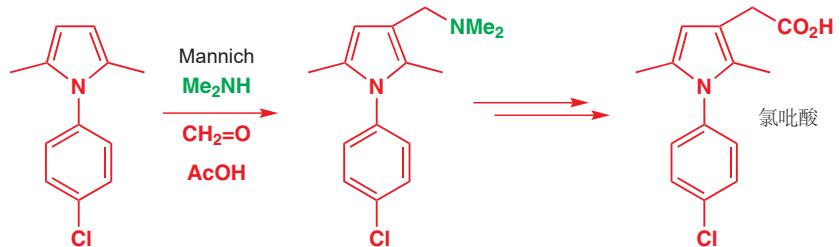
第一步的产物是一个亚铵阳离子，会与吡咯反应得到更稳定的亚铵盐。额外的稳定性来自吡咯氮和亚铵基的共轭作用。用  $\text{Na}_2\text{CO}_3$  水溶液后处理，则可水解亚铵盐，并可除去形成的任何酸(注：亲电取代中消去的质子)。这个反应尤其有用，是因为用  $\text{Me}_2\text{NCHO}$  (DMF) 可以很好地添加一个甲酰基 (formyl, CHO)。传统的 Friedel–Crafts 反应很难做到这一点。



Interactive mechanism for Vilsmeier reaction of pyrrole

► 回想一下 Chapter 26, p. 621 的 Mannich 反应。

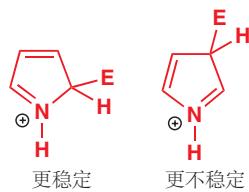
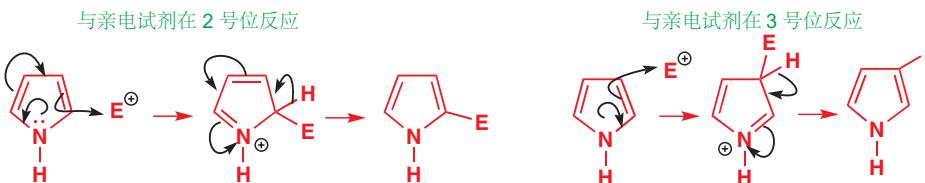
您可能已经注意到，这个反应仅在吡咯的 2 号位发生。虽然与像溴单质这样的试剂，会在所有位置反应，但大多数试剂还是会在 2 (或 5) 号位反应，仅仅在 2 和 5 号位被阻塞时，才会进攻 3 (或 4) 号位。一个很好的例子是 Mannich 反应。在下面的两个例子中，N-甲基吡咯 干净地在 2 号位上反应，另一种吡咯则由于 2 和 5 号位全部被甲基占用，才干净地在 3 号位反应。这些反应被用于非甾体抗炎化合物镇痛剂托美汀 (tolmetin) 和氯吡酸 (clopirac) 的批量生产上。



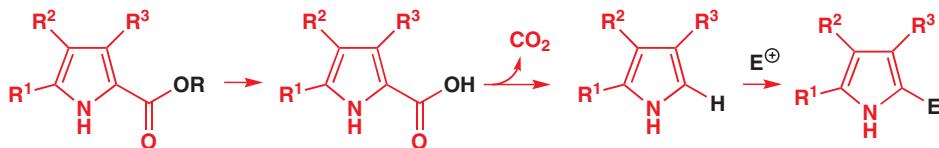
Interactive mechanism for the Mannich reaction on pyrrole

现在我们需要一个解释。2 和 3 号位取代反应的机理看起来都很好，我们会用概括性的  $\text{E}^+$  作为亲电试剂，画出这两种机理。这两种机理都能很容易地发生。在 2 号位的反应比 3 号位的稍微好些，但差别是很小的。取代反应在所有位置都有利。计算表明，吡咯的 HOMO 确实在 2 号位有较大的

系数，解释方法之一着眼于中间体的结构。两种中间体中，两根双键当然都彼此共轭，但只在第一种中间体中，它们才全都与  $N^+$  共轭（注：似乎说反了？）。第二种中间体是“交叉共轭的 (cross-conjugated)”，而第一种则是更稳定的线形共轭体系。



由于吡咯上的亲电取代反应发生得太容易，用一个可移去的取代基阻塞取代位点会是有用的。这通常用酯基完成。酯的水解 (对于叔丁酯尤其容易——见 Chapter 23) 可释放羧酸，继而在加热下脱酸。毫无疑问，最后的亲电取代反应必定发生在 C2 上。



脱羧是吡咯的一个一般反应：它是一种逆向的 Friedel–Crafts 反应，亲电试剂是一个质子 (由羧酸本身提供)，离去基团是而氧化态。质子化可能发生在任何地方发生，但只有在连有  $CO_2H$  基的位置质子化才会导致实质性的反应发生。



## 呋喃和噻吩是吡咯的氧和硫类似物

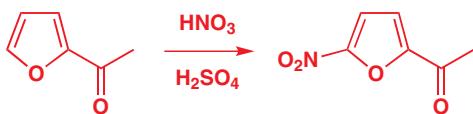
其他简单的五元杂环，还有用氧原子替代氮得到的呋喃 (furan)，和用硫替代得到的噻吩 (thiophene)。虽然不如吡咯，它们也非常容易发生芳香亲电取代反应。在这三者中，氮是最强的电子给体，氧其次，硫最差。噻吩的活性与苯相当。

噻吩是这三者中活性最差的，因为硫上与环共轭的，填有孤对电子的 p 轨道是 3p 轨道而不是 2p 轨道 (N 或 O 上的)，因此与碳的 2p 轨道重叠得不是很好。呋喃和噻吩或多或少都会参与一般的 Friedel–Crafts 反应，选用活性较弱的酸酐 (此处是醋酸酐，  $Ac_2O$ ) 代替酰氯，并优选比  $AlCl_3$  弱些的 Lewis 酸。



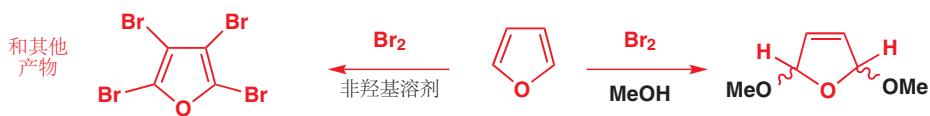
注意观察，区域选择性与吡咯的相同——两种情形中 2 号位都比 3 号位更活泼。酮产物面对亲电试剂，没有起始杂环活泼。然后，被钝化的呋喃可以被苯衍生物所用的试剂硝化。尽管有酮存在，

这个反应也发生在 5 号位上。发生 2- 和 5-取代反应的倾向性突出得很明显。



### 相比取代 呋喃可能更倾向于亲电加成

到目前为止，噻吩和呋喃看起来都很像吡咯，但在其他反应中，让它们的行为会大相径庭，我们将关注它们。呋喃比吡咯的芳香性弱，如果有形成像 C–O 单键这样的稳定键的希望，那么相比于取代反应，它就会倾向于这条路径。一个著名的例子便是呋喃在甲醇中与溴单质的反应。在非羟基溶剂 (non-hydroxylic solvents) 中，如您所料发生多溴代反应；而在 MeOH 中，则根本没有溴加入分子！



溴化反应以通常的方式开始，但一分子甲醇捕获了第一步反应形成的阳离子，并完成对呋喃的 1,4-加成。



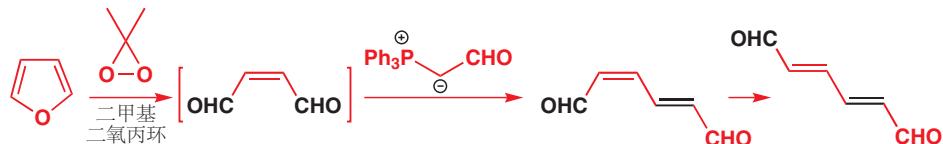
初期加入的溴原子现在会被呋喃氧原子推落，以得到一个相对稳定的共轭锌离子，继而添加第二分子的乙醇。



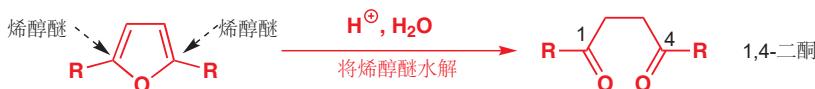
这个产物隐藏了一个有趣的分子。在环的两侧，都包含一个缩醛，如果我们将它们水解，则会得到“马来(二)醛 (maleic dialdehyde)” (顺丁烯二醛)——一个很不稳定，无法分离的分子。呋喃衍生物也许可以替代它被使用。



同样的 1,4-二醛 还可以通过用您在 p. 432 了解的温和的氧化剂二甲基二氧化丙环 (dimethyldioxirane) 氧化呋喃得到。在下面的流程中，产物被 Wittig 反应捕获，得到一个 E,Z-二烯，然后很容易会异构化为 E,E.



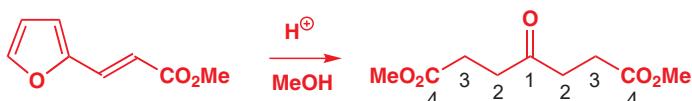
如果我们将呋喃考虑为一个在环的两侧的烯醇醚，那么我们可以将这个思路，拓宽到呋喃本身，1,4-二羰基化合物的来源上。如果呋喃中的两个烯醇醚被水解，我们便可得到一种 1,4-二酮。



这一次，箭头为实线，这是因为这个反应事实上真的能发生。您会在下一章探索到，呋喃同样可以由 1,4-二酮制取，因而整个过程是可逆的。我们选择的例子有其他值得注意的特征。包含呋喃的最便宜的起始原料是 2-呋喃甲醛 (furan-2-aldehyde) 或“糠醛 (furfural)”，早餐麦片工业生产的一种副产物。下面，它与一个被稳定的叶立德发生典型的 Wittig 过程。



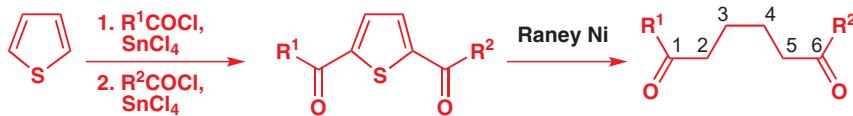
现在来到了最有趣的一步：用酸性甲醛处理这个呋喃，可得到有两个 1,4-二羰基关系存在的白色晶体化合物。您可能想要尝试画出这个反应的机理。



噻吩环也可以被开环，但经历的是非常不同的方式。用 Raney 镍进行的硫原子的还原去除，不但会还原 C–S 键，还会还原环中的双键，环中的四个碳原子会形成饱和烷基链。如果还原前，在噻吩上进行两次 Friedel–Crafts 反应，那么产物将会是一个 1,6-二酮，而不是从呋喃得到的 1,4-二酮。噻吩在 Friedel–Crafts 酰基化反应中表现良好，反应在 2 和 5 号位发生 (除非被阻塞)。

► 我们在 Chapter 28 中阐释过 1,4-双官能团化化合物制取的挑战性。

► Raney 镍已在 Chapter 23, p. 537 介绍过。

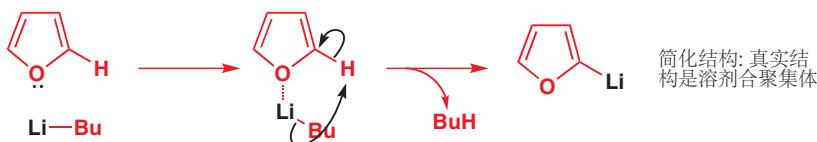


### 噻吩和呋喃的锂化反应

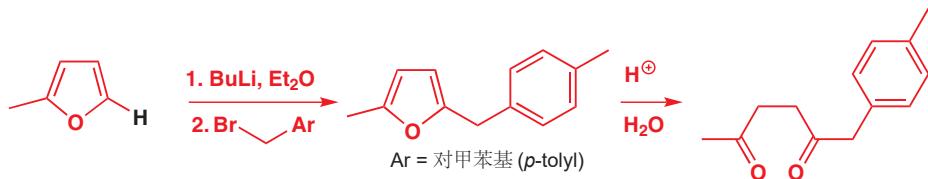
一个呋喃和噻吩都发生得尤其好，也很适合上两个反应的反应是金属化反应，尤其是锂化反应 (lithiation)，与杂原子相邻的 C–H 基的锂化反应。苯环的金属化反应 (Chapter 24) 通过锂卤 (Br 或 I) 交换——这种方法在杂环上也工作良好，我们稍后会见到吡啶的反应——或 (邻位) 锂化反应，直接锂化与 OMe 等活化基相邻的 C–H 基完成——对于噻吩和呋喃，环中杂原子便提供了必要的活化作用。



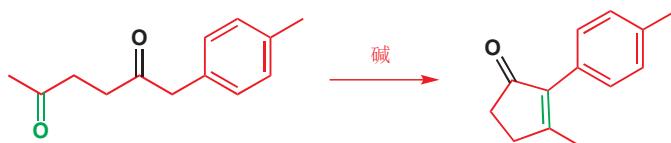
邻位锂化反应，通过 O 或 S 对 Li 的配位，和叔丁基对质子的移去完成——副产物是气态丁烷。这些锂化合物包含 碳–锂 σ 键，并且可溶于有机溶剂。我们对于它们的表达，非常简单，但事实上它们通常可能是二聚体或更复杂聚集体 (aggregates)，其中 Li 的配位层完全被 THF 分子占据。



这些锂化合物非常活泼，可与大多数亲电试剂结合——在下面的例子中，有机锂被一个苄基型(benzylic) 卤代物烷基化。用水溶性处理产物，则可使两个烯醇醚水解，得到 1,4-二酮。



将这个二酮用无水(*anhydrous*)酸处理，会重新得到呋喃(见 Chapter 30)；而在碱中，则会通过一个分子内的羟醛反应(Chapter 26)发生环化，得到环戊烯酮。

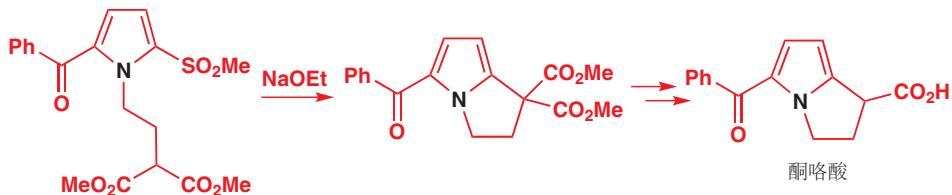


这完成了我们对噻吩、呋喃特殊化学性质的探索，现在，我们则将回到全部的三种杂环(尤其是吡咯)并着眼于亲核取代反应。

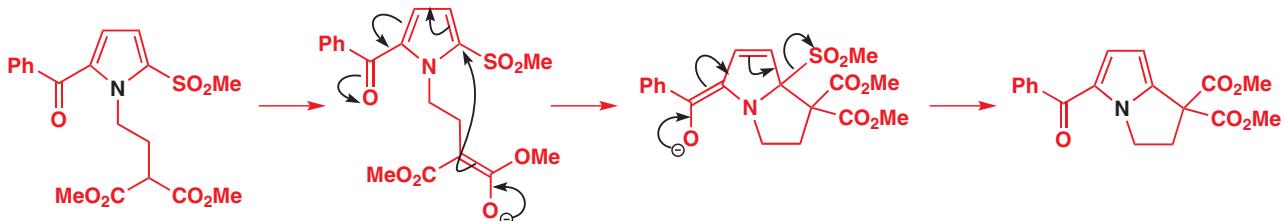
## 更多五元芳杂环的反应

### 亲核取代反应需求活化基

对于吡咯、噻吩，或呋喃，亲核取代反应是一个相对稀少的反应，若想让它们发生这类反应，与苯环类似(Chapter 22)，都需求硝基、羰基、硫酰基等活化基。下面的分子内例子被用于制取止痛药酮咯酸(ketorolac)。



亲核试剂是一个稳定的烯醇盐，离去基团是一个亚磺酸根阴离子。就像您在 Chapter 22 中了解的苯环的反应一样，在所形成的中间体中，负电荷离域到环上的羰基中。进攻发生在 2 号位，是因为离去基团在二号位，也是因为负电荷可以从那个位置离域到酮上。

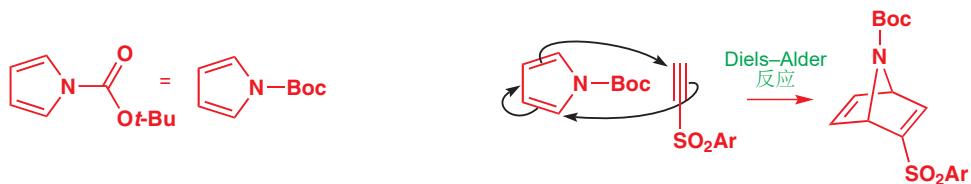


### 五元杂环在 Diels–Alder 反应中充当双烯体

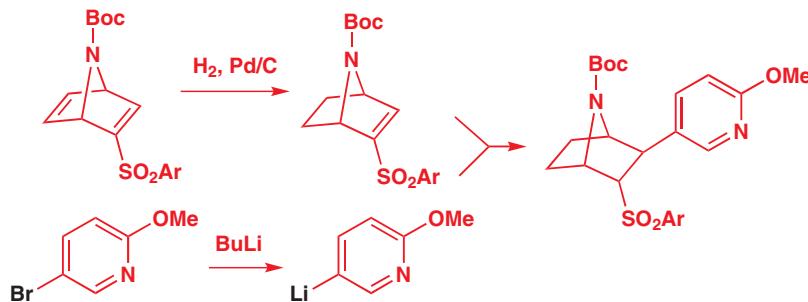
到目前为止，我们讨论的全部吡咯、呋喃和噻吩的反应都是苯的反应的变体。但杂环还可以发生完全与苯不同的反应，现在我们就将探索其中两个。

第一个反应是您将在 Chapter 34 中详细了解的反应。它被称作 Diels–Alder 反应 (狄尔斯-阿尔德反应, 简称 D–A 反应, Diels–Alder reaction), 虽然这个反应包含很多微妙之处, 而我们在此不会讨论, 但我们要了解的是, 它通过一个简单的环状机理, 其中六个电子 (三个弯曲箭头) 绕环移动形成一个新的六元环。

下面是一个吡咯的 Boc 衍生物的例子。吸电子的 Boc 基减弱了吡咯的亲核性, 并促进了与一个炔基砜的 Diels–Alder 反应。苯, 甚至其他很多杂环, 都无法进行这类反应。

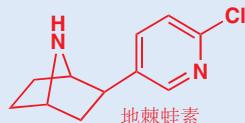


这个反应的产物是镇痛剂地棘蛙素 (epibatidine) 合成的中间体。下一步反应, 是选择性还原非共轭双键中的一根, 再将吡啶亲核试剂 (可由溴代吡啶制备的锂衍生物) 加成乙烯基砜上。

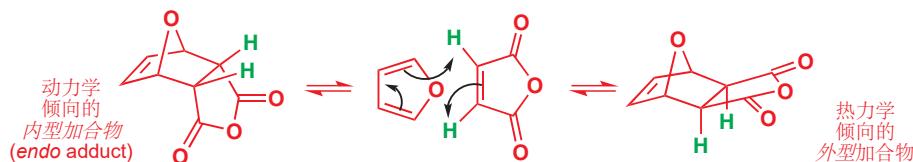


► Boc 保护基已于 Chapter 23, p. 558 讨论过。

**地棘蛙素**在 1992 年于厄瓜多尔蛙皮肤上被发现。它是一种格外强的镇静剂, 它与吗啡的作用机理不同, 因而人们希望它不会成瘾。这个化合物现在可以被合成, 并不再需要通过杀死青蛙获得——事实上, 它们是保护物种。

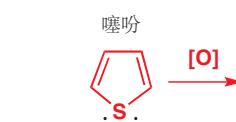
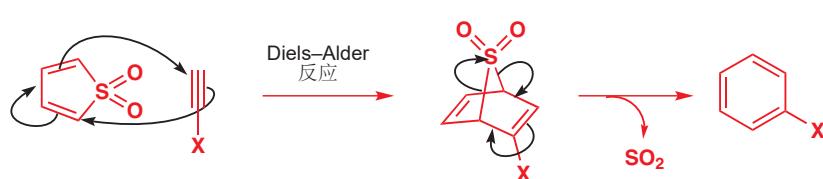


呋喃尤其适合进行 Diels–Alder 反应, 由于二烯体是芳香性的, 因而反应是可逆的, 并且得到热力学产物, 外型加合物 (*exo* adduct)。

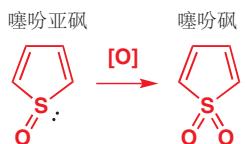


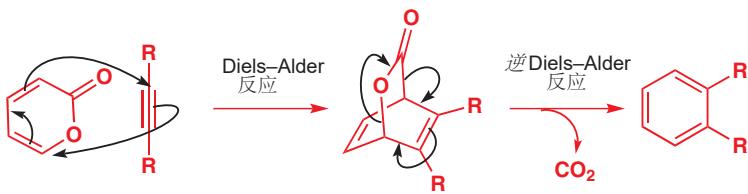
► 内型和外型 Diels–Alder 加合物将在 Chapter 34 被阐述。

芳香性阻止了噻吩参与 Diels–Alder 反应, 但可通过将噻吩氧化来破坏芳香性, 因为环状共轭体系所需的孤电子对都与氧成键了。噻吩砜不稳定, 会与自己反应, 但同样会发生 Diels–Alder 反应。与炔烃反应, 会失去 SO<sub>2</sub> 得到一个取代的苯衍生物。

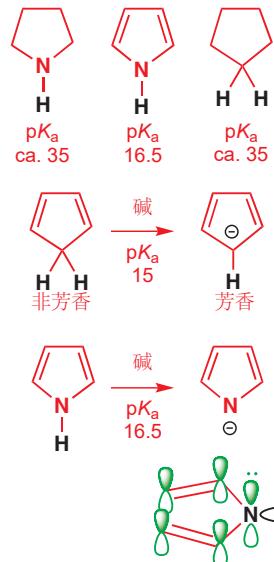


相似的反应可以在  $\alpha$ -吡喃酮上发生。它们也相当不稳定, 几乎没有芳香性, 与炔烃发生 Diels–Alder 反应后, 会继续发生逆 Diels–Alder 反应, 得到苯衍生物并失去 CO<sub>2</sub>。



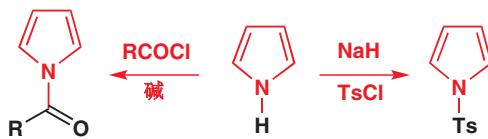


### 吡咯的氮阴离子很容易制取



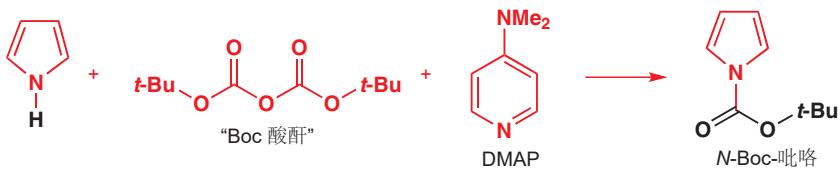
吡咯比类似的饱和胺酸性强得多（注：s轨道成分大，共轭碱稳定）。四氢吡咯/吡咯烷 (pyrrolidine/ineole) 的  $pK_a$  大约为 35, 而吡咯的  $pK_a$  为 16.5, 比前者酸  $10^{23}$  倍！吡咯与典型醇的酸性相近，因此比烷氧基阴离子强的碱即可将其转化为阴离子。不必惊讶的是，对应的烃类，环戊二烯，也具有较强的酸性， $pK_a$  为 15；这是因为虽然环戊二烯不是芳香的，但环戊二烯基阴离子（茂离子）是芳香的，有六个离域  $\pi$  电子，质子电离的过程获得了芳香性。

在目前我们见过的吡咯的所有反应中，新的基团都添加在环中的碳原子上。吡咯阴离子是有用的，因为它会在氮上反应。阴离子中的氮原子含有两对孤电子：一对离域在环中，另一对定域在氮原子的  $sp^2$  轨道上。较高能的后者是新的 HOMO，也是分子发生反应的位置。 $N$ -酰基化衍生物通常可通过这种方式制取。常用的碱是氢化钠 ( $NaH$ )，但更弱的碱也能产生足够反应发生的阴离子。



#### ● 吡咯阴离子可以与亲电试剂在氮上反应。

P. 739 地棘蛙素的合成所用的  $N$ -Boc 吡咯就是用这种方法制取的。所用的碱是吡啶衍生物 DMAP，您已在本章前文中见过 (p. 726, 注：酰基化/亲核催化剂)。它的共轭酸的  $pK_a$  为 9.7，因而产生少量的、平衡量的阴离子，并同时做亲核催化剂。“Boc 酸酐”被用作酰基化试剂。



在本章的下一个——关于当我们向吡咯环中放入更多的氮原子时发生的变化——的主节中，阴离子形成反应将会很重要。

## 包含两个或更多氮的五元环

### 咪唑

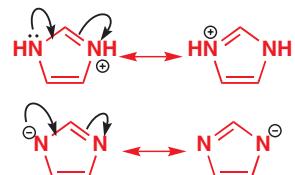
在本章的开始，我们便想象过向吡咯环中加入更多的氮原子，并发现，含有两个氮原子的化合物有两种：吡唑 (pyrazole) 和咪唑 (imidazole)。



在一个五元环中，只有一个氮原子能向芳香六隅体 (aromatic sextet) 提供两个电子。另一个氮原子则替换一个 CH 基，而不连有氢原子，如吡啶中的氮原子一样。黑色的氮原子是类吡咯 (pyrrole-like) 氮原子；绿色的则是类吡啶 (pyridine-like) 氮原子。黑色氮原子上的孤对电子在环中离域；绿色氮原子上的孤对电子则定域在自己的  $sp^2$  轨道中。我们可以料到，这些化合物的具有介于吡咯和吡啶之间的性质。咪唑是一个比吡咯和吡啶都强的碱——咪唑𬭩离子的  $pK_a$  几乎正好为 7，也就意味着中性水中会有 50% 的咪唑被质子化。咪唑的酸性同样比吡咯强， $pK_a$  为 14.5.



这些有趣的结果来源于两个氮原子的 1,3 关系。（质子化的）阳离子和（去质子化的）阴离子都在两个氮原子间平等地分享电荷——它们完美地对称，并不寻常地稳定。另一种考虑咪唑碱性的方法，是两个氮原子能同时作用于被进攻的质子。虽然捕获的质子的事实上是类吡啶氮原子，但吡咯氮也能用其离域电子，以下面的方式辅助这一过程：

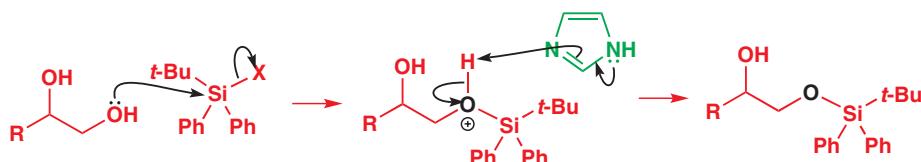


► DBU 的碱性也能用类似的效果解释，见 p. 175.

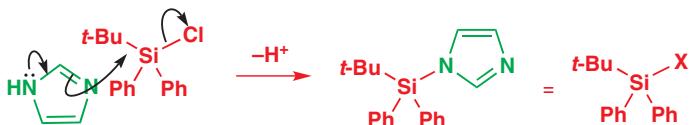
大自然利用了这一特征，将咪唑基以组氨酸的形式附着在蛋白质上，并在酶反应中让它们做亲核、碱、酸催化剂 (将在 Chapter 42 中讨论)。当我们向醇添加硅基时，也会用到这一特征。咪唑是这些反应受欢迎的催化剂。



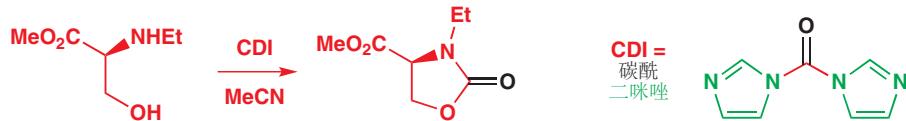
由于我们需要区别二醇中的伯醇和仲醇，因而需要的是一种弱碱催化剂。咪唑的碱性不足以移去醇的质子 ( $pK_a \sim 16$ )，但它可以在 OH 被硅原子进攻之后移去产物的质子。



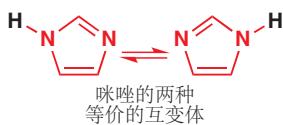
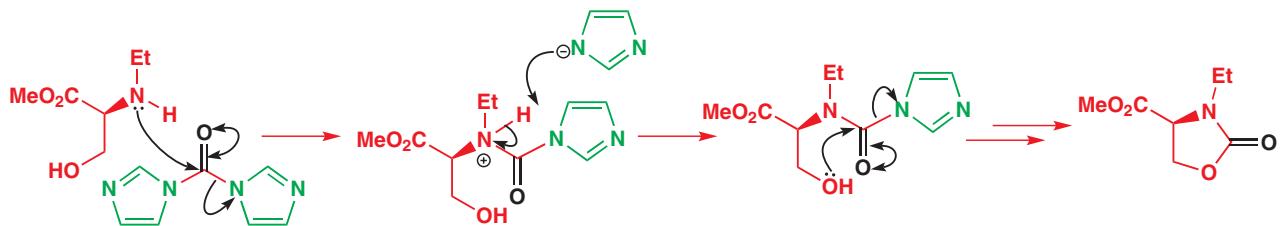
事实上，咪唑在这个反应中也做亲核催化剂，反应的第一步是咪唑对 Cl 的取代——这也是为什么在上一附图示中，我们将离去基表示为 “X” . 反应如这样开始：



运用相同的思路，我们可以将两个亲核试剂用一个羰基联系起来，并得到一个双亲电试剂，碳酰/羰基二咪唑 (carbonyl diimidazole, CDI)。光气 ( $\text{COCl}_2$ ) 也被用于这一用途，但它的毒性令人毛骨悚然（它的可怕效果在一战中被用作毒气）。CDI 安全、易控制得多。在这些反应中，咪唑被（两次）用于离去基团。



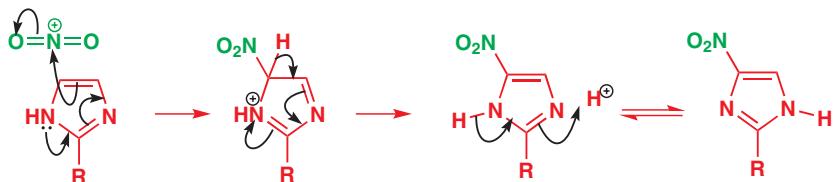
氨基很有可能率先进攻，并取代掉一个咪唑阴离子，咪唑阴离子会给铵盐去质子。然后，醇会在分子内进攻，取代掉第二个咪唑阴离子，继而给 OH 基去质子。该反应的副产物为两分子的咪唑。



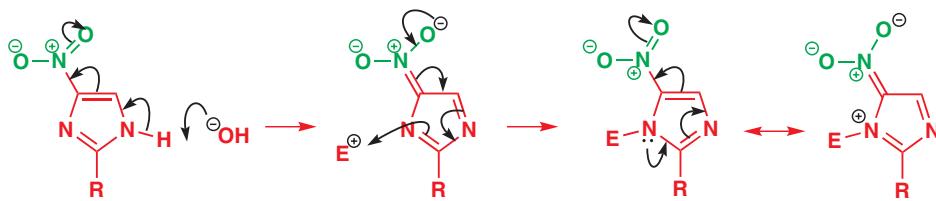
离域的咪唑阴离子与咪唑本身的关系，像是烯醇阴离子与烯醇的关系。因此像烯醇一样，室温下，咪唑在溶液中会快速地互变异构，这不足为奇。对于母体化合物本身，这两种互变体是相同的；但对于不对称的咪唑来说，互变异构就更有趣了。我们会将这个问题同咪唑的芳香亲电取代一起探究。包含在两个氮原子间（2 号位）的取代基的咪唑可以被通常的硝化试剂硝化，并得到以两种互变体的混合形式存在的产物。



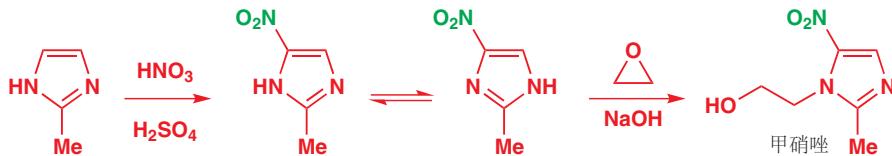
通过类吡咯氮原子上电子的推动，硝化可能发生在环剩余的两个位置中的任一个上。硝化后的互变异构也会导致混合。互变异构是快速的，互变体不能得到拆分。



互变异构可以通过在一个氮原子上烷基化得到阻止。如果在碱性溶液中完成，会有阴离子作为中间体，烷基会添加在硝基旁边的氮原子上。同样，阴离子由哪个互变体衍生并不重要——由它们得到的是同一种阴离子，同时在硝基和氮原子上离域。烷基化发生在硝基旁边的氮原子上的一个原因是，它包含一个处在类吡咯氮和硝基间的线性共轭体系（见 p. 734）。

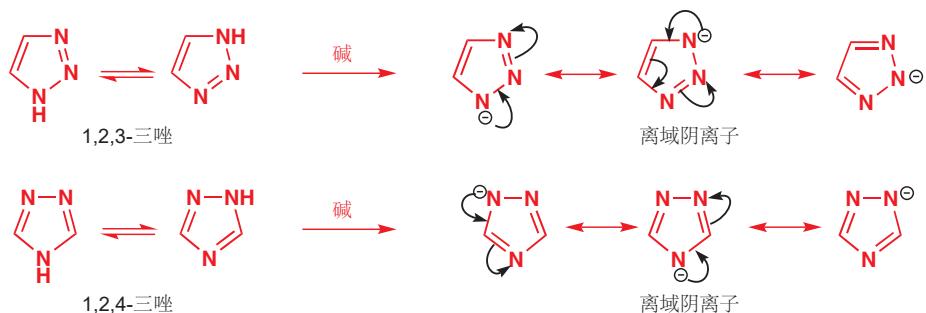


通过这种方式可制取重要的医药中间体。抗寄生虫药物甲硝唑 (metronidazole) 由 2-甲基咪唑通过硝化和碱性下与环氧的烷基化获得。

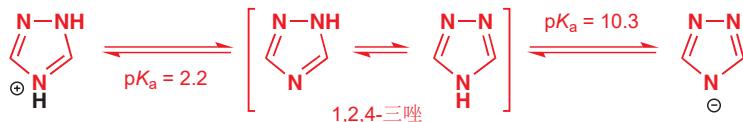


### 三唑

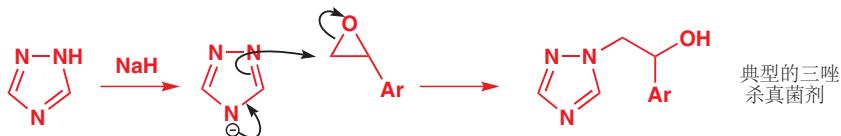
存在两种三唑，每种都含有一个类吡咯氮和两个类吡啶氮。它们都有互变异构的可能性 (在 1,2,3-三唑中，有两种互变体是等价的)，去质子形成的也都是同一阴离子。



**1,2,4-三唑** 更加重要，这是因为它是最好的现代农用杀真菌剂，及治疗人类真菌疾病的药物的基础。额外的氮原子，不可避免地是类吡啶的，这会使三唑的碱性比咪唑弱 (类吡啶氮只能诱导吸电子)，但酸性却强，阴离子更容易制取。

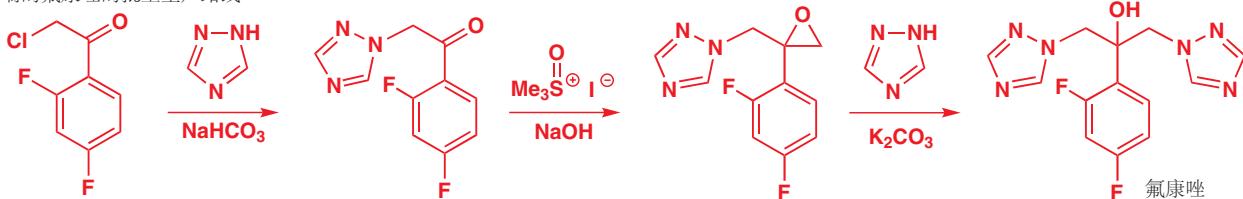


杀真菌剂通常通过三唑阴离子对环氧或其他碳亲电试剂的加成制取。阴离子通常在两个连起来的氮原子中的一个上反应 (无所谓在两个中的哪个上——产物是相同的)。

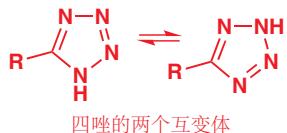


一个用于对抗人类真菌感染的现代离子是辉瑞公司的氟康唑 (fluconazole), 包含两个三唑。第一个以阴离子的形式添加到  $\alpha$ -氯代酮上, 而第二个则也以阴离子的形式添加到通过您在 Chapter 27 中学过的锍叶立德化学制得的环氧上。注意观察, 用于催化这些反应的都是弱碱。三唑的酸性较弱,  $\text{NaHCO}_3$  足以使其产生少量的阴离子。

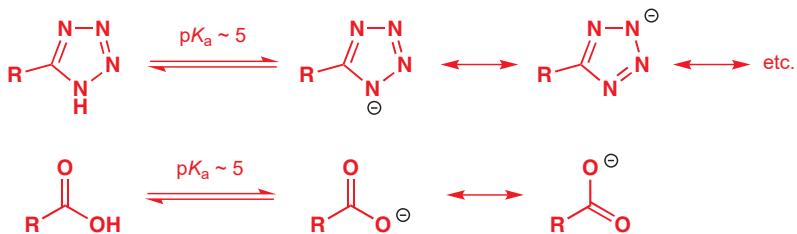
辉瑞的氟康唑的批量生产路线



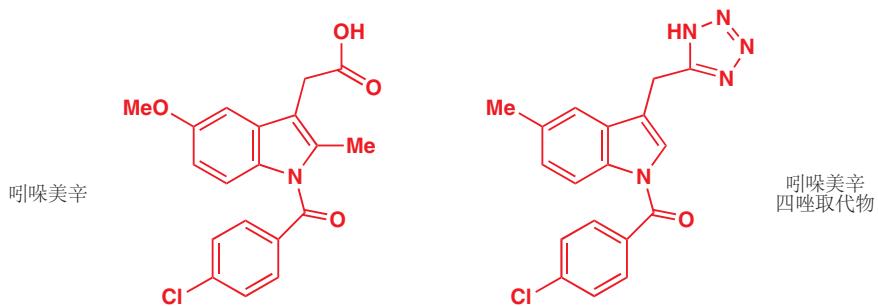
### 四唑



由于环上仅剩下一个碳原子, 四唑或 C-取代的四唑只有一种异构体, 但它们可能有很多互变体。对于四唑, 主要的兴趣在于, 它们的酸性相当强: 失去 NH 形成阴离子的  $\text{pK}_a$  大约为 5, 基本上与羧酸等同。阴离子在全部四个氮原子中离域 (同样也在碳原子上), 四个氮原子完成了两个氧原子的工作。



由于四唑的酸性与羧酸相似, 人类药物中的羧酸若有不理想的性质, 它们便可用于替代  $\text{CO}_2\text{H}$  单元。一个简单的例子是抗关节炎药物吲哚美辛 (indomethacin), 可以将它的羧基替换为四唑而不丧失任何活性。



### 氮原子和爆炸

包含连在一起的两个或三个氮原子的化合物, 如重氮甲烷 ( $\text{CH}_2\text{N}_2$ ) 或叠氮化物 ( $\text{RN}_3$ ), 都是潜在易爆的, 因为它们可以瞬间释放出稳定的氮气。带有更多氮原子的化合物, 例如四唑, 则很有可能更危险, 很少有人试图制备五唑。重氮四唑 (diazotetrazole) 达到了极限, 它的分子式为令人震惊的  $\text{CN}_6!$  通过 5-氨基四唑的重氮化制取, 首先得到的是重氮盐。



重氮盐极其危险：“应当强调的是，（重氮盐）尤其易爆，需要格外小心地处理。我们建议每次分离的量不超过 0.75 mmol。它们的醚类溶液稍微稳定些，但在 -70 °C 下放置 1 小时后便会发生爆炸。”那么对于重氮化合物呢？它极其不稳定，会失去一分子氮气，分解为卡宾，然后又会失去两分子氮气，得到…

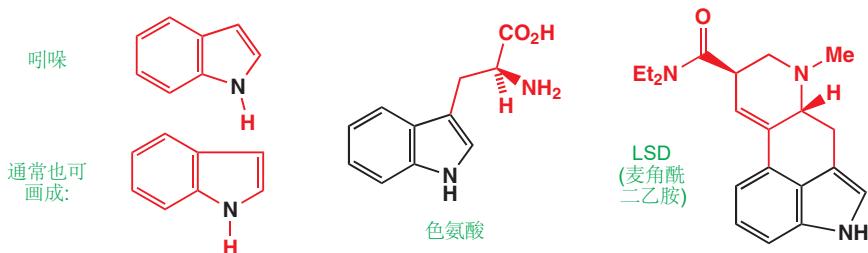


所剩的是一个碳原子，这也是少数用化学手段制得碳原子的方法之一。碳原子有很令人瞩目的反应，也已被简要地研究过，它们的起始原料危险的制备方法，打消了大多数研究者的念头。然而，您会在下一章看到，1-氨基四唑是抗过敏药物的制取上有用的起始原料。

## 苯并杂环

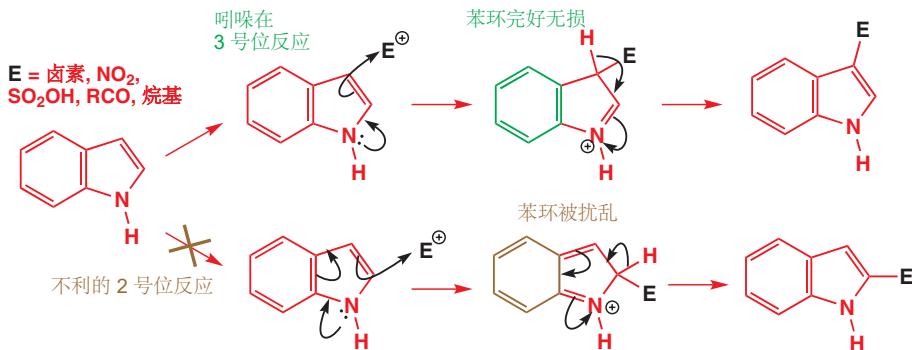
### 吲哚是苯并吡咯

吲哚美辛和它的四唑类似物，都包含吡咯环和稠合 (fuse) 在吡咯环旁的苯环。这样的双环杂环结构被称作**吲哚 (indoles)**，也是我们接下来的主题。吲哚本身包含一个苯环和一个吡咯环，它们分享一根双键，或者也可以看作，是一个带有 10 电子的芳香体系——来源于双键的八个电子，和来源于氮的一对孤电子。

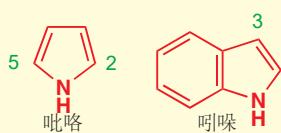


吲哚是一种重要的杂环因为它会以色氨酸的形式，被构筑到蛋白质中 (Chapter 42)；因为它是很多重要药物的基础，如吲哚美辛；同时也因为它为吲哚生物碱 (**indole alkaloids**) 提供了骨架——吲哚生物碱是来源于植物的生物活性化合物，包括士的宁/马钱子碱 (strychnine) 和 LSD (生物碱将于 Chapter 42 中讨论)。

许多方面，吲哚的化学性质都是一个活泼的吡咯环，和一个相对不活泼的、靠在一边的苯环的性质——比如，亲电取代往往都会发生在吡咯环上。但吲哚和吡咯在一个重要方面有所不同。在吲哚中，几乎所有试剂的亲电取代都倾向于在 3 号位发生，而对于吡咯，则应是 2 号位。卤代、磺化、Friedel–Crafts 酰基化、烷基化都干净地在该位置发生。



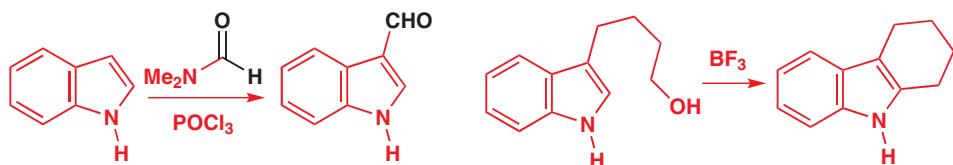
当然，这正好与吡咯的相反。那么为什么会这样呢？一个简单的解释是，在 3 号位的反应中，五元环仅仅包含相当孤立的烯胺体系，但苯环的芳香性没有被扰乱，中间体上的正电荷，当然会环绕整个苯环离域，但氮原子是最主要的稳定化因素。若不想严重地干扰苯环的芳香性，2 号位的反应无法发生。



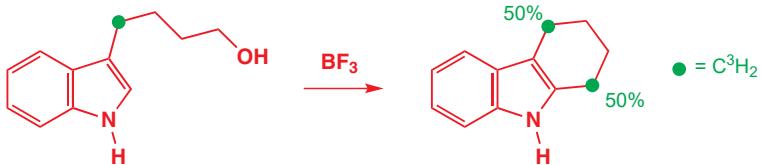
### ● 吡咯和吲哚上的亲电取代

吡咯（及吲哚中的吡咯）可以与亲电试剂在所有位置上反应，吡咯倾向于在 2 号和 5 号位，吲哚更倾向于在 3 号位。

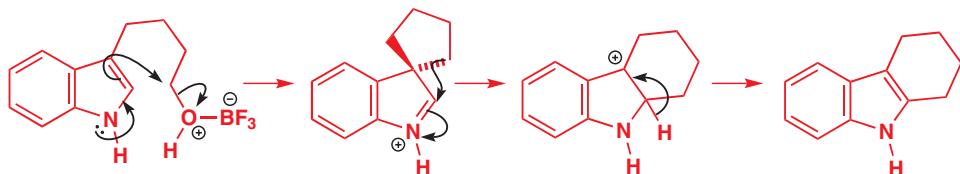
一个简单的亲电取代的例子，是与 DMF 和  $\text{POCl}_3$  发生的 Vilsmeier 甲酰化反应，该反应中，吲哚和吡咯有相似的反应性，只是区域选择性不同。如果 3 号位受阻，反应便会在 2 号位上，这似乎表明，带着电子以“错误方式”环绕五元环是没问题的。右下分子内的 Friedel-Crafts 酰基化便是一个例子。



一个巧妙的实验显示，这个酰基化反应并不能作为上述结论的例子。如果起始原料在与环相连的位置被氚（放射性的  $^3\text{H}$ ）标记，产物则在预期的位置显示确切的 50% 标记，而在非预期的位置也显示了 50%。

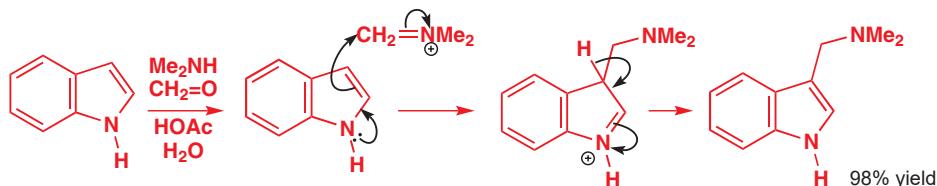


为了得到这个结果，反应必须包含一个对称的中间体，中间体也必须包含明显的进攻 3 号位的候选物。产物由中间体螺环化合物形成，该化合物包含一个与吡咯环成直角的五元环——每个  $\text{CH}_2$  基都有同等的机会发生迁移。

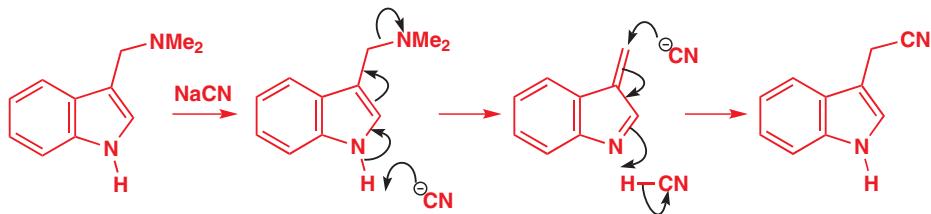


▶ 迁移类似 Chapter 36 中的频哪醇重排。

现在认为，大多数发生在 2 号位的取代反应，都是通过这个迁移完成的，但还有一些是通过扰乱苯环的直接进攻完成的。偏好吲哚 3 号位的一个很好的例子是 Mannich 反应，它与吲哚的反应和与吡咯、呋喃的一样好。



吲哚和吡咯氮原子给电子能力最好的表露，莫过于这些 Mannich 碱的(反应的产物)的用途。您可能还记得，一般的 Mannich 碱可以通过烷基化或消除转化为其他的化合物(见 p. 621)。由于在有 NaCN 在周围做碱和亲核试剂时，吲哚氮甚至可以直接脱去  $\text{Me}_2\text{N}$  基，因而无需烷基化。反应是缓慢的，产率也不是很精彩，但这能发生已经很令人惊奇了。这个反应在吡咯衍生物上更容易发生。

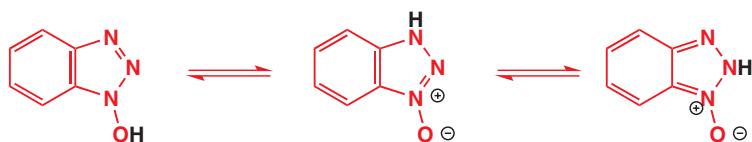


我们见过的所有五元环都有它们的苯并衍生物，但接下来，我们只会再关注其中一个，1-羟基苯并三唑(1-hydroxybenzotriazole)，既因为它是一种重要的化合物，又因为我们对于1,2,3-三唑本身谈论得还很少。

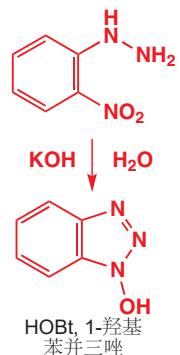
### HOt 是肽合成中重要的试剂

1-羟基苯并三唑(HOBt)是生化学家工作时的朋友。当需要一个氨基酸被活化的酯，与另一个氨基游离的氨基结合时(见 Chapter 23 中的一些例子)，它便会被加入反应中。它在十九世纪首次通过一个令人瞩目的简单反应制得。

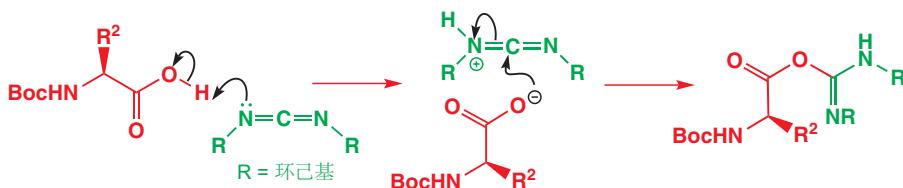
除了不稳定的N—O单键，HOBt的结构很容易理解，但我们还可以容易地画出一些其他的互变体，其中氧上的质子——杂环中唯一的质子——被移动到某个氮原子上。这些结构都是芳香的，第二个和第三个结构都是硝酮(nitrones)，第三个结构看起来不如前两个。



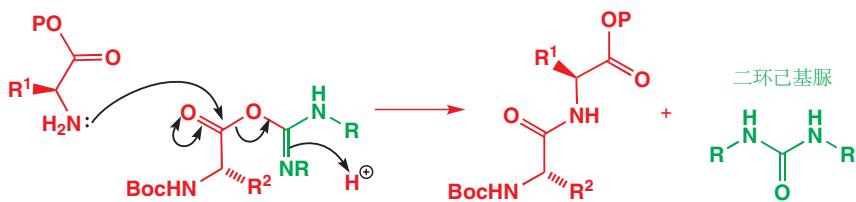
当在实验室中偶联氨基酸时，HOBt便会起到作用。这个反应是一个酰胺形成反应，但在 Chapter 23 中我们已经提到过，多肽的制取上，不能使用氨基酰氯——它们太过活泼，会引发副反应。相反，应该选用被活化的(有很好的作为离去基团的 $\text{RO}^-$ 基)氨基酯。在 Chapter 23 中我们使用的是苯酚酯，而在偶联反应中，最常用偶联试剂(coupling reagent)是 DCC，二环己基碳二亚胺(dicyclohexylcarbodiimide)。DCC与羧酸这样反应：



您会在 Chapter 34 中了解一些硝酮化学。

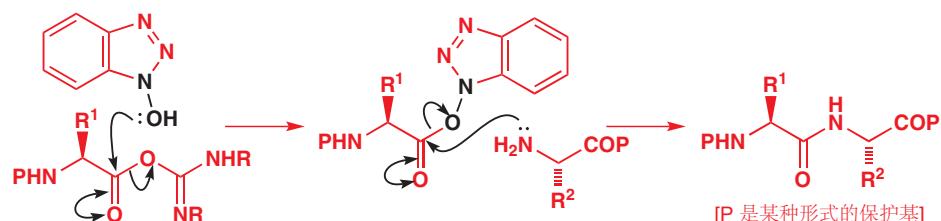


产物酯被亲核试剂取代时，会脱去一个非常稳定的脲作为离去基团，因而是被活化的。

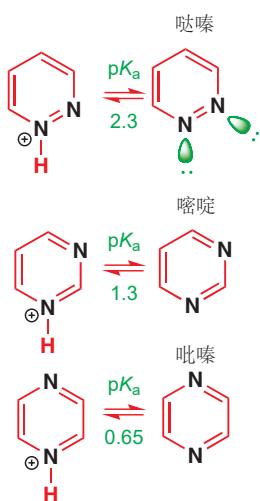


► Chapter 26 中有这样的观点：最亲电的羧酸衍生物也是最容易烯醇化的。

酯会被第二个氨基酸的氨基直接进攻，但问题在于，通常会发现，被活化的酯有一些外消旋化发生（通过烯醇互变）。一个很好的方法是使周围含有大量的 HOBT。它会提前于外消旋化，首先拦截被活化的酯，这主要是由于，反应被 HOBT 的加成高度加速。第二个在羰基上被保护的氨基酸，会进攻 HOBT 酯，以非常快速的，没有外消旋化的反应给出二肽。

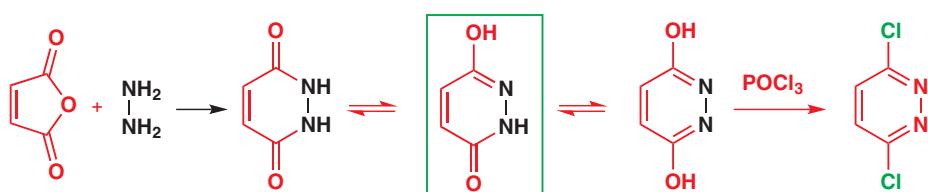


## 将更多氮原子放入六元环中

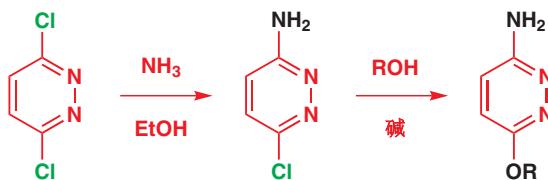


在本章的开始，我们提到了三种包含两个氮原子的六元芳杂环——哒嗪、嘧啶和吡嗪。这些化合物中，两个氮原子必定都是类吡啶氮，它们的孤对电子不离域在环中。

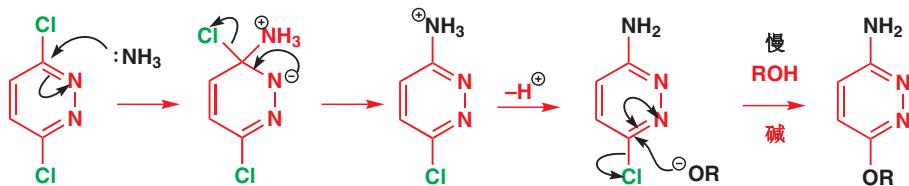
我们将在此简要地考察这些化合物。嘧啶的重要性超过其他两种，因为 DNA 和 RNA 中包含嘧啶——您会在 Chapter 42 中发现。全部三种化合物都是非常弱的碱——事实上几乎没有碱性。哒嗪比其他两种的碱性稍强，因为两对相邻的孤电子排斥彼此，使分子更加亲核（ $\alpha$  效应，见 p. 513)。这些非常缺电子的环的化学性质，主要涉及亲核进攻和醇、胺等亲核试剂对 Cl 等离去基团的取代。为了介绍这一主题，我们需要引入一个杂环合成的例子，但这是下一章的主题。这个化合物，马来酰肼 (maleic hydrazide) 已经被了解了有一段时间了，因为用马来酸酐使肼发生两次酰基化便能很容易制得。



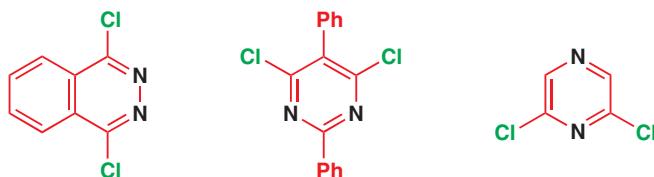
该化合物倾向于以第二种对映体存在（绿色框出的）。回想我们已经了解过的吡啶与  $\text{POCl}_3$  的反应，哒嗪的反应无疑会给出二氯哒嗪。二氯哒嗪中的两个氯原子，可以以此被氧或氮亲核试剂取代。在第一步反应中，只有一个氯原子被取代，因而，如果需要的话，可以选择另一种亲核试剂发生第二次取代。



这是如何做到的呢? 这个反应的机理是对哒嗪环的加成, 和离去基团的失去。吸电子基 (Cl) 被强的给电子基 ( $\text{NH}_2$ ) 取代, 因此反应后的化合物没有起始原料亲电, 反应的决速步, 亲核试剂加成的步骤便会更慢。

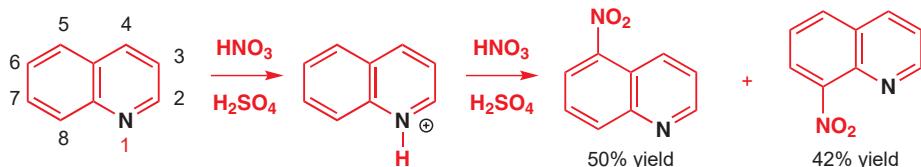
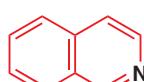
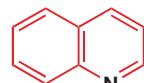


相同的原则也可应用于其他容易制得的, 这些环和它们苯并类似物的对称二氯衍生物。下面例子中所示的, 氮原子的相对关系可以是 1,2, 1,3, 或 1,4. 前两个分子被用于连接 Sharpless 不对称双羟基化反应中所需的喹啉衍生物配体, 我们将在 Chapter 41 中叙述。

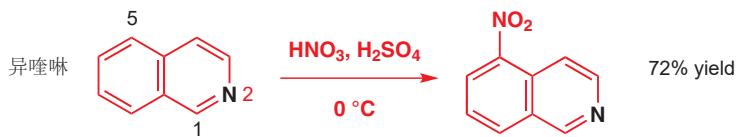


## 与吡啶稠合的环: 喹啉和异喹啉

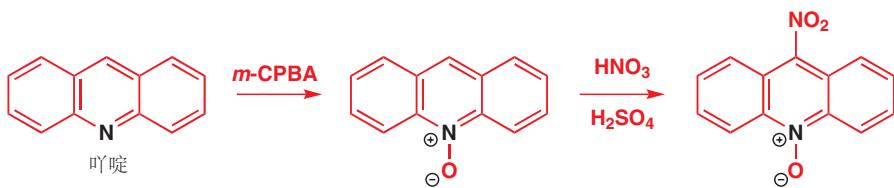
苯环可以以两种方式耦合在吡啶环上, 氮原子与苯环相邻时得到重要的杂环喹啉 (quinoline), 氮原子在另一个位置上得到的是异喹啉 (isoquinoline). 奎宁 (本章开篇展示过的结构) 中有部分由喹啉形成, 异喹啉则用于形成异喹啉生物碱 (将在 Chapter 42 讨论) 的中心骨架。在本章中, 我们不需要对喹啉讲太多内容, 因为它的行为如您所料——是苯和吡啶化学性质的混合。亲电取代反应倾向于在苯环上发生, 而亲核取代反应则有利于在吡咯环上发生。因此喹啉的硝化会给出两种产物——5-硝基喹啉 和 8-硝基喹啉——比例近乎相同 (您会意识到, 反应其实发生于质子化的喹啉上)。



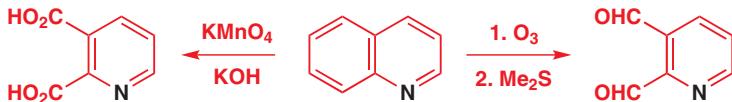
这很明显是相当不令人满意的, 但硝化反应实际上还算是表现得较好的反应。氯代反应会给出 (至少) 十种产物, 其中不少于物种是不同结构的氯代喹啉。异喹啉的硝化表现得好得多, 在  $0^\circ\text{C}$  下以 72% 产率给出一种异构体 (5-硝基异喹啉)。



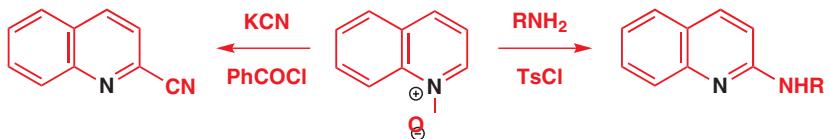
为了得到在吡啶环上的反应, 可以选用  $N$ -氧化物——如我们促进吡咯本身亲电取代的方法一样。一个很好的例子是吖啶 (acridine), 包含两个与吡啶稠合的苯环, 它会得到四种硝化产物, 都发生在苯环上。另一方面, 它的  $N$ -氧化物, 以很好地产率只给出一种, 发生在吡啶环上唯一所剩的位置的硝化产物。



一般来说，这些反应的用处不大，大多数取代基已在喹啉合成之前，就被放入前体中，我们将在下一章阐述。但有一对喹啉的反应，不寻常并令人感兴趣。剧烈的氧化反应发生在更富电子的苯环上，并会破坏喹啉，离去在 2 和 3 号位有羰基的吡啶环。



当在亲核试剂的存在下，用酰基化试剂处理 喹啉 *N*-氧化物 时，将会发生一个尤其有趣的反应。下面的两个例子显示，会在 2 号位发生亲核取代反应，您也许会将这类反应与吡啶 *N*-氧化物的亲核取代反应比较。它们的机理是相似的。



我们在考虑喹啉和吲哚中的稠环时，苯和杂环一直保持分开。但有一种方式，可以让它们更加紧密地结合，那就是在环的连接处放置氮原子。

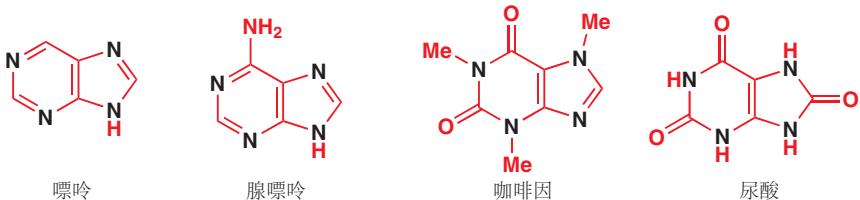
### 氮原子可以处在环的连接处



处在连接处的氮原子，由于需要成三根（三角型的） $\sigma$  键，因而需要是类吡咯氮，孤对电子在 p 轨道中。这意味着其中一个环需要是五元的，这类有趣的化合物中最简单的成员被称作中氮茚/吲哚 (indolizine)——它包含沿着一根 C–N 键稠合在一起的一个吡啶和一个吡咯环。如果您审视这个结构，您便会发现，吡咯环肯定存在，但吡啶环却并不完全存在。当然，孤对电子和  $\pi$  电子全都是离域的，但这个体系，与吲哚和喹啉的不同，将它，从外环的角度，视作十电子环，比将它视作两个连接在一起的六电子环好得多。正如所料，中氮茚与亲电试剂在五元环上发生取代反应。

### 多于一个氮原子的稠环

继续将氮原子嵌入稠环体系也是可行的，并且很多重要的化合物都属于它们。嘌呤 (purine-s) 是 DNA 和 RNA 的一部分，例子包括下面所示的腺嘌呤 (adenine) 和鸟嘌呤 (guanine, 在下一页文字框中)，简单的嘌呤在我们生命中也扮演着重要的角色。咖啡和茶的兴奋剂性质来源于咖啡因 (caffeine)，一个简单的三甲基嘌呤衍生物。它含有一个与嘧啶稠合的咪唑，尽管有两个羰基，它也仍是芳香的。



## 尿酸、痛风和别嘌醇

另一种嘌呤，尿酸 (uric acid) 在自然界中分布广泛——鸟类使用它，人类在某些程度上也使用它来排泄多余的氮——但当尿酸晶体在关节处沉积时，便会对人类造成很大的痛苦。我们称这种疼痛为“痛风”。解决方法是设计一种对产生尿酸的酶的特异性抑制剂，不出意料地，与尿酸类似的别嘌醇 (allopurinol) 是最佳的选择。



没有了两个羰基，咪唑环也被替换为吡唑环。DNA 中的鸟嘌呤在体内被降解为黄嘌呤 (xanthine)，然后被氧化为尿酸。别嘌醇与黄嘌呤氧化酶 (xanthine oxidase) 结合，只使其失去活性，而不与之反应。事实上，它模拟的不是尿酸，而是以竞争模式模拟真正的底物，黄嘌呤。这种酶在人体的新陈代谢中起到的是次要作用，因而抑制它并不会导致严重的结果——只会防止尿酸的过量产生。



很多稠合杂环具有非常吸引人的风味和气味性质。通常来说，吡嗪在很多强烈食品风味中是重要的：右侧，包含一个处在环连接处的氮原子的稠合吡嗪，烤肉味道中最重要的化合物之一。在下一页的文字框中，您可以阅读到有关提供青椒风味的简单吡嗪的内容。

最后，右侧的第二个化合物，形成了一组重要的药用分子，包括对人类的抗肿瘤化合物，和对动物的驱虫药 *anthelmintics* (驱赶寄生虫的药物)。它们由一个 6/5 稠合芳环体系衍生，该体系是一个包含三个氮原子的中氮茚环体系。

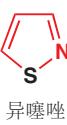
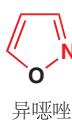
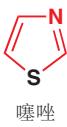
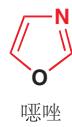
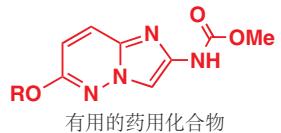
上述所有的多杂原子插入，涉及的都只有氮原子；现在，让我们简要地着眼于将氮与氧在杂环中结合时会发生什么。

## 芳杂环可以包含很多氮原子 却只能包含一个硫或氧原子

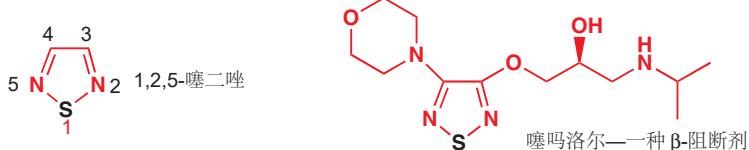
中性的氧和硫原子只能成两根键，因而它无法像吡啶中的氮原子一样加入环中——它只能以吡咯的方式加入。我们可以依我们所好，在环中加入很多类吡啶氮；但无法加入多于一个类吡咯氮。近似地，我们也只能在芳环中加入一个氧或硫原子。最简单的例子是噁唑 (oxazoles)、噻唑 (thiazoles)，及它们较不稳定的异构体异噁唑 (isoxazoles) 和异噻唑 (isothiazoles)。

“异-”化合物的不稳定性来自于弱的 O—N 或 S—N 键。这些键可以被还原剂切断，而还原剂通常还会继续还原剩余的官能团。还原 N—O 键得到的第一个产物是一个不稳定的亚胺-烯醇；烯醇会互变异构为酮，亚胺会被继续还原为胺。

带有更多氮原子的这样的杂环也可存在，但相对不重要，我们只会提及其中一个，1,2,5-噻二唑，由于它是一种药物，噻吗洛尔 (timolol) 的一部分。



■ 噻吗洛尔是一种  $\beta$ -阻断剂，可以阻断肾上腺素的某种行为，并通过抵抗高血压阻止心脏病的侵袭。



### 青椒的风味

对青椒风味化合物的探索为我们提供了回顾一些光谱法的机会。这种强效的化合物是由青椒(辣椒属菜椒变种 *Capsicum annuum var. grossum*)的油中分离得到的。油约占该青椒质量的 0.0001%，青椒主要的风味来源化合物又占油中的 30%。它的分子离子的分子量为 166，看起来像是没有氮的化合物，也许是  $C_{11}H_{18}O$ 。但高分辨率质谱法揭示， $M^+$  的分子量事实上是 166.1102，几乎精确地对应于  $C_9H_{14}N_2O$  (166.1106)。

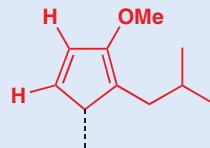
IR 中没有 OH, NH, 或 C=O 峰，质子 NMR 如下所示。

$\delta_H$ , ppm	积分	形状	$J$ , Hz	注释
0.91	6H	d	6.7	$Me_2CH^-$
1.1–2.4	1H	m	?	
2.61	2H	d	7.0	$CH_2CH^-$
3.91	3H	s	—	$-OMe?$
7.80	1H	d	2.4	芳香
7.93	1H	d	2.4	芳香

$Me_2CH$  和  $CH_2CH$  信号中的 “CH” 特征必定是同一个 CH，它也必定是 1.1–2.4 ppm 处的信号，是唯一一个显示出足够的偶合的，因而应描述为一个“多重峰”。它会是三重峰的七重峰，即 21 条。我们可以很容易地重建出分子的脂肪族部分，它包含连接在相同的 CH 基上的两个甲基和一个  $CH_2$  基。



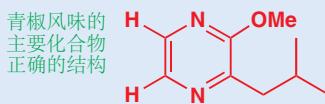
我们还有一个  $OMe$  基(只有氧的电负性足以将甲基带至 4 ppm 附近)。目前加起来是  $C_9H_{12}O$ ，所剩的还有  $C_4H_2N_2$ —没有关于氮官能团的线索。我们还要一个必定包含氮的芳环(由于仅剩下五个碳原子——不构成苯环！)两个芳香氢之间的偶合常数为 2.4 Hz。那么可能含有一个吡咯环吗？不可能，有两点理由。如果我们尝试构建这样的分子，我们便无法容纳最后的氮！如果我们将它放在虚线的末端，它便会成为可被检测到的  $NH_2$  基，但事实并非如此。



更好的理由是，化学位移都是错误的。富电子的吡咯环上的质子应在 6–6.5 ppm 周围，比苯(7.27 ppm)更高场。但这些质子位于 7.8–8.0 ppm，比苯低场。此处是一个被去屏蔽的(缺电子)环，而不是一个被屏蔽(富电子)的环。根据您目前对杂环化学的了解，这个环必定是一个六元环，因而也必定还要放入两个氮原子。下面是三种满足要求的方式。



小的偶合常数真正适合的只有是吡嗪，化学位移，虽然没有那么低场，也大约是正确的。这是由于环上还有一个向芳香体系供电子的 MeO 基，会略微提高屏蔽，并将电子向高场移动。这给了我们一个独特的结构。

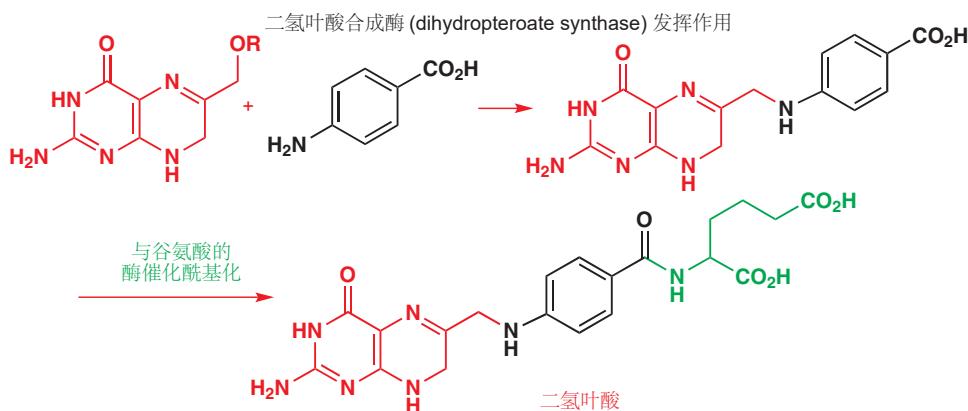
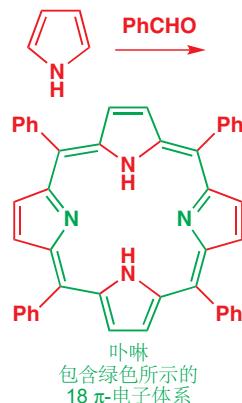


只有一种方法可以确定，那就是制取这种化合物，并看看它是否在各个方面都与天然产物一致，包括生物活性。调查人员这样做后，感到十分后悔。结构确实是正确的，但对于生物活性——青椒的味道——则太过强烈，以至于它们不得不将做这项研究的实验室封起来，没有人会再到那里研究。人类可以从水中侦察到  $10^{12}$  分之 2 的这种化合物。

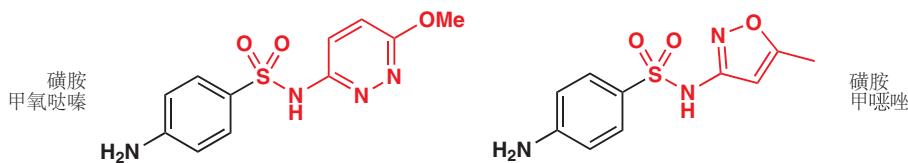
## 芳杂环另有成千上万种

另有成千上万种，本章没有涉及的芳杂环存在，但我们并不打算讨论它们，我们希望您会感激我们的这一举措。事实上，已经是时候停下来了，而我们则会留给您关于可能的复杂性的提示。如果将吡咯与苯甲醛结合，则会以很好的产率得到一种颜色鲜艳的结晶化合物：卟啉 (porphyrin)。那么，这个环体系是芳香的吗？它当然是高度离域的，而您对这一问题的答案，也显然取决于是否包含氮的孤对电子。事实上，如果您忽略类吡咯氮原子，只包括类吡啶氮原子，并考虑外圈，那么它含有九根双键， $18\pi$  个电子——符合  $4n + 2$ 。大多数人同一这个化合物是芳香的。

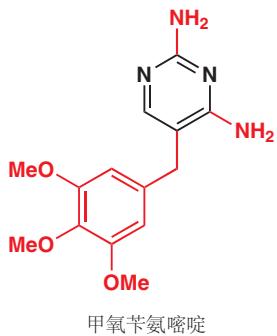
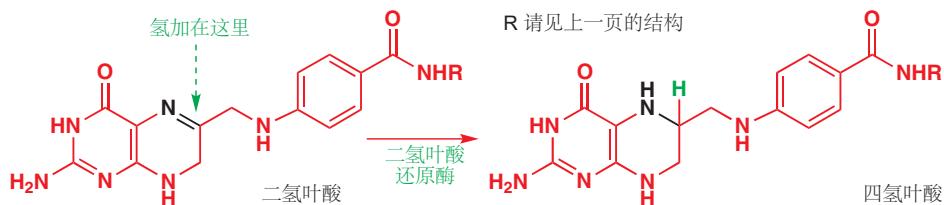
一些杂环比较简单，而一些则非常复杂，很多复杂的杂环还是我们生命的必需品。我们将以一个杂环化学发挥作用的精彩故事结束这一章。叶酸 (Folic acid) 如今在新闻中频繁以维生素出现，对于孕妇尤其重要，但涉及在所有生命体的新陈代谢中。叶酸在自然界中由三部分组成：杂环起始原料 (红色)，对氨基苯甲酸 (黑色)，和谷氨酸 (绿色)。如下，您便看到了它的前体，二氢叶酸 (dihydrofolic acid)。



虽然叶酸对于人体健康至关重要，但我们没有用来制造它的酶：它是一种维生素，这意味着我们必须在饮食中不断摄入，否则我们会死亡。另一方面，细菌是可以制造叶酸的。这会非常有用，因为这意味着如果我们能抑制叶酸合成所需的酶，我们便可以杀死细菌，并且我们不可能伤害到自己，因为我们没有那些酶。磺胺药物 (sulfa drugs)，例如磺胺甲氧嘧啶 (sulfamethoxypyridazine) 或磺胺甲噁唑 (sulfamethoxazole)，都能模拟对氨基苯甲酸，并抑制二氢叶酸合成酶。它们的磺酰胺部分，都各自含有一种新的杂环体系。



叶酸合成的下一步是将二氢叶酸还原为四氢叶酸。人类和细菌都可以完成这一步，尽管它看起来很微不足道（见分子中的黑色部分），但它只能由非常重要的**二氢叶酸还原酶** (dihydrofolate reductase) 完成。

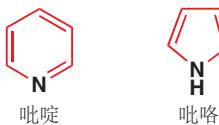


虽然细菌和人类都有这种酶，但二者有较大的不同，这使我们能用特定的药物去进攻细菌的那一种。一个例子是甲氧苄氨嘧啶 (trimethoprim)——另一个具有嘧啶核心（图中黑色）的杂环化合物。这两类破坏细菌叶酸代谢的药物通常一起使用。

我们会在下一章了解如何制取这些杂环体系，并在 Chapter 42 中了解其他体现杂环化合物在生命体中的重要性的例子。

## 您应当熟悉哪些芳杂环？

这当然，几乎是一个个人选择的问题。但任何有机化学家都必须知道最简单的杂环的名称，我们在下文列出了一个表格，并附有一些建议。首先，任何有机化学家都必须知道：



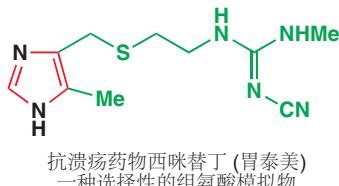
下面是我们建议的一个关于在生命和在人类医药的化学中，扮演重要角色的五个环系的表格——很多药物都基于这五种结构。

### 1 咪唑

最重要的含有两个氮原子的五元环

蛋白质中组氨酸的一部分，在酶催化机理中是重要的

取代的咪唑是抗溃疡药物西咪替丁的基本部分

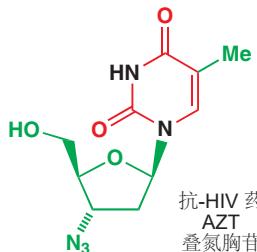
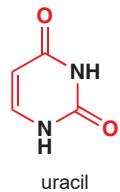
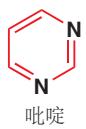


### 2 嘧啶

最重要的含有两个氮原子的六元环

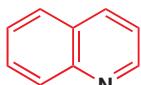
三种官能团化的嘧啶是 DNA 和 RNA 结构的组成部分，如尿嘧啶

很多抗病毒药物，尤其是抗-HIV 药物，都是修饰过的 DNA 片段并包含嘧啶



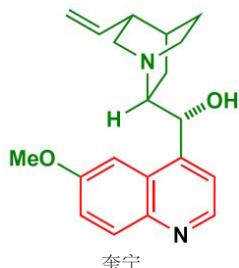
**3 喹啉**

两种苯并吡啶中的一种，有很多应用



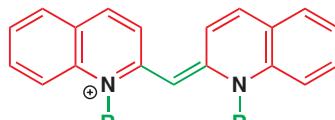
喹啉

天然地出现于重要的抗疟疾药物奎宁中



奎宁

在彩色摄影中用作特定光波长的感光剂的“花青色”染料



一种“花青色”染料

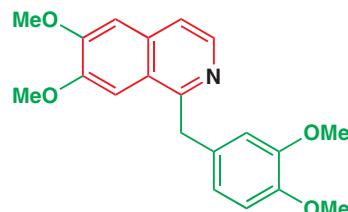
**4 异喹啉**

另一种苯并吡啶，也有很多应用



异喹啉

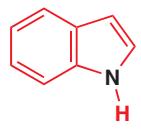
天然地出现于苄基异喹啉生物碱中，例如罂粟碱 (papaverine)



罂粟碱——一种苄基异喹啉生物碱

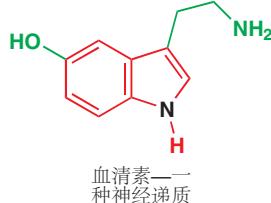
**5 吲哚**

苯并吡咯中更重要的一个



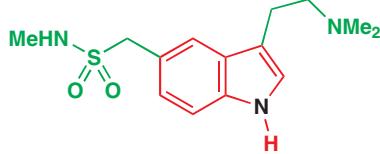
吲哚

以色氨酸形式出现于蛋白质中，以神经递质血清素 (serotonin, 5-hydroxy-tryptamine) 的形式出现于大脑中



血清素——一种神经递质

有很多基于色氨酸的重要现代药物，包括用于治疗偏头痛的舒马普坦 (sumatriptan)，和癌症化疗所用的止吐剂昂丹司琼 (ondansetron)



舒马普坦：治疗偏头痛

**延伸阅读**

基本介绍: *Aromatic Heterocyclic Chemistry*, D. T. Davies, Oxford Primer, OUP, 1992. 最好的关于杂环的总结性文本 (general text) 是 J. A. Joule 和 K. Mills, *Heterocyclic Chemistry*, 4th edn, Chapman and Hall, London, 2010. S. Warren 和 P. Wyatt, *Workbook for Organic Synthesis: the Disconnection Approach*, Wiley, Chichester, 2009, chapters 32, 34, and 35.

青椒化合物参考文章: R. G. Buttery, R.M. Seifert, R. E. Lundin, D. G. Guadagni, and L. C. Ling, *Chemistry and Industry (London)*, 1969, 490.

重氮四唑: P. B. Shevlin, *J. Am. Chem. Soc.* 1972, 94, 1379. 并被用于与巴克敏斯特富勒烯反应: R. M. Strongin and group, *J. Org. Chem.*, 1998, 63, 3522.

## Check your understanding

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To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 芳杂环 2: 合成

## 联系

### → 基础

- 芳香性 ch7
- 烯醇和烯醇盐 ch20
- 烯醇盐的 Michael 加成 ch25
- 烯醇盐的羟醛反应和酰基化反应 ch26
- 逆合成分析 ch28
- 芳杂环的反应 ch29

### 目标

- 热力学与我们同在
- 首先切断 碳–杂原子键
- 如何由 1,4-二羰基化合物 制取吡咯、噻吩和呋喃
- 如何制取吡啶和吡啶酮
- 如何制取哒嗪和吡唑
- 如何由 1,3-二羰基化合物 和脒制取嘧啶
- 如何制取噻唑
- 如何通过 1,3-偶极环加成 制取异𫫇唑和四唑
- Fischer 呋噪合成法
- 制取药物: 万艾可、舒马曲坦、昂丹司琼、吲哚美辛
- 如何制取喹啉和异喹啉

### → 展望

- 环加成 ch34
- 生物化学 ch42

在本章中，您将重新考察刚刚学过的杂环体系，并找出制取它们的方法。您也会遇到一些新的杂环体系，并也会寻找它们的制取方法。对于这么多将要考虑的杂环，您可能会失去信心，但不要担心。杂环的制取是容易的——这也正是杂环如此繁多的原因。这反映出...

- 制取 C–O, C–N, 和 C–S 键是容易的。
- 分子内的反应比分子间的反应更被喜欢。
- 形成五元和六元环是容易的。
- 我们在讨论的是芳香的，即，非常稳定的分子。

如果我们要将这些要点运用为我们的优势，那么开始前，我们必须思考策略。当我们制取苯化合物时，我们通常由一个预先得到的简单苯衍生物开始——加苯、苯酚、苯胺——并通过亲电取代反应添加侧链。而在本章中，我们的策略则常常是构建已经完成大多数取代的芳环，然后再添加一小部分，也许通过亲核取代反应，大多数通过亲核取代反应。

我们通常通过杂原子 (O, N, S) 作为亲核试剂，合适的官能化的碳原子作为亲电试剂的环化反应

制取。亲电试剂几乎总是某种羰基化合物，本章也会帮您复习 Chapters 10, 11, 20, 25, 和 26 中的羰基化学，及 Chapter 28 中叙述的合成方法。

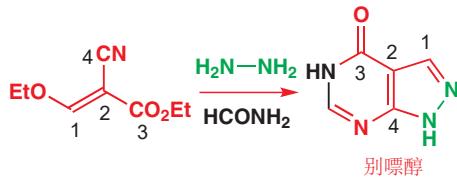
## 热力学与我们同在



我们将要遇到的一些合成将会令人惊奇地简单！有时候，我们似乎可以直接将正确数目的原子混合在一起，并让热力学做余下的工作。吡啶的一种商业合成方法，就是将乙醛与氨直接在一定的压力下结合。

产率仅约为 50%，但在这样一个简单的过程中，这有何妨呢？通过数原子，我们猜测，四分子的乙醛和一分子的氨反应，但真正的方式是热力学战胜了机理。复杂得多的分子有时候也很容易制取。例如您在上一章遇到的别嘌醇。原子到了什么地方并不难得出——肼很明显产生了吡唑环中相邻的一对氮，酯基也一定是羰基的来源（颜色和数字说明了这些问题）——但您会计划用这种合成吗？

► Chapter 29, p. 751 讨论了别嘌醇。



我们会发现，这种“女巫的酿造 (witch's brew)”方法只对于少部分基础环系可用，一般来说，仔细的设计在这里也一样重要。芳杂环合成与其他合成的差异在于容忍性——它通常“正确”，很少错误。现在，我们将认真地着眼于芳环合成的设计。

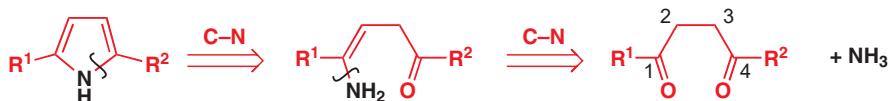
## 首先切断 碳–杂原子键

最简单的思路，是移去杂原子，并观察我们需要什么亲电试剂。我们会用吡咯作为例子。吡咯中的，氮在环的两侧各形成一个烯胺，我们知道，烯胺可通过羰基化合物和胺制得。

► 这是您在 Chapter 28 中遇到的逆合成箭头。



如果我们对吡咯做同样的切断，并忽略中间状态，我们便可再两侧各重复一次 C–N 切断。



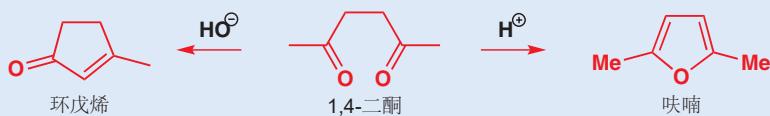
因而，我们所需的是一个胺——在此情况下是氨——和一个二酮。如果两个羰基处于 1,4 关系，那么我们会得到一个吡咯。因此 2,5-己二酮 与氨反应会高产率地给出 2,5-二甲基吡咯。制取呋喃更加容易，因为杂原子(氧)已经在那里了。与酸一同加热就足够了。



### 避免羟醛产物

1,4-二酮 同样相当容易通过分子内羟醛反应 (见 Chapter 26, p. 636) 自缩合以得到含有全碳五元环的环戊烯。这也是一个有用的反应，但我们需要知道如何控制它。通常的规则是：

- 碱催化得到环戊烯。
- 酸催化得到呋喃。

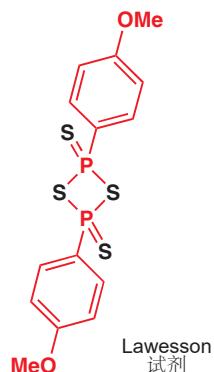


对于噻吩，理论上我们可以使用  $\text{H}_2\text{S}$  或其他一些硫亲核试剂；但在实践上，通常用亲电试剂将两个  $\text{C}=\text{O}$  键转化为  $\text{C}=\text{S}$  键。硫酮 / Thioketones 比酮不稳定得多，因而环化马上发生。常见的选择是  $\text{P}_2\text{S}_5$  和 Lawesson 试剂 / Lawesson's reagent



### ● 制取五元杂环

1,4-二羰基化合物与氮、硫，或氧发生环化反应，得到五元芳杂环吡咯、噻吩，和呋喃。



将此拓展到用 1,5-二酮 制取吡啶似乎是合乎逻辑的，但有一个小问题，两个烯胺生成时只引入了所需的三个双键中的两个。若要得到吡啶，则起初就要在量羰基间的碳链上存在一个双键。但另一个问题便产生了——环化若想发生，这个双键必须是顺式的。



大体上说，用饱和 1,5-二酮，并将产物氧化为吡啶是更容易的。这一过程由非芳香性化合物生成了芳香性化合物，因而氧化是容易的，上图中的问号，可以是几乎任何一种简单氧化剂，我们稍后就会了解到。

### ● 制取六元芳杂环

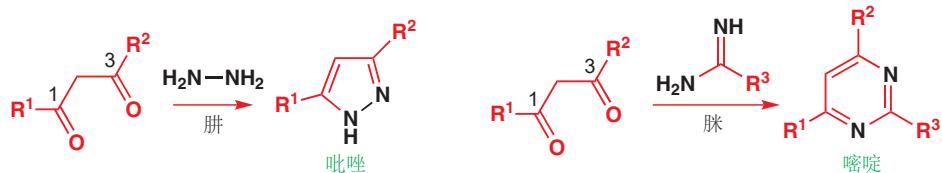
1,5-二羰基化合物 与氮亲核试剂的环化产物，可被氧化为六元芳杂环吡啶。

### 含两个氮原子的杂环也可用相同策略得到

将 1,4-二酮 与肼 ( $\text{NH}_2\text{NH}_2$ ) 反应，可以再次制得烯胺，然后仅需一个氧化步骤即可得到哒嗪。这是一个很好的合成路线。



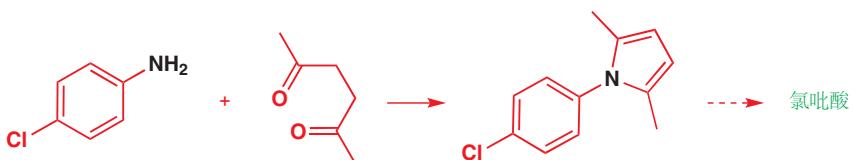
如果我们用 1,3-二酮，那么则会得到五元杂环，并且所形成的亚胺和烯胺已经足够得到芳香性，无需任何氧化。产物是吡唑。当然，这个策略不要求两个杂原子相连。用脒与相同的 1,3-二羰基化合物结合，所得的是六元杂环，由于亲核试剂也包含一根双键，得到的直接是芳香的嘧啶。



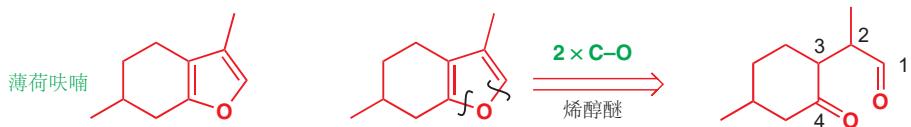
由于二酮和其他二羰基化合物可以通过烯醇盐化学 (Chapters 25, 26, 和 28) 很容易地制得，这个策略也十分受欢迎，在讨论针对不同类别的芳环的特殊制取反应前，我们会先着眼于一些详细的例子。

## 吡咯、噻吩和呋喃来源于 1,4-二羰基化合物

我们需要说明的一点是，用伯胺完成吡咯合成，与用氨是一样好的；我们在 Chapter 29 中讨论过的氯吡酸所需的吡咯，便是这一过程的很好的例子。合成非常简单。



有关呋喃合成的例子，我们选取的是薄荷呋喃 (menthofuran)，它贡献了薄荷的香味。它包含第二个环，但如之前的其他情况一样，简单地切断烯醇醚，也不会有任何问题。

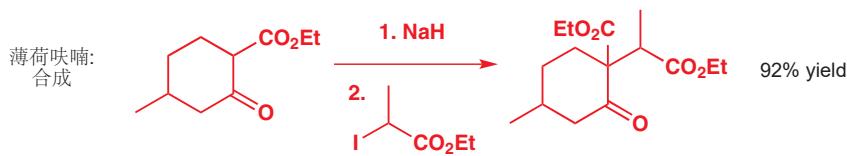


起始原料还是一个 1,4-二羰基化合物，呋喃的 C1 上没有任何取代基，与之一致地，该位点是一个醛而非酮。这可能会在合成中导致问题，因此在进一步切断前，需要对中间体做出一些更改（您在 Chapter 28 见过的记号）。

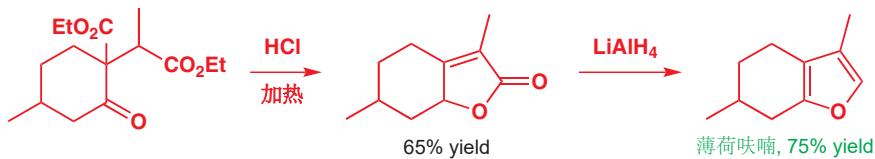


■ 卤代醛很不稳定，应当避免。

尤其注意，我们将醛氧化为酯，以使之更稳定——在合成中，会需要还原。下面是合成中的烷基化步骤，在  $\alpha$ -碘代酯上确实发生得非常好。



酸性的环化一次性完成了许多个反应。首先，1,4-二羰基化合物会环化为一个内酯而不是一个呋喃；多余的酯基通过水解和脱羧失去。注意，形成的双键会与内酯羰基共轭。最后，通过还原得到呋喃；无需特殊的措施——一旦酯被部分地还原了，它便会脱水得到呋喃，而呋喃的芳香性又会阻止进一步的还原，即使是  $\text{LiAlH}_4$  也是没用的。

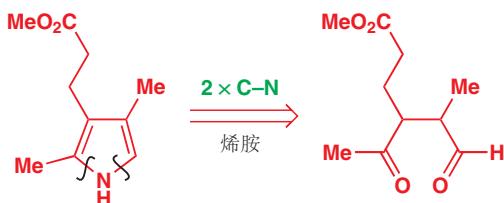


### ● 提醒

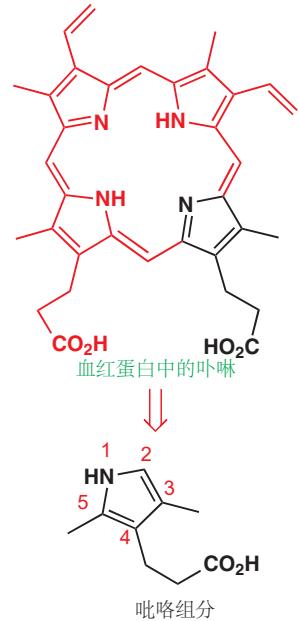
1,4-二羰基化合物与氮、硫，或氧发生环化反应，得到五元芳杂环吡咯、噻吩，和呋喃。

现在，我们需要进一步考察这些思路，并讨论一种遵循这一策略的，而又包含一个巧妙的转折的，重要的吡咯合成。这开始于血液中的卟啉。在 Chapter 29 中，我们给出了卟啉的结构，并且向您展示了，它含有通过一个大环（macrocyclic）连接的四个吡咯环。我们将要着眼于其中一个吡咯。

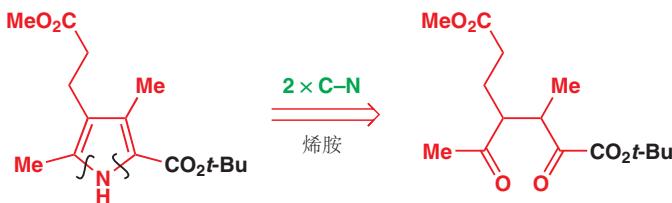
卟啉可以通过将种种吡咯以正确的顺序连接起来得到，标出的部分（及其旁边的一个）所需的是一个在 3 号和 4 号位有正确的基团，5 号位有甲基，2 号位有氢原子的吡咯。2 号位必须是空的。如下将其更方便地表示出来，然后用刚才使用过的方式切断。



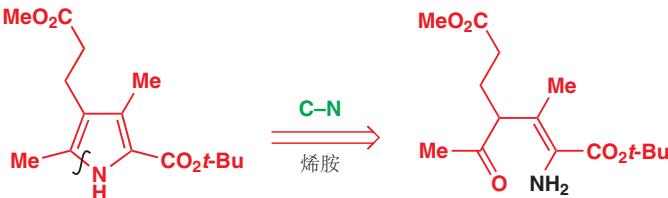
毫无疑问，这样的合成是可行的，但出于一些原因，值得我们换一种方式进行。我们并不喜欢制取在 C2 位空缺的吡咯，因为这样的吡咯会非常活泼，据 Chapter 29，我们可以用叔丁酯基可逆地阻碍这个位点。这给予我们了一个非常困难的，包含四个不同的羰基的起始原料。



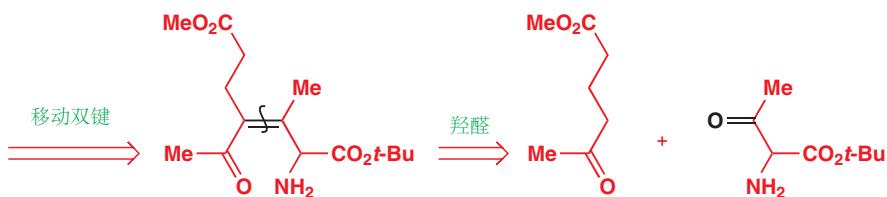
关于如何控制吡咯反应性的讨论请见 p. 733.



两个彼此相邻的羰基，便是我们给自己制造的选择性麻烦。我们可以通过将其中一个替换为胺来避免这个问题吗？这种方式所得的是一个  $\alpha$  氨基酸的酯，一个比之前好得多的起始原料，这也对应于只断裂一根 C–N 键。



这样观察似乎并不能看出什么进展，但假如我们将双键移动倒与酮共轭，那么事情就不一样了。总之，双键开始时在哪里并不重要——我们往往会得到芳香产物。



■ 与 1,3-二羰基化合物发生的共轭加成已在 Chapter 26 中讨论过。如果您已阅读过 Chapter 28，那么您应当能意识到这样的反应是制取 1,5-双官能化化合物的极好方法。

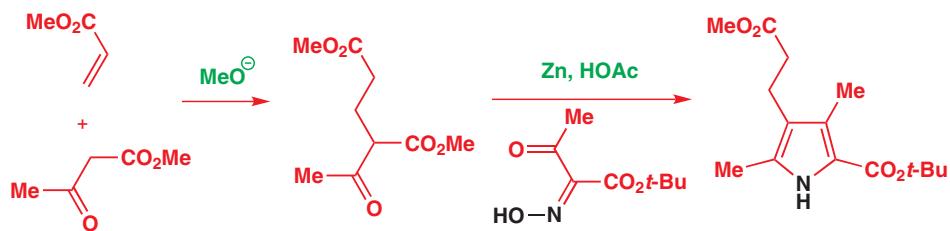
所得的两种简单得多的原料仍需要制取。酮酯是一个 1,5-二羰基化合物，因此可以通过烯醇盐的共轭加成制取，若加入第二个酯基，这一过程便会得到很大程度的促进。



另一个化合物是一个氨基酮酯，如果我们试图制取纯化合物，那么它便一定会与自己反应。解决方案使之在最终的反应混合物中生成，这可以通过另一种稳定烯醇盐的亚硝化（得到肟）和还原（得到胺本身，Chapter 20）完成。

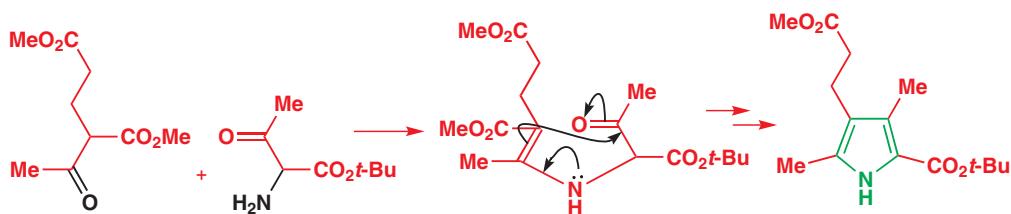


醋酸中的锌（Chapter 23）可以将肟还原回胺。我们的合成，开始于共轭加成，而后是在酮二酯的存在下肟的还原。

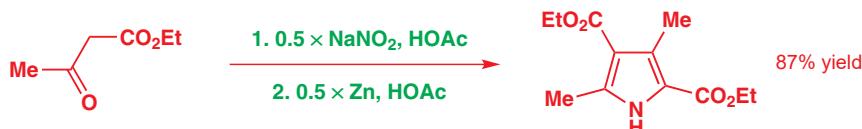


这个反应在一步中形成了所需的吡咯！首先，肟被还原为胺，然后氨基与酮二酯中最活泼的羰基

(酮羰基) 形成亚胺。最后, 非常形成的烯胺环化到 (cyclizes onto) 另一个酮上。



这个吡咯合成方法足够重要, 以至于它被以它的发明者命名为——Knorr 吡咯合成法 (Knorr pyrrole synthesis)。Knorr 本人用一个格外有效的反应制得了一个较简单的吡咯。看看您是否能搞清楚发生了什么。



### 杂环合成方法的名称

标准的杂环合成方法往往有与它们关联的名称。很多名称都很少有化学家使用, 只有其中著名的几个: 我们会提到 Knorr 吡咯合成法, Hantzsch 吡啶合成法, 和 Fischer、Reissert 咪唑合成法。我们不会将由 1,4-二羰基化合物 生成呋喃的方法叫做 Feist–Benary 合成法, 当然这类的名称还有很多。如果您真的对其他的这类名称感兴趣, 那么我们建议您阅读杂环化学的专业书籍。

## 如何制取吡啶: Hantzsch 吡啶合成法

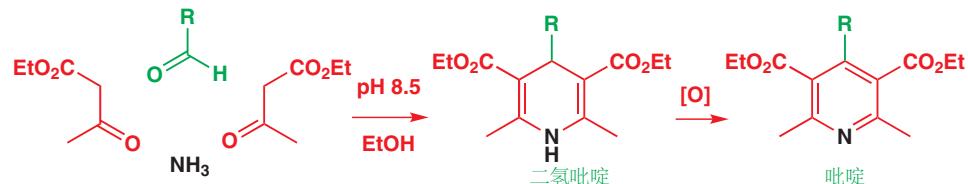
将两个酮酯以一个氮原子偶联的思路, 除去需要额外碳原子的情况, 对于吡啶也是适用的。我们还需要一个醛, 并且另一个重要的差异是, 氮原子以亲核试剂而非亲电试剂的形式添加。这是 Hantzsch 吡啶合成法 (Hantzsch pyridine synthesis) 的特征, 它是一个由简单起始原料完成的四组分反应。



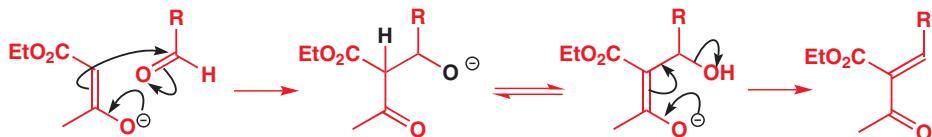
**Arthur Hantzsch**, 1857–1935, 莱比锡“狂热的立体化学家”, 因他与 Werner 在苏黎世的 ETH (苏黎世联邦理工学院) 的工作闻名, 1890 年, 他在那里提出肟可以以顺式和反式形式存在。

从图示中, 很难理解反应背后所依据的原理, 因此让我们来探索它的细节吧。反应的产物事实上是一个二氢吡啶, 它可以被  $\text{HNO}_3$ ,  $\text{Ce}(\text{IV})$ , 或喹啉等试剂氧化为吡啶。

仅仅将组分以正确的比例在乙醇中混合, 反应便会非常简单地发生。水的存在不会破坏反应, 加入的氨, 有时是胺, 也可保证所需的微碱性的 pH. 任何醛, 甚至是甲醛都可以使用, 结晶的二氢吡啶的产率通常非常高。

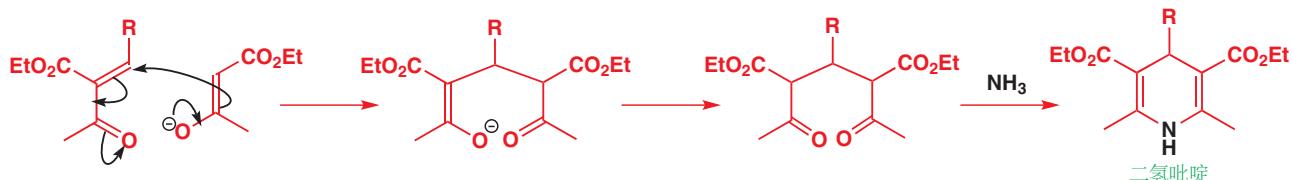


这个反应令人印象深刻的小分子的分子识别 (molecular recognition) 的例子，写出详尽的机理是一种大胆的挑战。我们可以看出，某些事情必定会发生，但它们发生的先后顺序都只是猜测。氨必定会进攻酮基，但它会倾向于进攻更亲电的醛，因此这很有可能不是第一步反应。酮酯的烯醇或烯醇盐必定会 (两次) 进攻醛，因此让我们从这个过程开始。



Interactive mechanism for Hantzsch pyridine synthesis

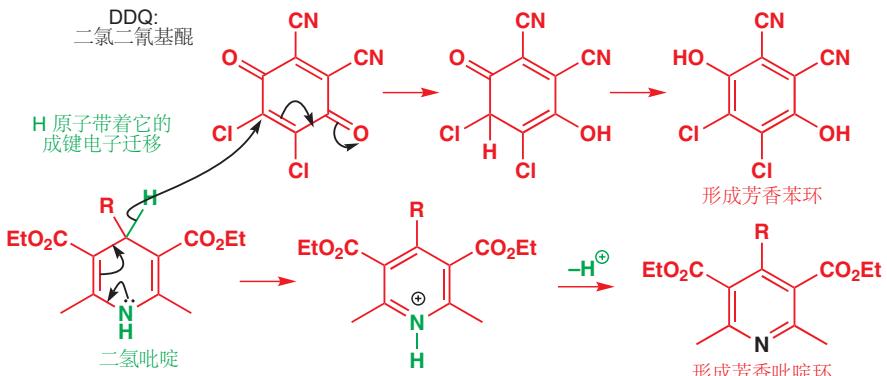
加合物与酮酯的稳定烯醇盐式处在平衡中，平衡现在会给出不饱和羰基化合物。这个过程关联的是我们在 Chapter 26 中讨论过的羟醛反应。所得的烯基酮在双键的一侧有两个羰基，因此是一个非常好的 Michael 受体 (Chapter 25)。第二分子的烯醇盐会通过共轭加成，来完成分子碳骨架的构建。现在，氨会进攻任意一个酮，继而将环化到另一个酮上。由于酮比酯更加亲电，可以料到，氨是倾向于如此反应的。



■ 我们将在 Chapter 42 中展示，自然界用相关的二氢吡啶作为生命体中的还原剂。

Interactive mechanism for quinone oxidation of dihydropyridines

必要的氧化反应是简单的，既因为产物是芳香的，又因为氮原子可以帮助排出 4 号位上的氢原子，以及它的电子对。如果我们用醌 (quinone) 作为氧化剂，同步步中两个化合物都会变为芳香。

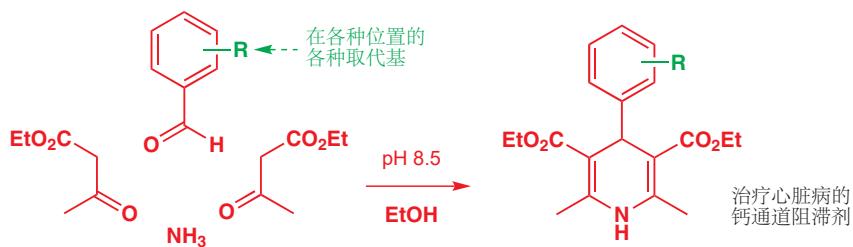


概括这个机理，它的要点为：

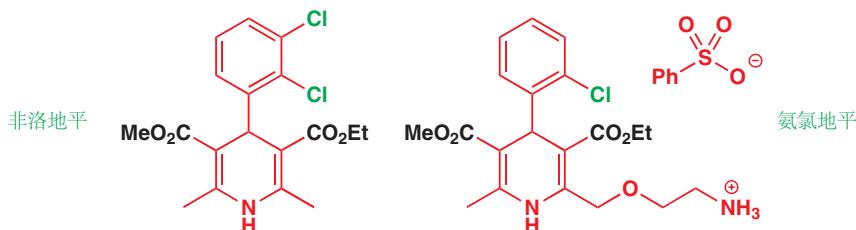
- 醛和酮酯间的羟醛反应
- 另一酮酯对烯基酮的 Michael (共轭) 加成
- 氨对其中一个酮的加成
- 亚胺或烯胺环化到另一个酮上。

其中一些步骤可能会以不同的顺序发生。

Hantzsch 吡啶合成法是一个古老的发现 (1882)，在 1980s 年代，随着对于——由芳香醛制备的二氢吡啶中间体是钙通道阻滞剂 (calcium channel-blocking agents)，进而可作为有价值的心脏病药物，治疗心绞痛和高血压——的发现，它突然变得显要。

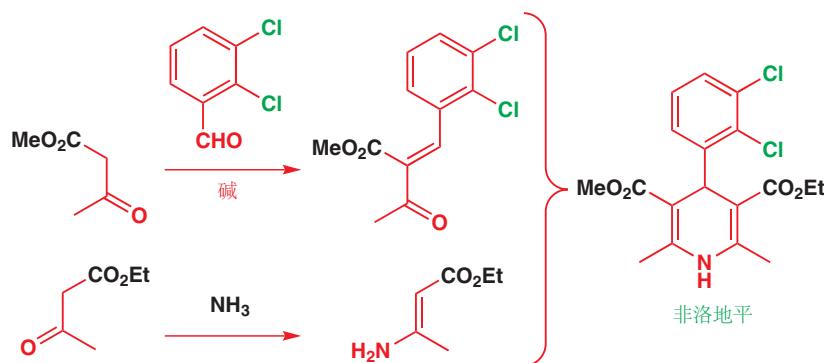


到目前为止都不错。同样有一点变得越来越清晰, 即最好的药物是不对称的——有些的对称性很细微, 比如非洛地平 (felodipine), 有些则十分严重, 比如辉瑞的氨氯地平 (amlodipine). 虽然乍一看它们非常简单, 但方便的 Hantzsch 合成法却不能合成这些化合物。



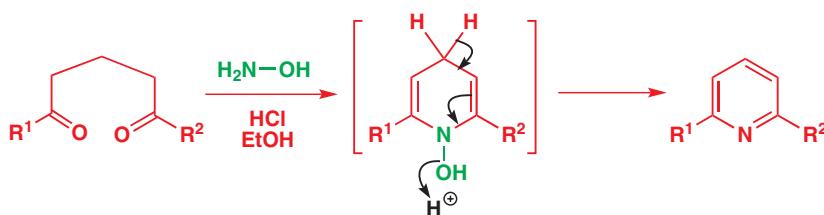
这些药物抑制  $\text{Ca}^{2+}$  例子跨细胞膜的运输, 并在不影响心脏工作的情况下, 选择性地舒张肌肉组织。它们可以降低高血压。辉瑞的氨氯地平(Istin™ 或 脉优 Norvasc™) 是一种非常重要的药物。

显然, 分子的一半在第一步组装中需要修饰。解决方案来自由 Robinson 完成的早期工作, 它是第一个由酮酯和胺制出烯胺的人。分子的一半由烯胺制得, 另一半则来源于与之分开的烯基酮的合成。我们可以用非洛地平作为一个简单的例子。

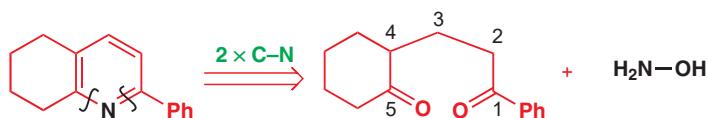


## 其他的吡啶合成法

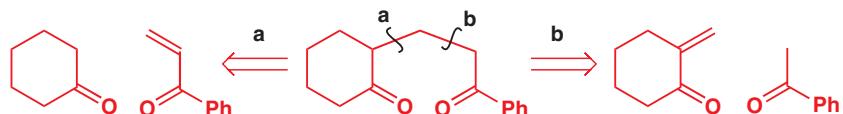
Hantzsch 合成法产生的是被还原的吡啶, 而还有很多合成法是直接通向吡啶的。其中最简单的一种是用羟胺 ( $\text{NH}_2\text{OH}$ ) 替代氨做亲核试剂。1,5-二酮 与之反应会得到氮上带有羟基的二氢吡啶, 然后它会失去水, 无需氧化便形成了吡啶。



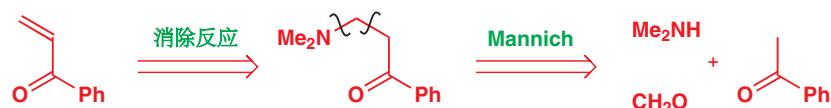
下一页的例子展示了这些 1,5-二酮 如何能快速地由 Mannich (Chapter 26) 和 Michael (Chapter 25) 反应制得。我们的吡啶含有一个苯取代基和一个稠合的饱和环。首先我们必须切断 1,5-二酮。



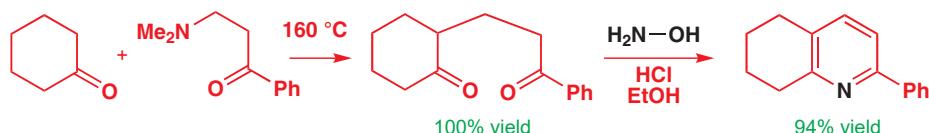
进一步的切断会显露出一个酮和一个烯基酮。这里出现了一个选择，两种路径都会很好地工作。



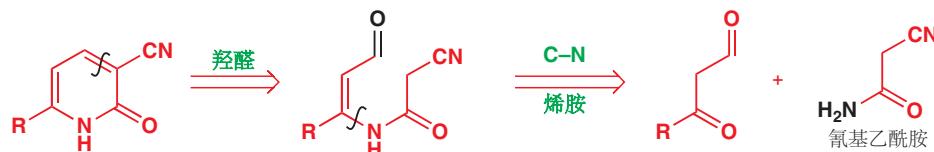
用 Mannich 反应的胺产物（“Mannich 碱”）替代将会非常不稳定的不饱和酮是很方便的，我们将选择切断“a”继续进行。



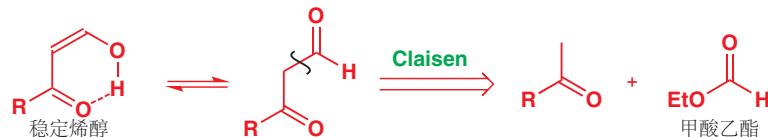
合成已经异常简单了。稳定得 Mannich 碱只需于另一个酮简单地加热，即可以高产率给出 1,5-二酮。用  $\text{NH}_2\text{OH}$  的 HCl 盐在 EtOH 中处理它，即可直接得到吡啶，产率同样很高。



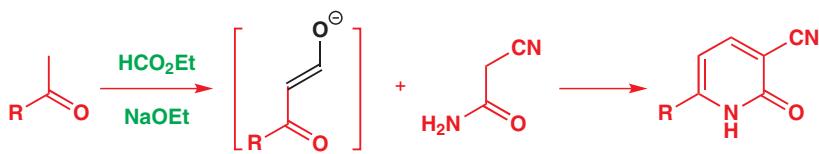
还有另一条路线，可直接得到吡啶酮。这些有用的化合物是在吡啶环上发生亲核取代反应的基础 (Chapter 29). 我们选择了一个在 3 号位放有氰基的例子。烟酰胺 (nicotinamide) 在生命体中扮演的重要角色 (Chapter 42)，使人们对这种化合物的制取很感兴趣。在 3-氰基吡咯酮上的羟醛切断为我们开启了正确的道路。现在，如果我们在环的另一侧切断形成烯胺的 C–N 键，那么我们就会得到真正的起始原料。这种方法是不寻常的，因为将变为吡咯氮的氮原子并不以氨的形式添加，而是已经存在于一分子的氰基乙酰胺中了。



用甲基酮与做亲电试剂的甲酸甲酯 ( $\text{HCO}_2\text{Et}$ )，发生简单的 Claisen 酯缩合反应 (Chapter 26)，即可得到酮醛。事实上，它像很多 1,3-二羰基化合物一样，以稳定的烯醇盐的形式存在 (Chapter 20)。

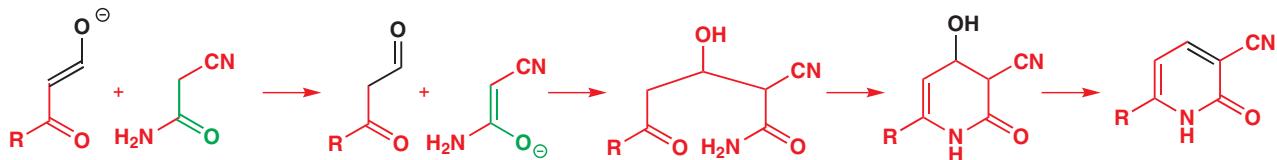


在合成中，Claisen 酯缩合的产物事实上是酮醛的烯醇阴离子，它不经分离便可在一锅中，直接与氰基乙酰胺结合。



■ 如果先发生脱水，所得的烯烃中只有Z型能够继续环化，而主要产物，E烯则会浪费掉。

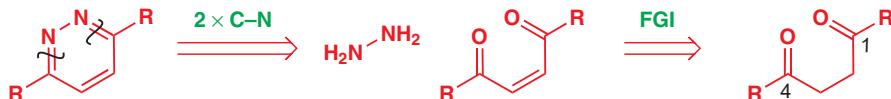
在羟醛反应发生前，这两个化合物应先交换质子（或者说，转换烯醇盐）。接下来的环化反应很有可能通过C–N键的形成发生，最后会被迫脱水得到Z烯烃。



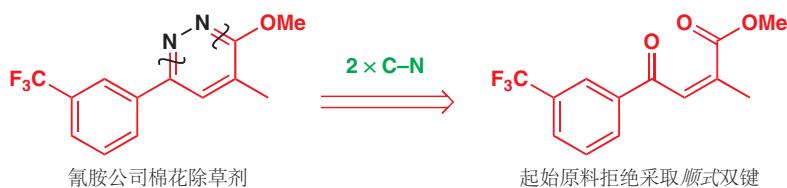
在设计由二羰基化合物合成吡咯或吡啶的方法时，氧化态可能发生相当大的改变。我们应该根据后续碳骨架的切断如何更简单，而选择氧化态。下面我们便可以看到，相同的原则也适用于吡唑和哒嗪。

## 吡唑和哒嗪来源于肼和二羰基化合物

哒嗪的切断将显露出一分子的肼和一个1,4-二酮，但它也有与吡啶相同的条件，即产物会是二氢哒嗪，需要将其氧化为芳香化合物。与吡啶相同，我们更喜欢避免顺式双键问题。

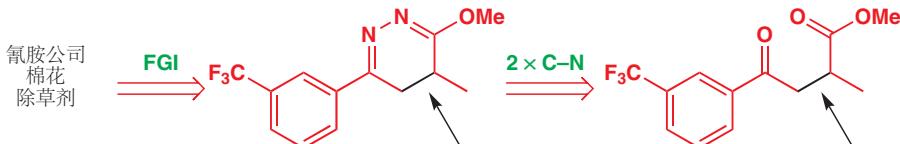


我们可以用氰胺公司 (Cyanamid) 制造的棉花除草剂作为一个例子。对肼的直接去除，会要求起始原料含有一个有问题的顺式双键。

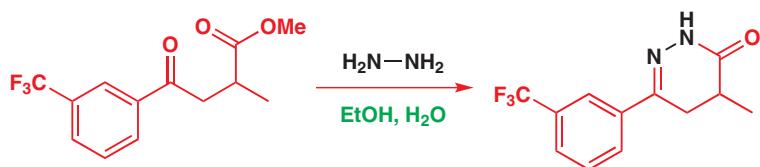


■ 除草剂可杀死棉花作物中的杂草，而不伤害棉花本身。

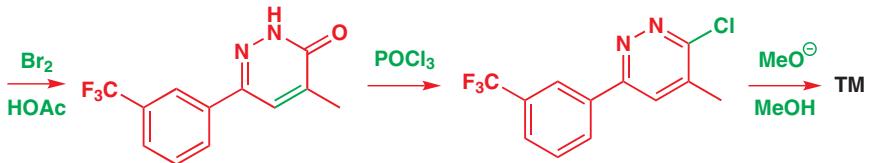
如果我们先去除双键，那么浮现出的会是一个简单得多的化合物。注意这是一个酮酯而不是一个二酮。



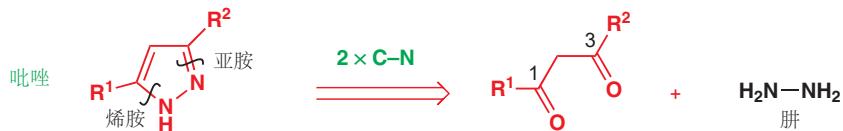
当将肼添加到酮酯上时，肼会与酮反应形成一个亚胺，但在酯上发生的酰基化并不会得到我们设计的亚胺-醚，而是会得到一个酰胺。



用溴单质，可通过溴化和脱氢溴酸，完成芳构化(aromatization)，现在，我们将调用在 Chapter 29 中介绍的亲核取代反应。首先我们用  $\text{POCl}_3$  生成氯代物，然后用甲醇取代之。

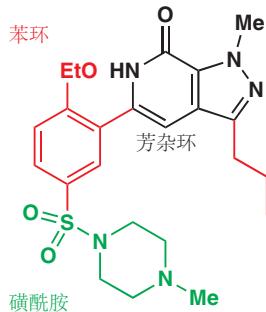


五元吡唑环甚至更简单，因为起始原料是一个可由羟醛反应或 Claisen 酯缩合获得的 1,3-二羰基化合物。

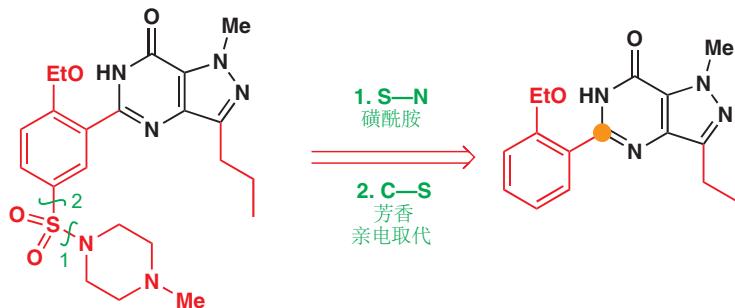


### 化学上了头条——万艾可

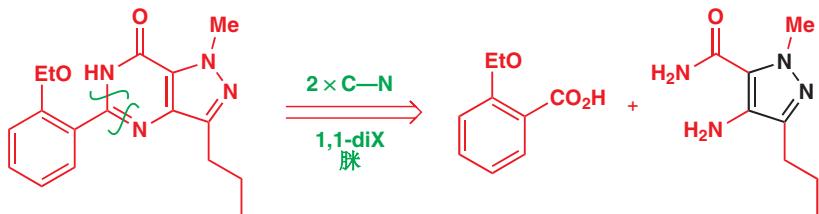
万艾可：  
辉瑞治疗男性勃起  
功能障碍的药物



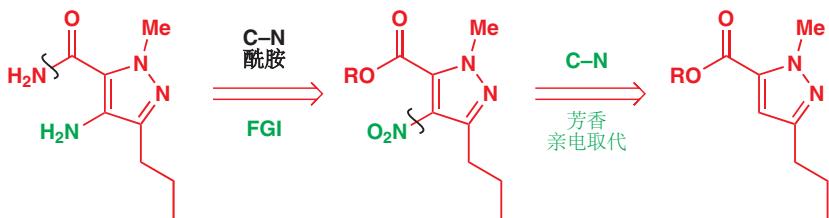
1998 年，化学突然以一种特殊的方式出现在了媒体上。化学一般并不是电视或报纸的最爱，但这一次，它提供的故事囊括所有正确的要素——性、浪漫、人类智慧——这一切都来源于一种吡唑。在对于心脏药物的研究上，辉瑞发现了一种能使阳痿男性拥有活跃的性生活的化合物。他们称之为万艾可（俗称伟哥，Viagra）。这个分子包含一个磺酰胺基和一个苯环，以及最令我们感兴趣的部分——一个双环芳杂环体系，包含一个稠和在嘧啶上的吡唑；稍后我们将细致地讨论辉瑞如何制造这一部分，而其余部分则将一笔带过。磺酰胺可以通过磺酸得到，磺酸可以通过苯的芳香亲电取代得到 (Chapter 21)。



检查余下的部分，可知杂环中与苯环相邻的碳原子（橘色点出）处于羧酸氧化程度。因而如果我们切断与这个原子相连的两根 C–N 键，那么我们便会得到两个简单得多的起始原料。



芳香酸是可获得的，我们需要考虑的只有图示中黑色的吡唑。芳香氨基可由通过硝化和还原加入，酰胺可由通过对应的酯制得。由此留下的碳骨架，必须通过环合成法制取。

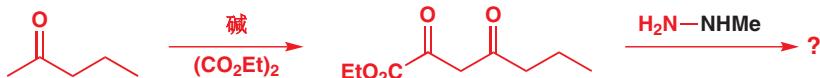


遵循我们在本章中建立的方法，我们可由将肼的部分移去，以显露出一个 1,3-二羰基化合物。事实上，这是一个三羰基化合物，一个二酮酯，算上以及存在的酯基，它包含 1,2-, 1,3-, 和 1,4- 二羰基关系。最简单的合成通过 Claisen 酯缩合完成，切断后得到活泼，不能烯醇化的(草酸)二酯。

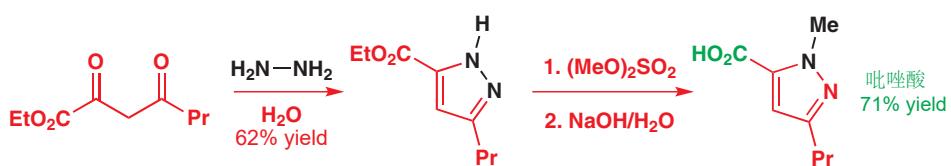
而后唯一需要的控制是酮的烯醇化位置。



碱处理的 Claisen 酯缩合可得到正确的产物。其原因已于 Chapter 26 中讨论过。然后，我们计划用甲基肼处理这个二酮，对于这个反应的区域选择性也存在疑问——酮比酯亲电是对的，但酮会被哪个氮原子进攻呢？

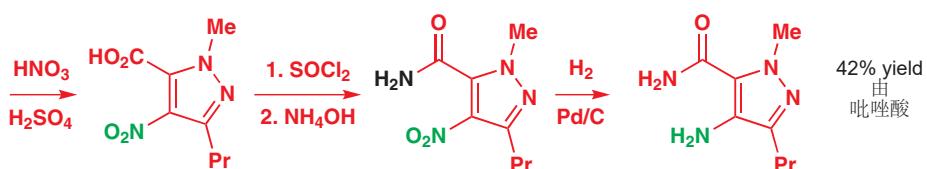


我们已经在 Chapter 29 中见过这个问题的解决办法。如果我们用对称的肼，那么我们可以在之后通过酰基化解决区域选择性问题。硫酸二甲酯是最佳的试剂。

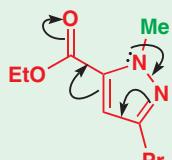


■ 烷基化是区域选择性的，因为甲基取代的氮必定是类吡咯氮，分子喜欢是最长的共轭体系，最长的共轭体系便是包含在酯基邻位的类吡咯氮，和酯基的共轭体系。  
(p. 742)

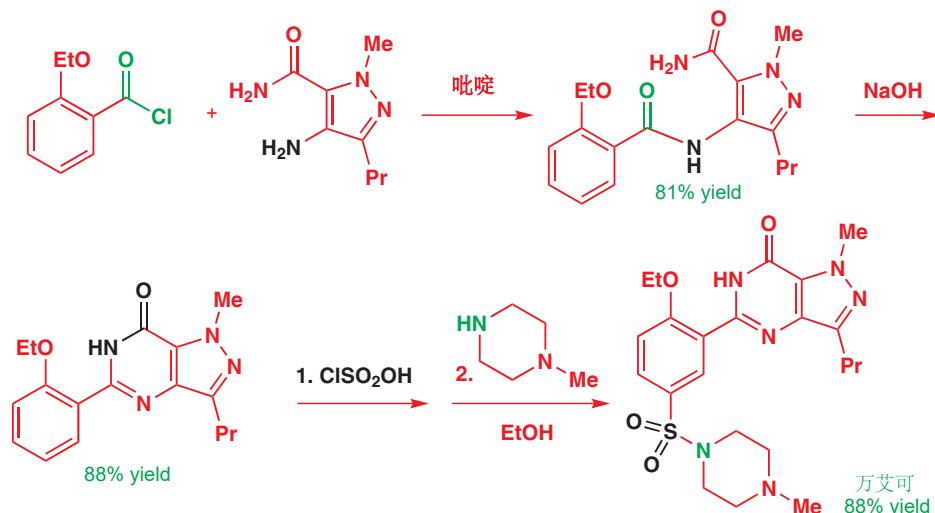
由酯水解得到的稳定的吡唑酸，是万艾可生产中关键的中间体。硝化仅会在唯一空缺的位置上发生，然后是酰胺的形成，以及还原反应，这便完成了将要组装为万艾可的，氨基吡唑酰胺的合成。



孤电子离域进酯基

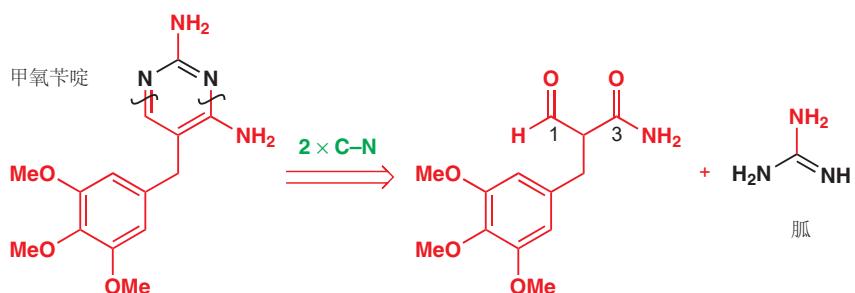


由于合成的剩余部分涉及的大多都是本章讨论范围之外的内容，我们将非常简短地总结。您可能会注意到，第二个杂环（嘧啶）的构筑是多么容易——若非产物是芳香的，酰胺中氮原子对另一个羰基的进攻，是肯定不会发生的。

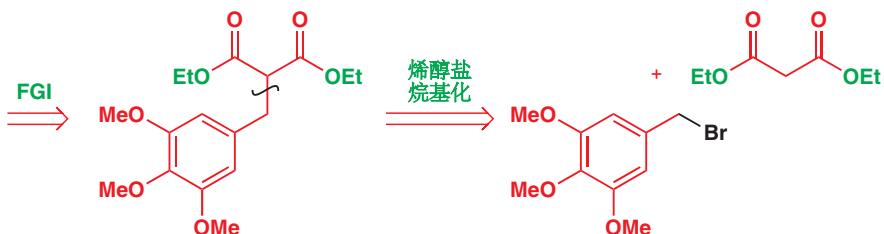


### 嘧啶可由 1,3-二羰基化合物和脒制取

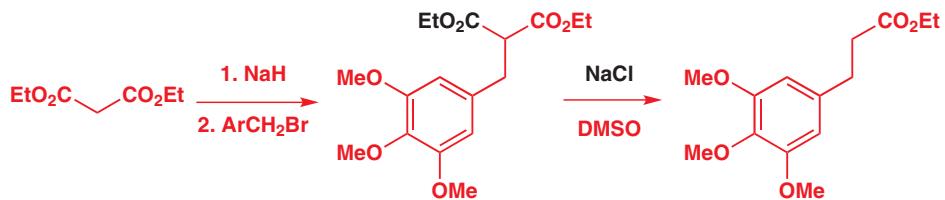
在 Chapter 29 中，我们遇到了一些干扰叶酸代谢，并被用作抗真菌剂的化合物。其中一个是甲氧苄啶，它包含一个嘧啶环（图中黑色）。它的合成与万艾可中嘧啶环的合成是相反的，我们将简短地考察。此处，我们将它切断为一分子胍和一个 1,3-二羰基化合物。



所得的 1,3-二羰基化合物 是一个醛和一个酰胺的结合，它与缩苹果酸酯非常相似，我们会将这个化合物思考为，稳定的烯醇盐，与方便的溴化苄烷基化的结果 (Chapter 25)。

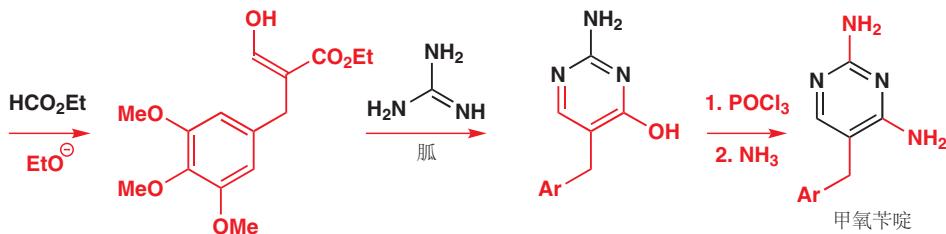


这个合成的效果良好, (在将酯基替换为醛基的步骤中, )结果表明, 脱羧后将醛基作为亲电试剂加入 (比较 p. 766 的吡咯酮合成) 是比试图将酯还原为醛更好的选择。另一个酯基以及处于正确的氧化程度了。



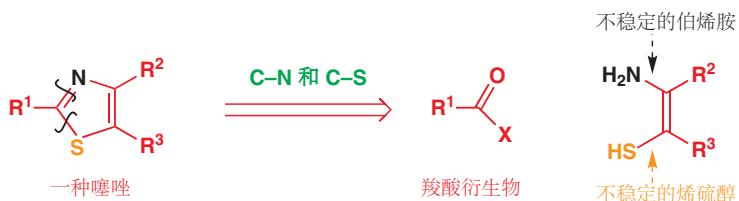
■ 注意脱羧所用的是  
NaCl 方法 (Chapter 25, p.  
597).

发生与甲酸乙酯的缩合 ( $\text{HCO}_2\text{Et}$ ) 和与胍的环化, 即可得到嘧啶环烯, 只是所需的氨基被 OH 替代。Chapter 29 中吡啶方式的芳香亲核取代则可给出甲氧基啶。

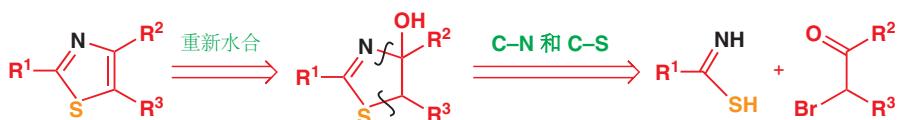


## 不对称亲核试剂会导致选择性问题

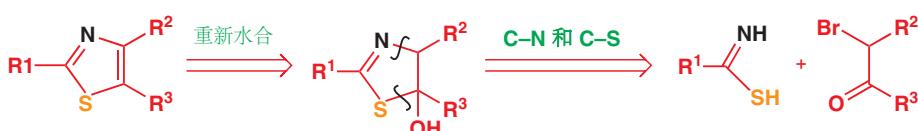
由于区域选择性问题, 嘧唑的合成尤其有趣。如果我们试验刚刚用于嘧啶的两种策略, 第一种策略要求一个羧酸衍生物与最怪异的烯胺, 同时也是烯硫醇 (thioenol), 反应。这看起来不像一个稳定化合物。



另一种切断方式, 是切断杂原子另一侧的 C–N 和 C–S 键。在这里我们必须小心, 因为我们想要, 或将会吧氧化态弄错。我们将一步一步地完成以保证正确。将双键重新水合的方式有两种。第一种, 我们可以尝试将 OH 基放置在氮旁边。



或者, 我们可以反过来水合, 将 OH 基放置在硫原子旁边, 并以相同方式切断。两种情况下, 我们都需要一个处在醇氧化程度的亲电碳原子, 和一个处在酮氧化程度的亲电碳原子。换句话说, 我们需要一个  $\alpha$ -卤代酮。

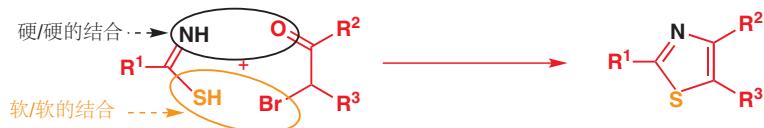


► Lawesson 试剂的结构位于 p. 759.

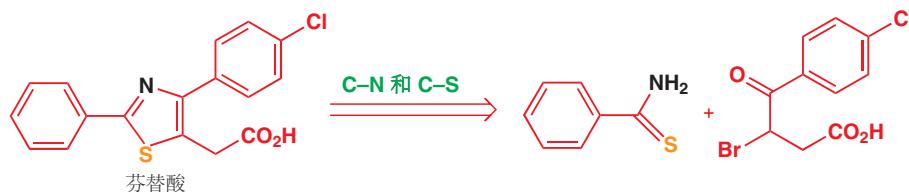
两种情况中的亲核试剂是同样的，如果我们没有意识到它只不过是硫代酰胺 (thioamide) 的一个互变体，它看起来确实挺奇怪的。硫代酰胺并不奇怪，相反，它是为数不多的稳定的硫代羰基衍生物之一，可以很容易地由普通酰胺和  $P_2S_5$  或 Lawesson 试剂制取。



因此，剩下的唯一一个问题时：当硫代酰胺与  $\alpha$ -卤代酮结合时，哪个亲核原子 (N 或 S) 会进攻酮，哪个 (N 或 S) 又会进攻卤代烃呢？羰基是“硬”的亲电试剂——它们的反应主要受电荷控制，因此它们与碱性亲核试剂反应得最好 (Chapter 10)。卤代烃是“软”的亲电试剂——它们的反应主要受前线轨道控制，因此它们与大的、不带电的，来源于周期表高周期的亲核试剂反应得最好。酮会与氮反应，卤代烃会与硫反应。



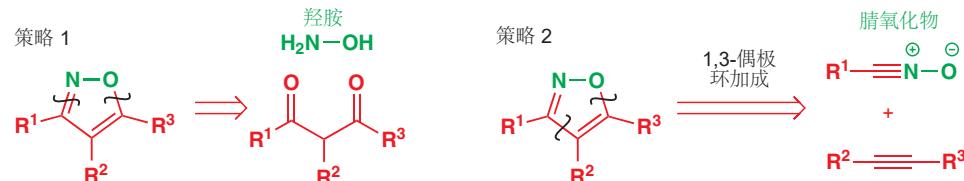
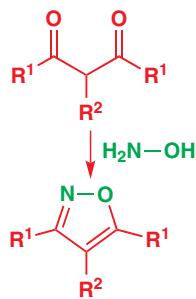
芬替酸 (Fentiazac)，一种非甾体抗炎药是一个简单的例子。切断表明，我们需要一个硫代苯甲酸胺和一个容易制得的  $\alpha$ -卤代酮 (由于酮只能在这一侧烯醇化，所以容易——见 Chapter 20)。



合成中包含将两个化合物加热在一起的过程，正确的噻唑很容易形成，双键也会在产物中找到它们正确的位置——唯一能形成稳定芳杂环的位置。

## 异噁唑由羟胺制取或通过环加成制取

合成异噁唑的两条主要路线是 (a) 羟胺 ( $NH_2OH$ ) 对二酮的进攻，和 (b) 氮氧化物/氧化氮 (nitrile oxides) 的一种称为 1,3-偶极环加成 (1,3-dipolar cycloaddition) 的反应。因此它在我们之前讨论过的策略 (包含两个杂原子的亲核试剂和包含两个亲电碳原子的化合物的环化) 和将要讨论的下一个策略——环加成反应——间建立了联系。

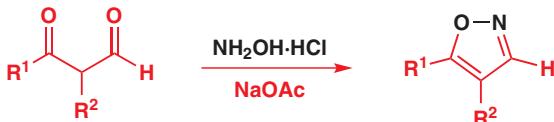
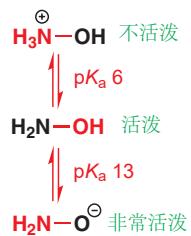


简单的对称异噁唑很容易通过羟胺流程制取。如果  $R^1 = R^3$ ，我们还拥有了一个对称而容易制备的起始原料 1,3-二酮。中心  $R^2$  基可以通过二酮的稳定烯醇盐的烷基化反应插入 (Chapter 25)。

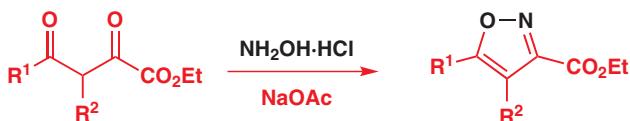
■ 我们将在 Chapter 34 中细致地阐述环加成——事实上，您已经在上一章中遇到过其中一个例子了：Diels-Alder 反应 (p. 739) 就是一个环加成反应。此处的环加成包含一个 1,3-偶极体，形成一个五元环，通过涉及六个电子的环状机理发生。

当  $R^1 \neq R^3$  时，二羰基化合物是不对称的，我们必须确保我们知道反应沿着哪个方向进行。 $NH_2OH$  更亲核的一端会进攻更亲电的羰基。似乎很明显， $NH_2OH$  更亲核的一端是氮原子，但这取决于溶液的 pH. 一般，羟胺以结晶的盐酸盐的形式提供应，需要加入某种碱以得到亲核试剂。相关的  $pK_a$ s 如侧边栏所示。如吡啶或醋酸钠等碱便可在较不活泼的阳离子的存在下，产生一些活泼的中性  $NH_2OH$ ，而如  $NaOEt$  这样的碱便会产生阴离子。在醋酸缓冲溶液中完成二者的反应，得到的通常是氮进攻醛所衍生的异噁唑。

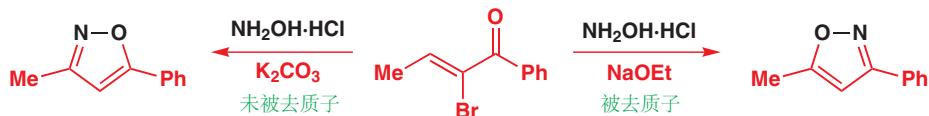
羟胺的状态随 pH 的变化：  
更亲电的原子已用黑色标出



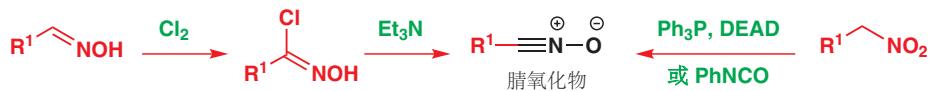
对亲电试剂修饰后或许也能成功。羟胺与 1,2,4-三酮酯 的反应，通常得到由氮进攻较活泼的酮羰基的异噁唑。



溴代烯基酮的反应为选择性提供了一个清晰的演示。亲电试剂的哪一端更亲电并不一目了然，但反应会告诉我们答案。



另一种制取异噁唑的方法依赖于腈氧化物与炔烃的反应。我们将在 Chapter 34 中看到，有两种生成这类活泼化合物的良好路线，氯代肟的  $\gamma$ -消除或硝基烷烃的脱水。



Interactive mechanism for nitrile oxide formation

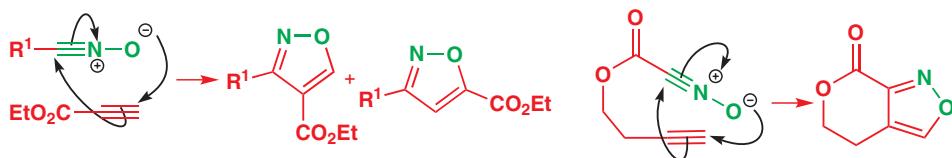
少数腈氧化物足够稳定，可以被分离（例如带有吸电子基或高度共轭基取代的）；但大多数情况下，则用以上方法中的一种，在炔烃存在时制备，否则它们会迅速地二聚。这两种形成腈氧化物的方法，都和它们与炔烃的迅速反应兼容。与芳基炔的反应通常干净而具区域选择性。



Interactive mechanism for nitrile oxide cycloaddition

反应在单一步骤中形成五元环：这是一个环加成反应，其中炔烃用其 HOMO 进攻了腈氧化物的 LUMO (Chapter 34 中会有阐释)。如果炔烃带有吸电子基团，那么由于腈氧化物的 HOMO 同样会进攻炔烃的 LUMO，便会产生异构体的混合物。分子内反应通常强迫发生某一种环化，无论电

子取向如何，这样的反应也是干净的。下面的例子，由于反应物种的直线型特征，即使最有利的取向看起来非常差，但同样只有一种异构体形成。



## 四唑和三唑同样通过环加成制取

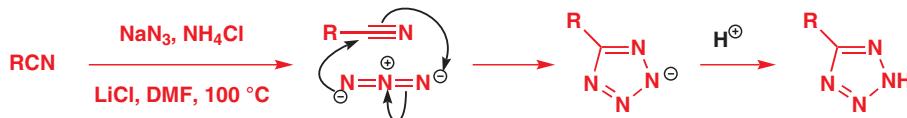
用 1,3-偶极环加成 拆分四唑的方式，一旦我们意识到腈 ( $\text{RCN}$ ) 会是其中的一个组分，就会很容易想到了。两种方式可以完成它：对中性化合物的切断需求危险的叠氮酸/氢叠氮酸 (hydrazoic acid,  $\text{HN}_3$ ) 做偶极体，但阴离子可直接切断为叠氮根离子。



■ Chapter 29 中您了解到，四唑的酸性与羧酸相当。

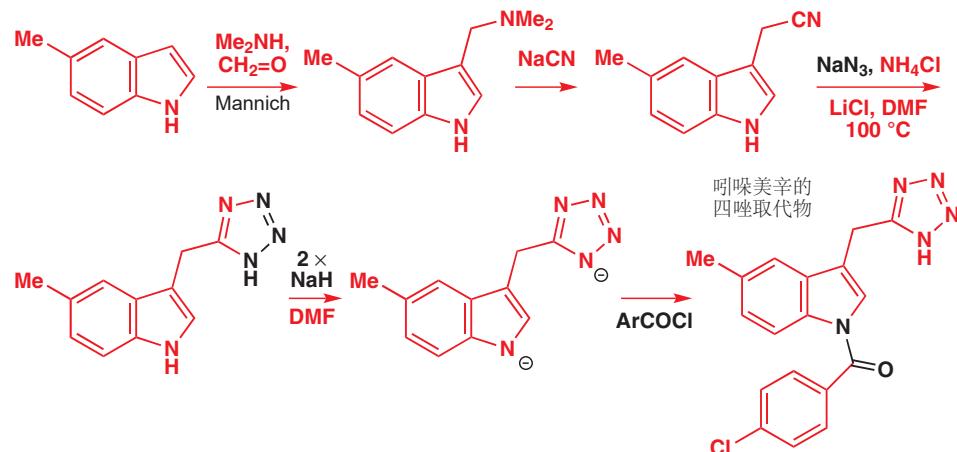
虽然这个反应可能看上去没有希望，但如果用叠氮化钠和腈的氯化铵缓冲混合物在 DMF 中加热，这事实上是有效的。真正的试剂是叠氮化铵，若 R 中有吸电子取代基时，反应发生得会更快。在反应混合物中，形成四唑的阴离子，用酸中和则可得到游离的四唑。

Interactive mechanism for tetrazole formation



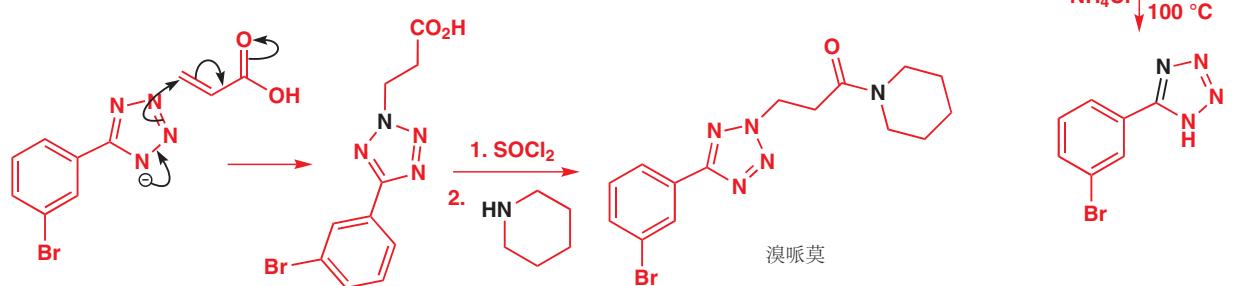
由于腈一般很容易获得，这也是制取简单四唑的主要路线。更复杂的四唑可通过环加成产物的烷基化制取。我们在 Chapter 29 中提到的吲哚美辛的四唑取代物，就是用这种方法制造的。首先，由吲哚制备腈。所得的腈，即使相当容易形成“烯醇”，但刚刚讨论的叠氮根流程中的 1,3-偶极环加成仍然很好地工作。最终，吲哚氮被酰基化；四唑酸性更强，因而为了使反应在正确的位置上发生，有必要形成双阴离子；遵循双阴离子的通常规则 (见 Chapter 23)——最后形成的阴离子最不稳定，并首先反应。

► 这种取代模式的吲哚可以通过 Fischer 吲哚合成法合成 (p. 777).

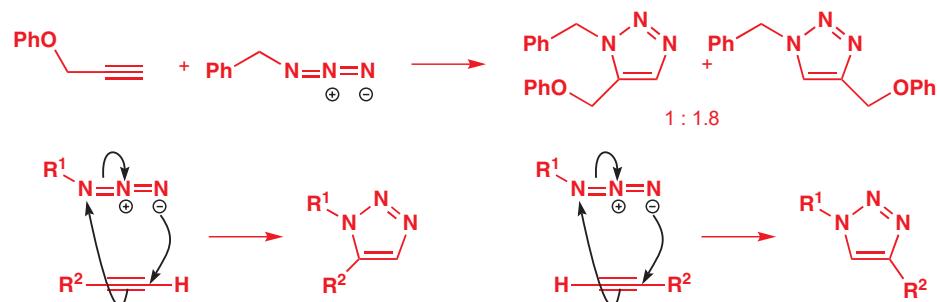


抗炎药溴哌莫 (broperamole) 的合成说明了用四唑的阴离子完成修饰的方法。四唑同样由腈构建——腈是一个带有吸电子取代基的芳香腈，因此这会是一个很好的反应。

四唑与丙烯酸发生共轭加成 (Chapter 22)，得到我们所画出的结构的互变体。阴离子中间体当然是离域的，可以在任何一个氮原子上反应。形成酰胺即可完成溴哌莫的合成。

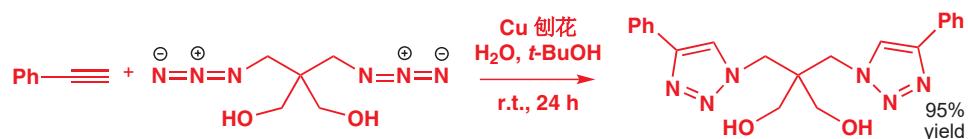


这类环加成中发生的最好的，是取代的叠氮根与炔烃的反应。仅仅将它们混合在一起，并加热即可得到三唑，通常是两种区域异构体的混合物。



Interactive mechanism for triazole formation

然而，对反应混合物做出一个简单的添加，便会大大地改善这个情况：催化量的 Cu(I)，通常通过添加 CuSO<sub>4</sub> 和温和的还原剂在反应混合物中生成，会使反应快得多，并且选择性地得到 1,4-取代的四唑。Sharpless 的工作不但使这个反应成为非常强效的三唑制取方法，而且也是将两种除此之外相对不活泼的分子联系在一起的简单方法——这个反应即使在水中仍能工作。



■ 1,2,4-三唑化合物则通常直接由未取代的 1,2,4-三唑阴离子与亲电试剂制取(反应位点在连起来的两个氮中的一个上)，见 Chapter 29。

■ 可能看上去叠氮根更亲电的一端进攻了炔烃错误的一端，氮您会在 Chapter 34 中了解，(1) 1,3-偶极体更亲核的一端是非常难以预测的，(2) 主导反应的可能是偶极的 HOMO 和炔烃的 LUMO，也可能是偶极的 LUMO 和炔烃的 HOMO。

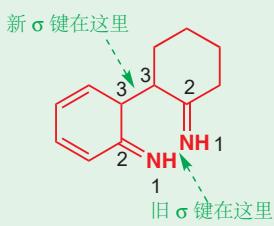
## Fischer 呋唑合成法

您将要看到的是有机化学中伟大的发明之一。它是一个引人注目的反应，拥有令人惊叹的机理，它由最伟大的有机化学家之一，Emil Fischer (埃米尔·费歇尔) 于 1883 年发现。Fischer 是苯肼 (PhHNHNH<sub>2</sub>) 的早期发现者，Fischer 呋唑合成法最简单的形式，当苯肼于一个醛或酮在酸性溶液中加热时便会发生。



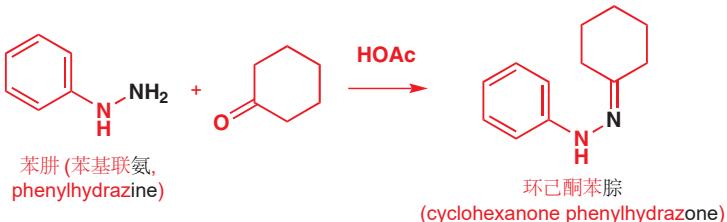
**Emil Fischer** (1852–1919), 作为 PhD 学生, 在 1875 年发现了苯肼, 在 1900 年于柏林接替了在那里建立了世界上最大的化学研究所的 Hofmann, 并于 1902 年获得诺贝尔奖。除了对于吲哚的研究, 他还通过研究主要糖类的结构和合成法奠定了糖化学 (carbohydrate chemistry) 的基础。要是他没有发明 Fischer 投影式就好了。

■ 这一步是一个 [3,3]-σ重排, 您会在 Chapter 35 中发现: 新形成的单键 (C–C) 与旧的单键 (N–N) 之间存在 3,3 关系。

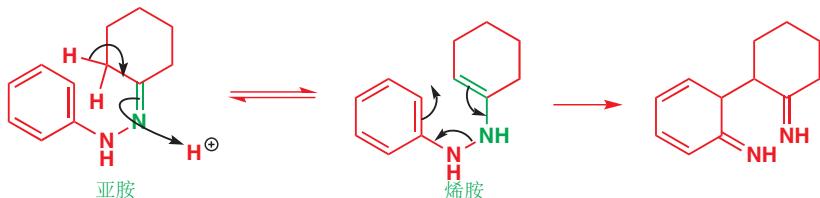


Interactive mechanism for Fischer indole synthesis

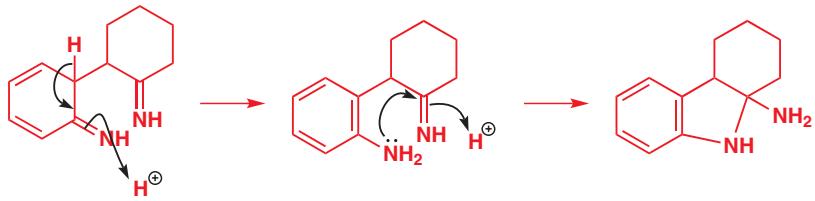
机理的第一步是酮的苯腙 phenylhydrazone (腙: 氮上连有另一个氮的亚胺) 的形成。它可以分离为一种稳定的化合物 (Chapter 11)。



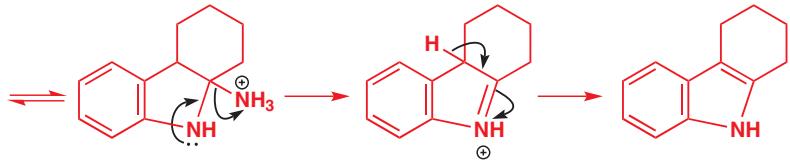
然后, 胍需要异构化为烯胺, 并来到反应的关键步骤。烯胺可以通过电子绕六元环移动, 发生包含 C–C 强键的形成, 和 N–N 弱单键的断裂的重排过程。



接下来, 苯环 (通过由碳到氮的质子转移) 重新芳构化得到一种芳香胺, 它会立刻进攻另一个亚胺。这就产生了缩醛胺 (aminal), 缩醛 (acetal) 的氮等价物。

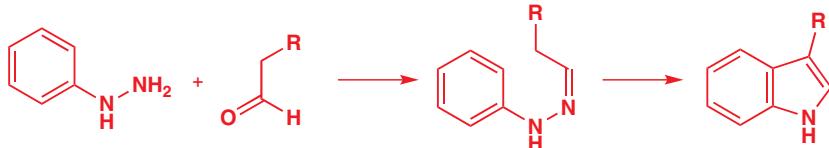


最终, 缩醛胺以缩醛方式发生酸催化分解, 逐出氨, 失去一个质子并形成芳香吲哚。

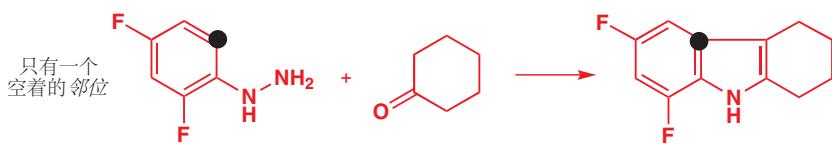


这个机理诚然很复杂, 但如果您能记忆它的关键步骤——烯胺的重排——那么剩下的部分就很容易完成了。关键点是以 N–N 弱键为代价的 C–C 键的建立。自然, Fischer 对这个机理中的任何一步都不清楚。但他足够敏锐, 观察到了所发生的变化; 技巧也足够丰富, 搞清楚了得到的是什么。

Fischer 方法是制取吲哚的主要方法, 但它并不适用于全部的吲哚。现在, 我们需要考虑它对于合成各种取代模式的吲哚的适用性。如果羰基化合物只能在一侧烯醇化, 比如醛的情况, 产物会很明显。

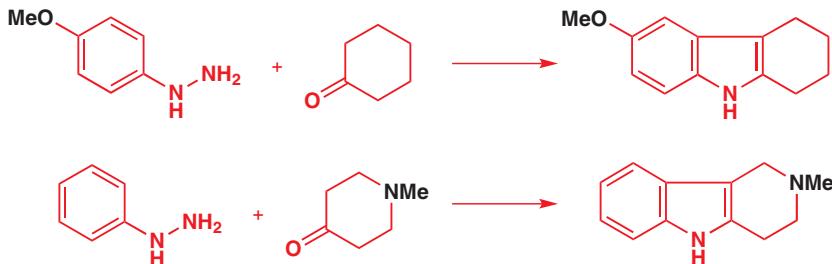


如果苯环只有一个邻位空着，那么环化也必定在这个位置发生。环上的其他取代基是无关紧要的。

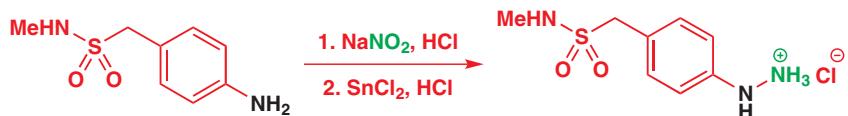
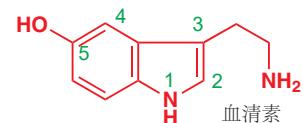


■ 此后，我们将不再画出中间体苯腙。

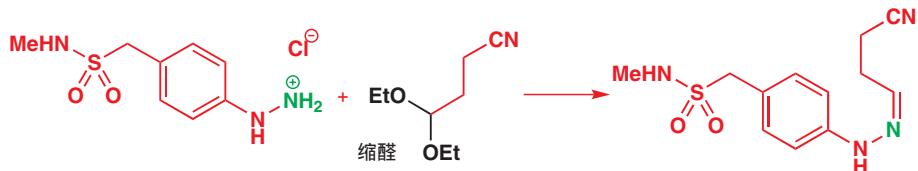
另一种由 Fischer 呋噪合成法获得单一的吲哚产物的方法，是确保试剂是对称的。这两个例子应该清楚地说明了由对称的起始原料获得的吲哚。



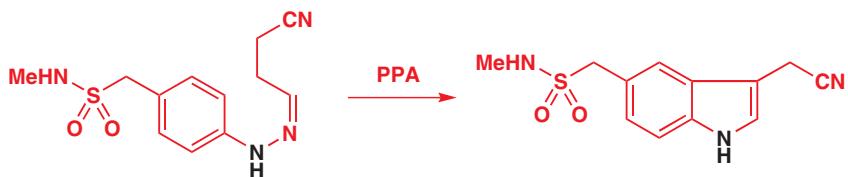
第一个例子的取代模式尤其重要，因为神经递质血清素是一个在 5 号位有羟基的吲哚，很多重要的药物也遵循这个模式。舒马普坦 Sumatriptan (以英明格 Imigran 为名出售，用于治疗偏头痛) 是血清素的类似物，它的合成开始于由下面的苯胺形成重氮盐 (Chapter 22). 亚硝化得到的重氮盐再用  $\text{SnCl}_2$  和  $\text{HCl}$  还原，可转化为苯肼。



为避免自缩合，所需的醛 (3-氰基丙醛) 以缩醛的形式添加。酸性条件会释放醛，继而形成苯腙，等待下一步。



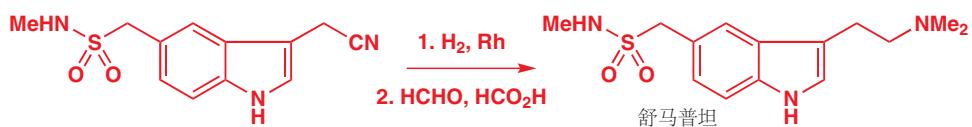
这个情形中的 Fischer 呋噪合成本身被多聚磷酸 (polyphosphoric acid~PPA) 催化，多聚磷酸是一种基于磷酸 ( $\text{H}_3\text{PO}_4$ ) 但被脱水了的粘性胶 (: $\text{H}_3\text{PO}_4/\text{H}_2\text{O}$ ) 它包含一些低聚物在其中。它经常在有机反应中被用作催化剂，在水中残留的多聚磷酸很容易去除。



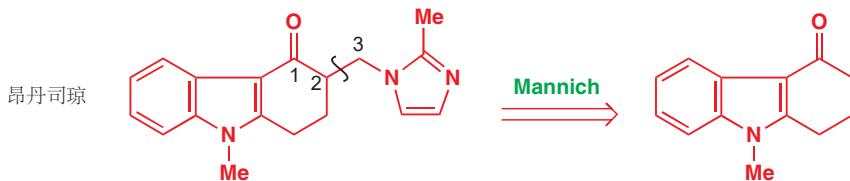
剩下需要做的就是引入二甲氨基了。腈通过氢化反应被还原，剩下的两个甲基通过还原氯化反应

引入，还原剂为甲酸，过程均为依次进行的亚胺（亚铵）的形成和还原。

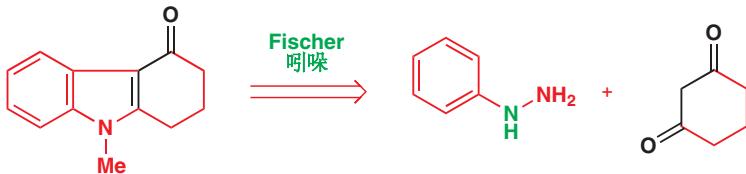
■ 通过这种方法进行的伯胺的双甲基化（或仲胺的甲基化）有时被称作 Eschweiler–Clarke 方法 (method)，我们同样在 Chapter 28, p. 716 提及了它。



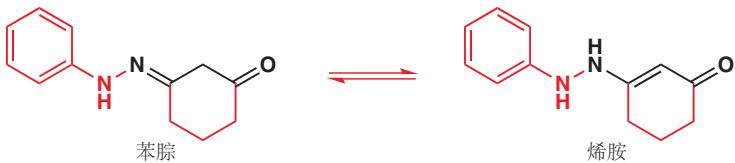
对于某些吲哚的合成，控制与不对称羰基的区域选择性是必要的。昂丹司琼 (Ondansetron) 是其中一个例子，它是一种为了帮助癌症患者能服用比以往更大剂量的抗肿瘤化合物的抗恶心 (anti-nausea) 化合物。它包含一个吲哚环和一个咪唑环。



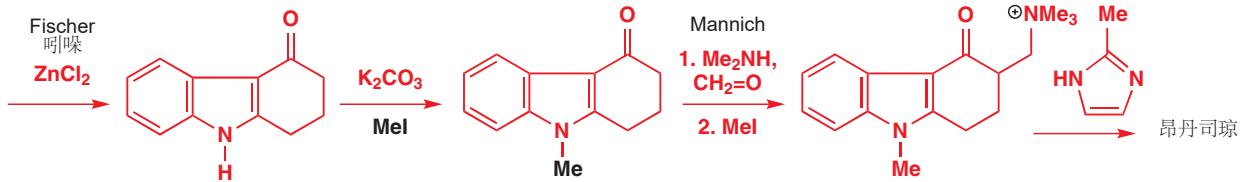
C–N 和 C–O 间的 1,3 关系表明吲哚环通过一个 Mannich 反应添加 (Chapters 26 和 28)，切断后得到一个右侧不对称的吲哚，带有一个额外的酮羰基。Fischer 切断会显露出一个作为苯肼搭档的二酮。将甲基添加到吡啶氮上的方法我们暂且放在一边。



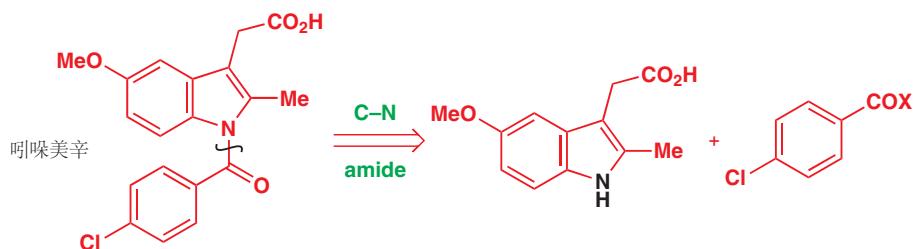
二酮有两个完全相同的羰基，它们的烯醇化 (或形成烯胺) 都完全朝着另一个酮。因而苯腙只会形成我们想要的烯胺。



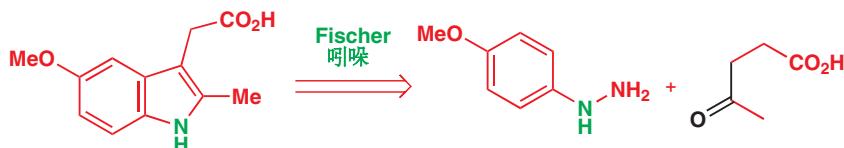
在这个情形中，Fischer 吲哚反应被一种 Lewis 酸， $ZnCl_2$  催化；然后是碱催化的甲基化。最后阶段总结如下。



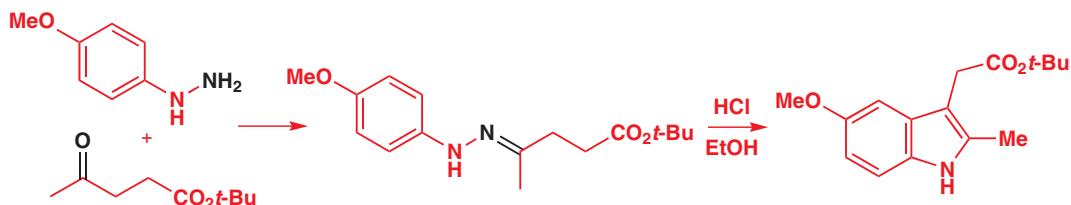
最差的情况，是烯胺在两侧形成没有如此简单的区别，那么我们必须依靠其他方法控制。非甾体抗炎药吲哚美辛便是一个很好的例子。N-酰基的移去会显露出一个在分子的两半都有取代基的吲哚。



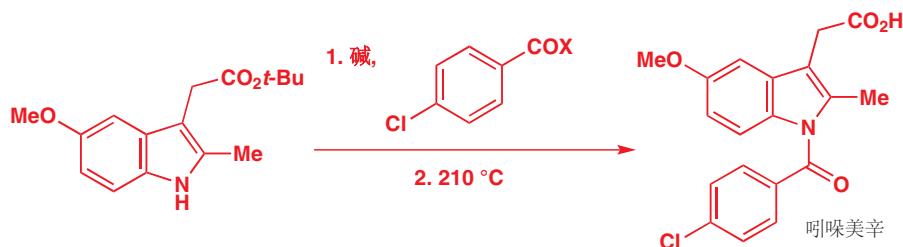
苯环的部分是对称的，也是 Fischer 合成法中理想的；当右半部分却必须来源于一个不对称的开链酮酸。这样的合成能得到控制吗？



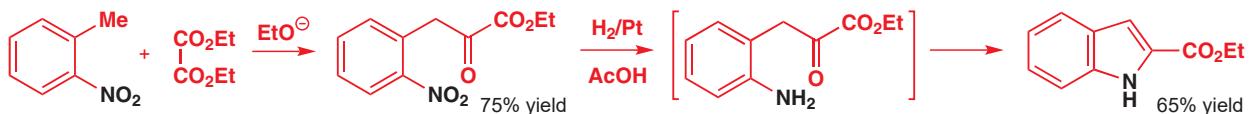
Fischer 呃噪是酸催化的，我们必须问：酸性溶液中，您觉得酮会在哪一侧烯醇化（因此形成烯胺）呢？答案（见 Chapter 20）是远离甲基，在烷基链中烯醇化。这是我们希望的，反应也确实依此方式。事实上，所用的是叔丁酯而不是游离酸。



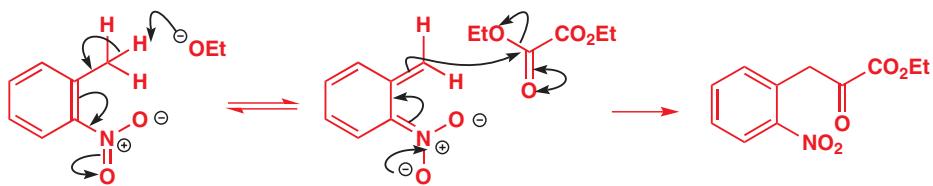
在呡噪氮原子上的酰基化通过与酰氯在碱中反应完成，然后将叔丁酯去除则可得到游离的呡噪美辛。



还有很多其他的呡噪合成，但我们仅会简要地提及其中的一个，它允许合成在苯环上拥有不同取代模式的呡噪。如果您喜欢人名，那么您可能叫它 Reissert 合成法 (synthesis)，下面是基本的反应。

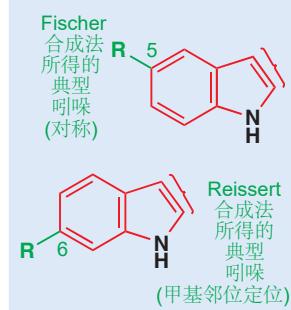


乙氧基阴离子的碱性足够去除原料中甲基上的质子，并将阴离子离域到硝基中。阴离子然后会进攻活泼的二酯（草酸二乙酯），并被它酰基化。

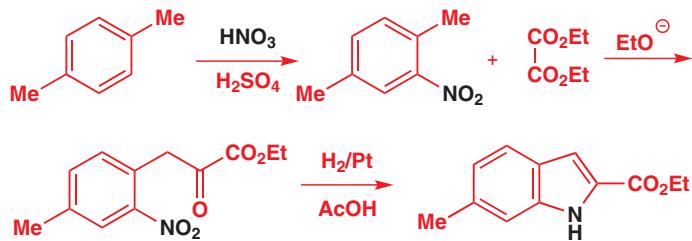


### Fischer vs Reissert

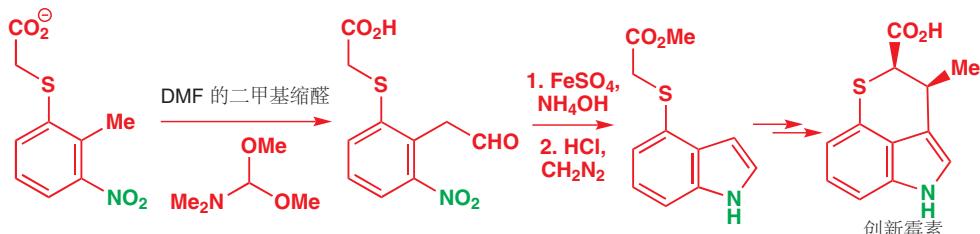
我们可以比较通过 Fischer 和 Reissert 合成法制取的吲哚的取代基不同的理想位置。当然，都不是唯一可能的取代模式。



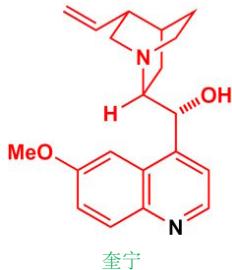
合成中所剩下的更加简单：硝基可以被还原为胺，继而立刻通过对较活泼的羰基（酮羰基）的分子内进攻形成一个烯胺，以得到吲哚。由于硝基由苯环的酰基化反应制取，它与 Fischer 合成法所偏爱的对称性非常不同。对二甲苯的硝化就是一个很好的例子。



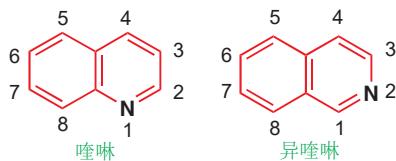
如果需要一个游离吲哚，那么酯基可以通过我们上一章讨论过机理的水解和脱羧去除。任何情况下，都不必用草酸二乙酯作为亲电的羰基化合物。下面的合成，是奇异的抗生素创新霉素(chuangxinmycin)合成的一部分，使用了 DMF 的缩醛作为亲电试剂



### 喹啉和异喹啉



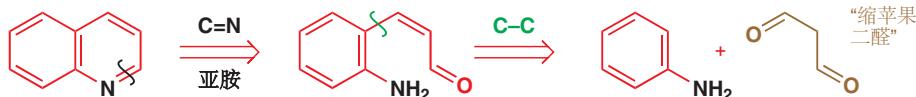
喹啉是奎宁结构的一部分，奎宁是一种在金鸡纳树 (cinchona) 树皮中发现的疟疾治疗药物，自印加文明 (Incas) 的时代就为人所知。奎宁是一个有 6-MeO 取代基和在 C4 上连接了侧链的喹啉。在讨论喹啉的合成时，我们将尤其对这种 (取代) 模式感兴趣。这是因为对抗疟疾化合物的研究还在继续，其他含有类似结构的喹啉也在现有的抗疟药物之中。



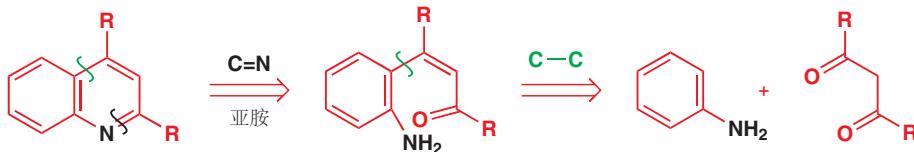
我们也将对喹诺酮 (quinolones)，吡啶酮的类似物，在 2 或 4 号位有羰基，非常感兴趣，因为它们是有用的抗生素。一个简单的例子是培氟沙星 (pefloxacin)，含有经典的 6-F 和 7-哌嗪取代基。



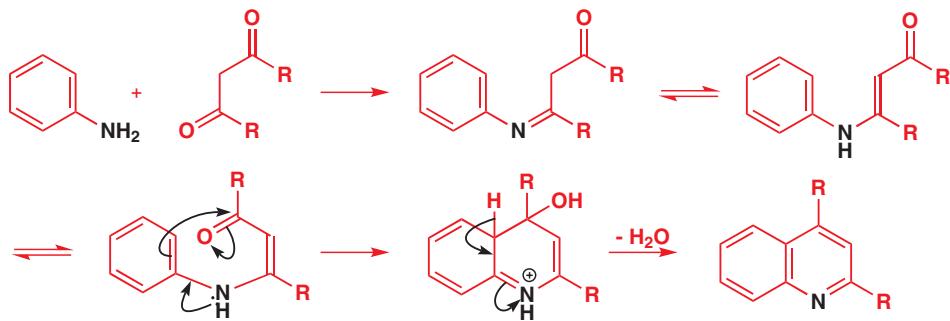
当我们考虑一种喹啉的合成时，最明显的切断，首先是对吡咯环中 C–N 键的切断，然后是对连接苯环和侧链的 C–C 键的切断。我们会需要一个三碳 ( $C_3$ ) 合成子，在两端都亲电，并在并入后得到两根双键。明显的选择是 1,3-二羰基化合物。



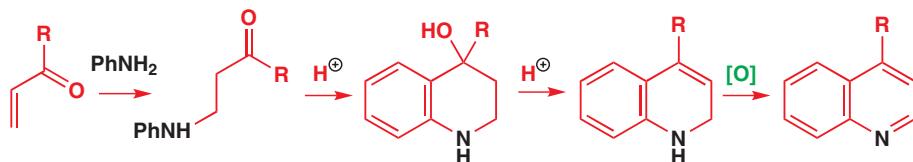
选择用芳香胺是很好的，因为不但  $NH_2$  基可以很好地与羧基化合物反应，二醛它还活化在邻位的亲电进攻。然而，所需的二醛是缩苹果二醛（丙二醛，malonic dialdehyde），一种并不存在的化合物，因此必须找到某些替代物。如果喹啉在 2 和 4 号位被取代，那么这个流程看起来会更好。



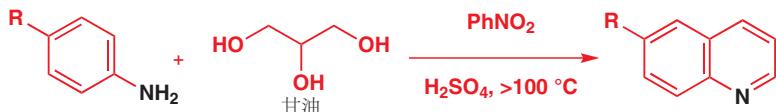
起初形成的亚胺会互变为共轭的烯胺，然后通过芳香亲电取代发生环化。但烯胺一般更喜欢采取所示的第一种构型（亚胺式），这样就会使得环化不能发送，因而这（也许因为这个原因，也许是由于难以预测由不对称 1,3-二羰基化合物 形成哪一种喹啉）还不足以证明这是一个非常重要的喹啉合成法。然而，这个合成计划是可行的，我们将描述这一主题的两种重要变体，其中一个用于喹啉，另一个用于喹诺酮。



吡啶的合成证实了，制得一个二氢吡咯，然后再将其氧化为吡咯是有好处的方法。同样的思路在可能是最有名的喹啉合成法 Skraup 反应 (reaction) 上，也很好地工作。二酮被不饱和羰基化合物替代，因而喹啉的形成会是区域选择性的。第一步是胺的共轭加成。在酸催化剂下，酮会以和刚才一样的方式环化，脱水后得到二氢喹啉。得到芳香喹啉的氧化反应，用很多可行的氧化剂都很容易实现。

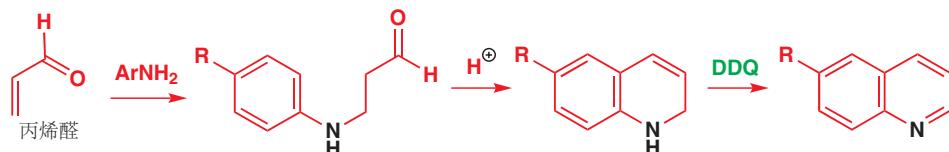


传统上，将所有东西混合在一起，并让它们毫无拘束地进行，即可完成 Skraup 氧化。用于合成在吡啶环上没有取代基的喹啉的经典方法，是将芳香胺、浓硫酸、甘油和硝基苯在一个大烧瓶中混合，并加热到 100 °C 以上，配有一个宽冷凝器 (wide condenser)。



Skraup 反应这个难听的名字被用在这样的，所有杂环合成法中最差的“女巫的酿造”是恰如其分的。一些研究者会添加奇怪的氧化剂，如砷酸、铁 (III) 盐、锡 (IV) 盐，及有各种取代模式的硝基苯，或碘来使反应“更好地进行”。

甘油用于通过脱水提供丙烯醛 ( $\text{CH}_2=\text{CH-CHO}$ )，硝基苯作为氧化剂，宽冷凝器很多时候，Skraup 反应确实毫无拘束——并导致了毁灭性的结果。更安全的方法是先制备共轭加合物，再在酸性溶液中环化，然后再用我们在吡咯合成中描述过的氧化剂之一，尤其是醌类，例如 DDQ 氧化它。

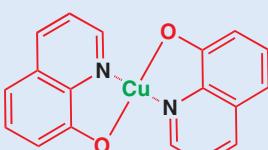


Skraup 合成更加现代的方式被用于合成 8-喹啉酚/羟基喹啉，也叫“喔星 (oxine)” 。邻氨基酚只有一个空着的氨基邻位，同时也非常亲核，因此可以用仅有痕量强酸的弱酸环境，完成它与丙烯醛的反应。铁(III) 是氧化剂，为了运气，再加一点硼酸，产率会是极好的。



## 喔星

这个化合物很重要，因为它可以与 Mg(II) 或 Al(III) 等金属离子形成不寻常的稳定的金属配合物。它同样被用作铜的缓蚀剂 (corrosion inhibitor)，因为它可以形成 Cu(II) 配合物的稳定层，并阻止内部的铜氧化。



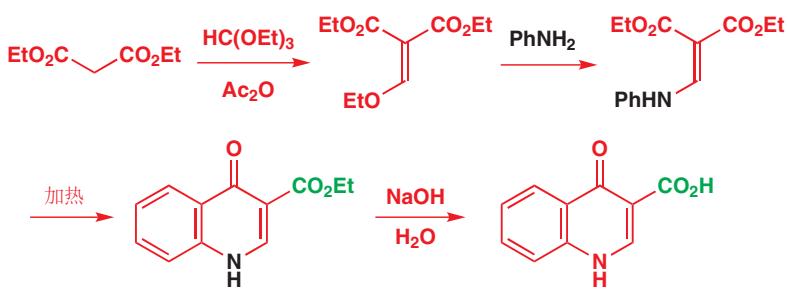
铜的喔星配合物

## 喹诺酮同样由苯胺在邻位的环化得到

用通常方法制取喹诺酮类抗生素是可行的，因为它们都包含一个在 3 号位的羧酸。用与喹啉一致的方法切断，会得到一个相当不稳定得缩苹果酸酯衍生物作为起始原料。



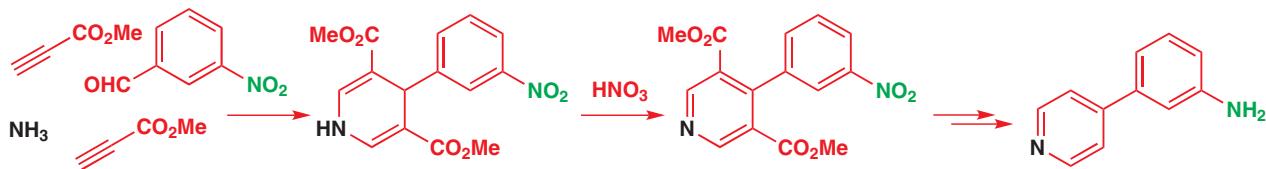
事实上，这个化合物的烯醇醚很容易由缩苹果酸二乙酯和原甲酸 (orthoformate) 乙酯  $[\text{HC}(\text{OEt})_3]$  制取。芳香胺会与这种化合物，通过一个加成-消除流程反应，所得的烯胺会在加热时环化。这次烯胺的几何结构不会令人担心。



对于喹诺酮类抗生素的例子，我们选择了合成路线已在 Chapter 22 中详细讨论过的氧氟沙星，和合成路线将会在下文讨论的罗索沙星 (rosoxacin)。两个分子都包含相同的喹诺酮羧酸框架，以黑色表示，还包含在 7 号位的另一个杂环体系，及在各处的各种各样的其他取代基。



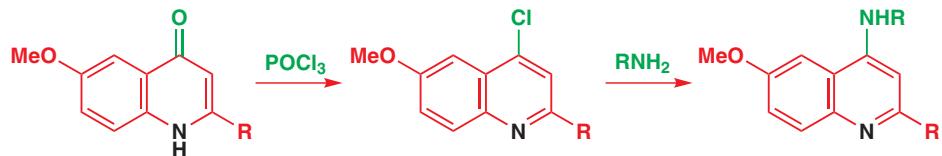
为了制取罗索沙星，必须构建两个杂环体系。制药公司 Sterling 的研究者决定通过用炔基酯在 3-硝基苯甲酸 上发生 Hantzsch 合成法的一个巧妙版本制取吡啶。氨基通过乙酸铵添加。用硝基氧化可制取吡啶，将酯水解后再脱羧即可移去羧基，再用 Fe(II) 和 HCl 还原可将硝基转化为喹诺酮合成法所需的氨基。



现在，可以用我们之前使用的相同的试剂，成功地完成喹诺酮的合成，唯一所剩的是酯水解和在氮上的烷基化。注意，由于氨基有两个不同的邻位，理论上，喹诺酮环化可以以两种方式发生。实践中，环化会远离吡啶环发生，另一种方式得到的喹诺酮会很拥挤。



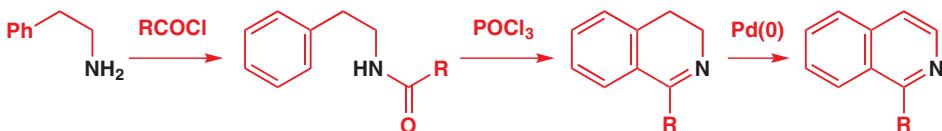
由于喹诺酮，像吡啶酮一样，可以与  $\text{POCl}_3$  反应转化为氯代化合物，氯代物可以被用在亲核取代反应中，以构建更多复杂的喹啉。



■ 用 DMF 的 Vilsmeier 反应位于 p. 734.

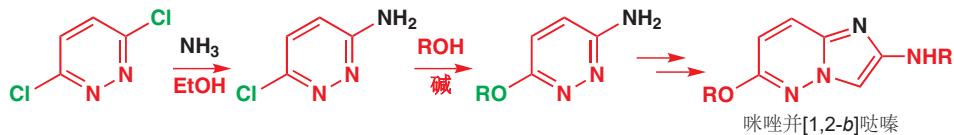
■ 与 Pd 的反应仅仅是 Pd-催化氢化反应的逆反应。

在这里，我们只会给出一种异喹啉的重要合成。它是一个接近分子内 Vilsmeier 反应的二氢异喹啉合成法，亲电试剂由酰胺和  $\text{POCl}_3$  反应得到。然后将其氧化（此处所用的是  $\text{Pd}(0)$  的脱氢反应）即可得到喹啉。

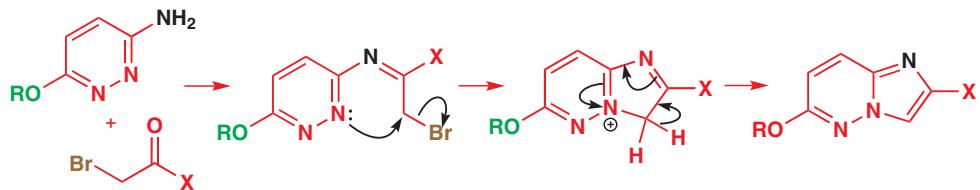


## 稠环中更多的杂原子意味着更多的合成法选择

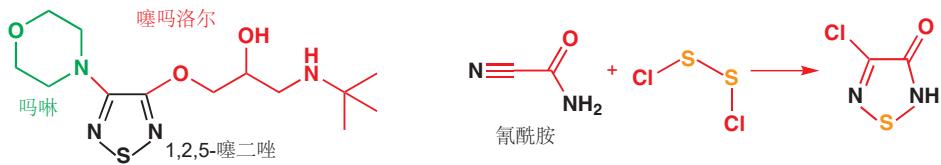
咪唑并吡嗪 (imidazo-pyridazine) 环系是很多人类、动物药物的基础。这个体系的合成用到了 Chapter 29 讨论过的知识来构筑哒嗪环。在那里，我们提出，二氯哒嗪的制取很容易，吡嗪可以用不同的亲核试剂一一取代氯原子。现在，我们将讨论得到双环体系的这些中间体的制取。



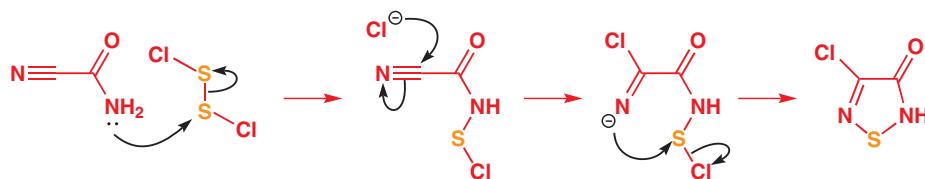
一种 2-溴代酸衍生物是重要的试剂。它可以用羧基在氨基氮原子上反应，并用卤代烃在哒嗪环氮原子上反应。这是将分子组织成一个十电子芳香体系的唯一方法。



在 Chapter 29 中，我们同样给出过噻吗洛尔 (timolol) 的结构，这是一种用于降低高血压的，基于噻二唑的， $\beta$ -阻滞剂药物。这个化合物包含一个芳香 1,2,5-噻二唑环系，一个饱和吗啉环，以及一个脂肪族侧链。它的合成依赖于一个相当有趣的环化方法，然后是一个和上一个合成中类似的选择性的亲核取代反应。芳环由  $\text{S}_2\text{Cl}_2$  在“氰酰胺”上的作用得到。

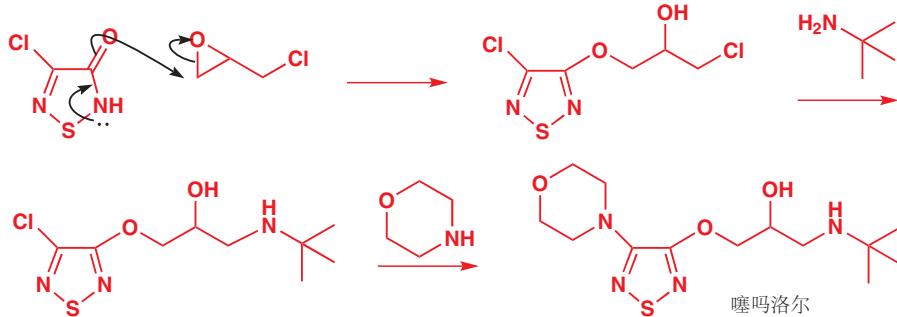


这个反应必定由酰胺氮对亲电的硫原子的进攻开始。由于腈的直线型结构，环化还不能发生，因此必定先有氯离子（由  $\text{ClS}^-$  歧化得到）进攻  $\text{CN}$ 。此后环化便简单了。



然后与环氧氯丙烷反应，再在侧链上进行胺取代，最后用吗啉在环上发生亲核取代反应，则可完成这个合成。

我们在 Chapter 28 中多次使用了环氧氯丙烷。



## 总结: 芳杂环的三种主要合成方法

我们将以对三种主要的杂环合成策略的总结，结束这一章：

- 通过离子型反应构筑环
- 通过环加成反应构筑环
- 通过亲电、亲核芳香取代，或锂化后于亲电试剂反应来修饰已经存在的环。

我们将总结这三种策略的不同应用，同时也会提出各种策略所不适合的情境。本节也将回顾 Chapter 29 中的材料，因为绝大部分的环修饰方法都出现在那里。

■ 这只是一个总结。在 Chapters 29 和 30 中的相关节中有更多的细节。对于这些杂环的制取，还有很多很多的其他方法。如上我们所提供的那些方法，只起到带您迈进大门的作用。

### 通过离子型环化反应构筑环

面对杂环合成时，您应当尝试的第一种策略是切断杂原子于碳之间的键，中心思想是用杂原子作为亲核试剂，用碳碎片作为双亲电试剂。

#### 带有一个杂原子的杂环

五元环

- 吡咯、噻吩，和呋喃可以通过这种策略，由

1,4-二羰基化合物 理想地制得



## 六元环

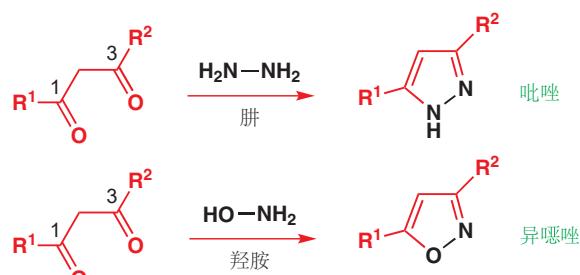
- 吡啶可以通过这种策略，由 1,5-二羰基化合物及氧化反应制得



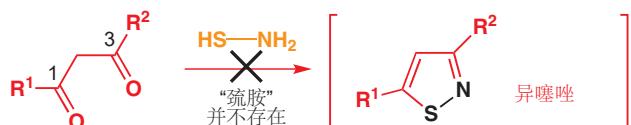
## 带有两个相邻杂原子的杂环

## 五元环

- 吡唑和异恶唑可以通过这种策略，由 1,3-二羰基化合物理想地制得

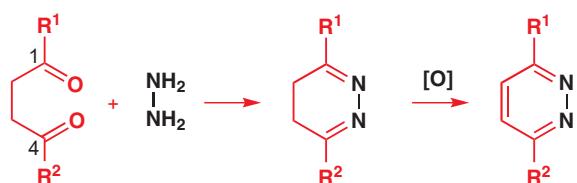


注意。这种策略不适用于异恶唑，因为“巯胺”是不存在的



## 六元环

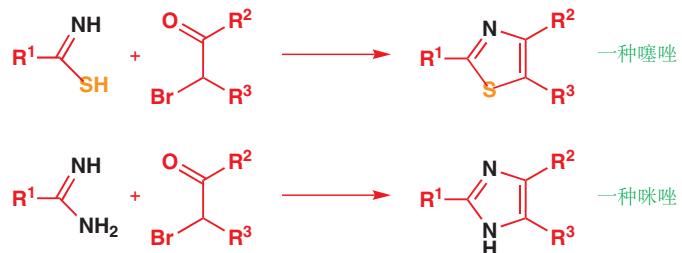
- 嘁唑可以通过这种策略，由 1,4-二羰基化合物 及氧化反应理想地制得



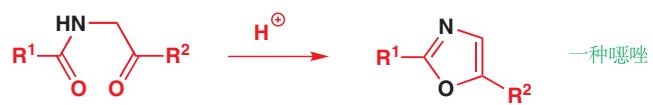
## 带有两个分开的杂原子的杂环

## 五元环

- 咪唑和噻唑可以通过这种策略，由  $\alpha$ -卤代羰基化合物理想地制得

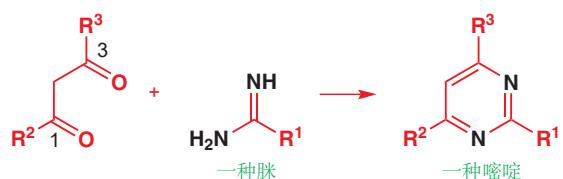


注意。这种策略并不适用于恶唑，因为酰胺的活性通常不够：酰基化的羰基化合物的反应通常才是首选



## 六元环

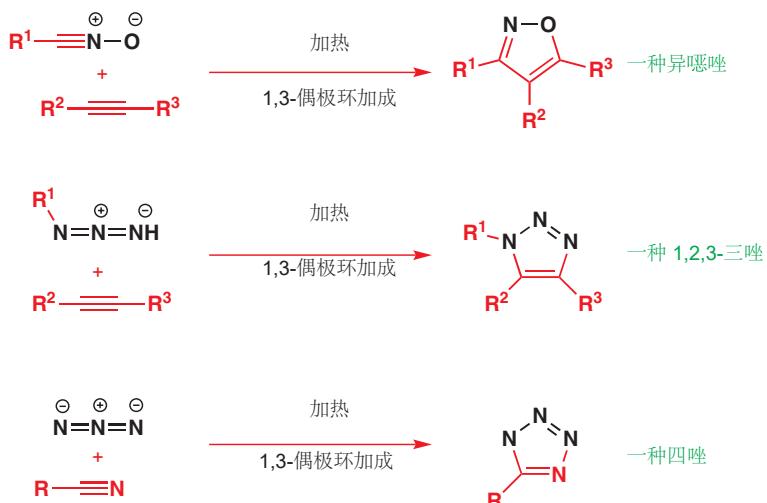
- 噻啶可以通过这种策略，由 1,3-二羰基化合物理想地制得



## 通过环加成反应构筑环

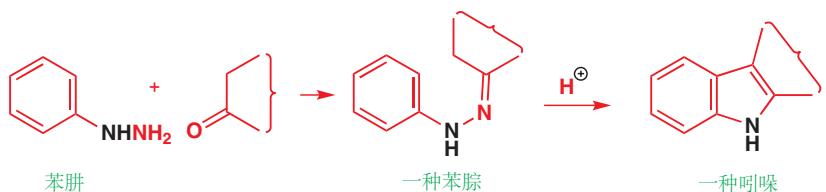
### 1,3-偶极环加成反应

- 异噁唑、1,2,3-三唑，和四唑理想的构筑方法



### ...或 σ 重排

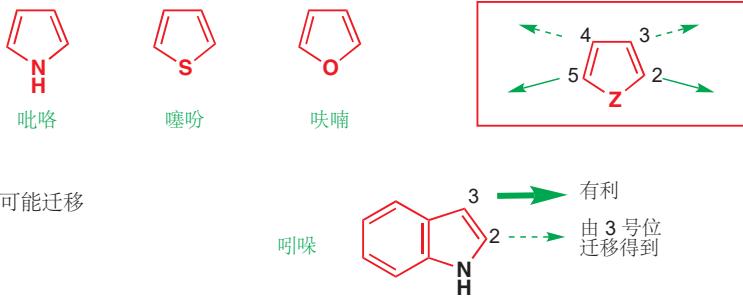
- 一个特殊的反应，也是 Fischer 呋喃合成必不可少的步骤



## 环修饰

### 芳香亲电取代

- 在吡咯、噻吩，和呋喃上工作良好，最佳位点是 2 和 5 号位，但在 3 和 4 号位也几乎一样好
- 通常，阻塞住不想使之取代的位点是最好的
- 在吲哚上工作良好——只在 3 号位发生，但亲电试剂仍可能迁移
- 到 2 号位



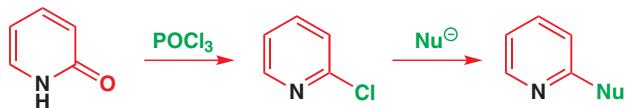
- 对于带有硫、氧，或类吡咯氮原子的五元环工作良好，反应会发生在任何没有被阻塞的位点。(见前面的节) 注意。不推荐用于吡啶、喹啉，或异噁唑。

### 芳香亲核取代

- 对于能使中间体中的电荷停留在氮上的吡啶和喹啉工作得尤其好



- 对于吡啶酮、喹诺酮特别重要，可通过将其转化为氯代化合物，再用亲核试剂取代氯，对于喹啉，可以取代苯环上的氟原子。



- 对于带有两个氮原子的六元环 (哒嗪、嘧啶，和哌嗪) 在所有位点都工作良好



### 锂化和于亲电试剂的反应

- 对于吡咯 (如果 NH 被阻塞)、噻吩、呋喃在杂原子邻位都工作良好。将 Br 或 I 交换为 Li 的方法，当任何酸性氢 (包括环上的 NH) 都被阻塞时，对于大多数亲电试剂都工作良好



## 延伸阅读

关于杂环的最好的一般性文本是: J. A. Joule and K. Mills, S. Warren and P. Wyatt, *Workbook for Organic Synthesis: the Disconnection Approach*, Wiley, Chichester, 2009, chapters 34–35.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 饱和杂环 和立体电子效应

# 31

## 联系

### → 基础

- 缩醛和半缩醛 ch11
- 立体化学 ch13
- 环状分子的构象 ch16
- 立体专一性的消除反应 ch17
- 质子 NMR ch18
- 羟醛反应 ch26
- 芳杂环 ch29 & ch30

### 目标

- 将杂原子放入环中工会改变杂原子的反应性
- 开环反应: 环张力的影响
- 杂环中的孤对电子具有准确的定位效应
- 一些取代基在六元饱和杂环中倾向于直立
- 孤对电子与空轨道的相互作用可由控制构象
- 闭环反应: 为什么五元环形成得快而四元环形成得慢
- Baldwin 规则: 为什么有些闭环可由很好地发生而另一些则根本不发生
- 构象和环的大小如何影响偶合常数
- Geminal 偶联
- 对称性和 NMR 光谱的关系: 非对映异构性

### → 展望

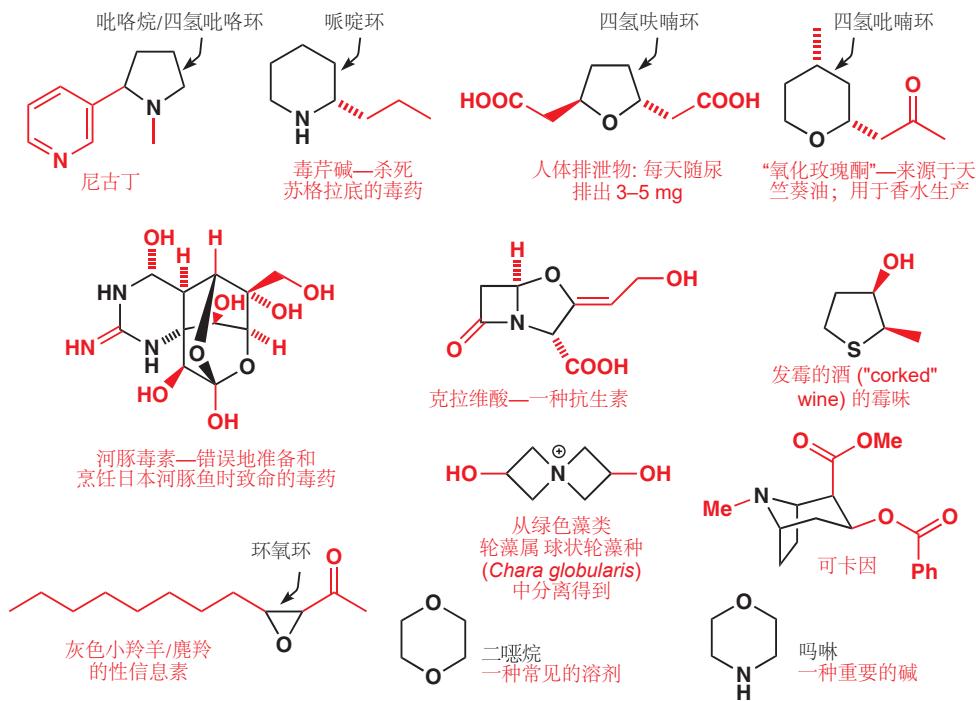
- 环状体系中的立体选择性 ch32
- 非对映选择性 ch33
- 不对称合成 ch41
- 生命的化学 ch42

## 引入

环对分子的反应方式，和可行的合成方法都有影响。我们刚刚才用两章讨论了平面型的芳香杂环的反应和合成。而在本章，及紧跟着的一章中，我们还会继续着眼于环，但不是平面型的芳香环。环中的原子一旦是饱和原子，它们便会更加灵活，并表现出有趣的化学特征。我们在 Chapter 16 中介绍了讨论环的构象的方法 (conformation)，而在此我们还会回顾它们——环，由于限制了分子可以采取的构象的数目，因而使我们对其立体化学的思考更加容易，本章便会建立在这样一种思路上。我们还将介绍一种我们会在本书接下来的几章中不断发展的主题：立体选择性 (stereoselectivity)——如何制取单一非对映体的产物。

可能看起来有些奇怪，杂环——不仅包含碳原子，而且包含氧、氮，或硫的环——值得用整整三章来讨论，但您很快就会发现，这是合情合理的，这囿于杂环庞大的数目和种类，以及它们特殊的

化学特征。在前两章中，我们讨论了芳杂环特殊的立体化学特征，尤其是它们独特的反应性、稳定性和合成的容易性。下面示出了一些饱和杂环的例子，您或许熟悉其中的一些。



饱和杂环以黑色显示，最重要的几类环的名称也已给出：有一些（如哌啶 piperidine、吗啉 morpholine）是您需要记住的；其他一些（四氢呋喃 tetrahydrofuran、吡咯烷/四氢吡咯 pyrrolidine）则很显然衍生于芳杂环的名称。这些化合物中，有一些（尼古丁、毒芹碱、可卡因）是属于生物碱（alkaloids）一类的植物产物，将于 Chapter 42 中讨论。另一类重要的饱和杂环，糖（sugars），也将出现于 Chapter 42。

但什么是饱和杂环“特殊的化学特征”呢？在环中放入杂原子，会完成两件重要的事情，它们便是本章中最重要的两个新话题。

■ 虽然只有本章，立体电子效应出现在了标题中，但您很快就会意识到，我们将在此处涵盖的思路，与 E2 消除反应立体专一性的观点（Chapter 17），以及轨道重叠对 NMR 偶合常数的影响（Chapter 18）之间，具有相似之处。未来，我们还会用轨道排列来解释 Karplus 关系（Chapter 32）、Felkin-Anh 过渡态（Chapter 33），以及重排和碎片化反应中的构想需求（Chapter 36）。

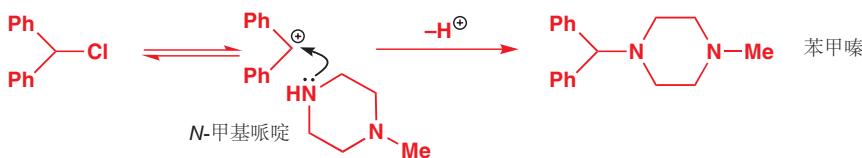
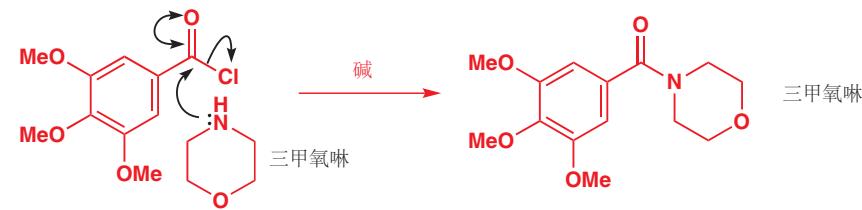
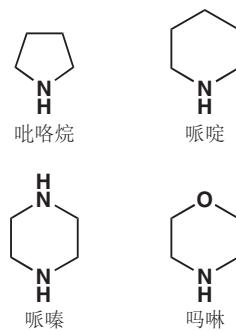
- 首先，杂原子使环容易通过关环反应（ring-closing reaction）制取，或者（有些情况下）容易通过开环（ring-opening）反应断裂。环的开、关反应是您将必须掌握的内容，控制这些反应的原则将在本章的后文中讨论。
  - 其次，环固定了杂原子——相对于环绕它的原子——的取向——尤其是它们孤对电子的取向。这对杂环的反应性和构象有所影响，其影响可用立体电子效应（stereoelectronics）解释。
- 立体电子效应，是轨道在空间中的排列，在化学上造成的影响。

## 饱和杂环的反应

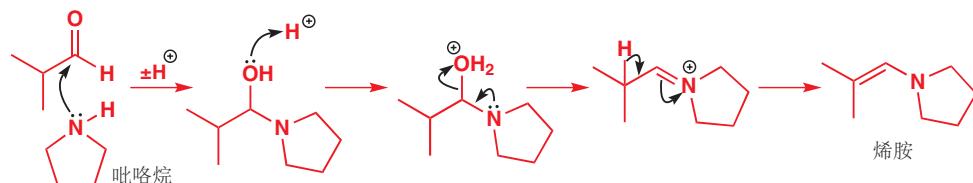
### 饱和氮杂环：胺，但更加亲核

在很多反应中，简单饱和氮杂环——哌啶、吡咯烷、哌嗪（piperazine），和吗啉——都仅仅表现为

恰巧是环状的仲胺。它们会发生其他胺发生的反应种类，如做加成和取代反应的亲核试剂。例如吗啉，可以被 3,4,5-三甲基苯甲酰氯 酰基化，得到镇静剂和肌肉松弛剂三甲氧咻 (trimetozine)，而 N-甲基哌啶可以在与二苯基甲基氯的 S<sub>N</sub>1 反应中被烷基化，并得到晕车药苯甲嗪 (cyclizine)。



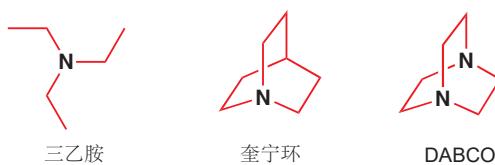
吡咯烷对醛和酮的加成是一个尤其重要的反应，因为这个反应，会得到我们在 Chapter 25 中讨论的有价值的烯醇等价物，烯胺。



由吡咯烷、哌啶形成的烯胺尤其稳定，这是因为吡咯烷、哌啶相比于其他可比较的非环状胺，如二乙胺相当更加亲核。这是一个环状胺（及环状醚）的一般特征，这是一个立体效应。烷基取代基，被绑在后面的环中，避开了亲核试剂的孤对电子，使其能够没有空隙地接近亲电试剂。通过比较碘甲烷与三种胺——这次是叔胺——的反应速率，可以很好地说明这一效应。两种环状化合物都是桥环——奎宁环 (quinuclidine) 是一种桥连/侨联的 (bridged) 哌啶；另一种二胺，被称作 DABCO (1,4-二氮杂双环[2.2.2]辛烷, 1,4-diazabicyclo[2.2.2]octane) 是一种侨联的哌嗪。下表展示了三乙胺，奎宁环和 DABCO 的相对反应速率，及 pK<sub>a</sub> 值。

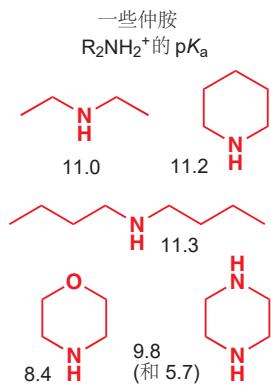


胺与碘甲烷的反应速率



相对反应速率 <sup>a</sup>	1	63	40
R <sub>3</sub> NH <sup>+</sup> 的 pK <sub>a</sub>	10.7	11.0	8.8 (和 3.0)

<sup>a</sup>20°C 下在 MeCN 中与 MeI 反应的相对速率。



奎宁环和 DABCO 的活性比三乙胺高 40–60 倍。这同样是由于环结构使氮的取代基与用于进攻亲电试剂的孤对电子保持远离。您还应当比较环状结构对胺碱性的影响：没有影响！三乙胺和奎宁环的碱性等同，如侧边栏中所示，二乙胺、二丁胺，和哌啶的碱性也差不多。这是由于，质子太小，几乎并不关心烷基是否被绑在后面。

决定  $\text{pK}_a$  的因素中，重要得多的是氮富电子的程度，这也是奎宁环与 DABCO 的碱性，哌啶 ( $\text{pK}_a$  11.2) 与吗啉 ( $\text{pK}_a$  9.8) 或哌嗪 ( $\text{pK}_a$  8.4) 的碱性存在显眼的差异的原因。额外的杂原子，通过诱导作用，从氮原子上吸取电子密度，使其亲核性更弱，碱性也更弱。从这个意义上，吗啉可以作为非常实用的碱，碱性比三乙胺弱但又比吡啶 ( $\text{pK}_a$  5.2) 的碱性稍大。注意观察二胺 DABCO 和哌嗪的二级  $\text{pK}_a$  (即第二个氮质子化的  $\text{pK}_a$ ) 低了多少：单质子化的胺上被质子化的氮原子会非常有效地从未被质子化的氮上吸电子。

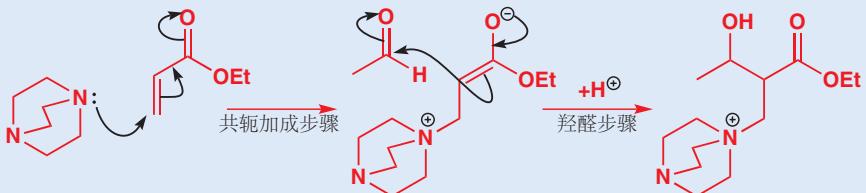
■ 澄清一下：我们在此讨论的  $\text{pK}_a$ s 都是铵离子  $\text{R}_2\text{NH}_2^+$  的  $\text{pK}_a$ 。

### Baylis–Hillman 反应

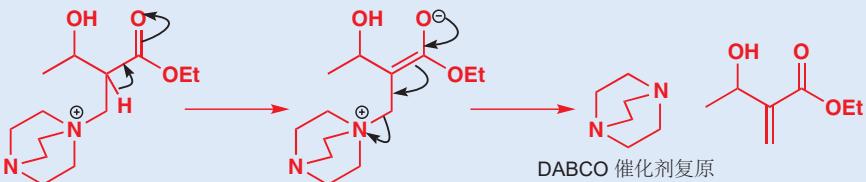
DABCO 最重要的应用之一出现于 Baylis–Hillman 反应中，由纽约的塞拉尼斯公司 (Celanese Corporation) 的两名化学家在 1972 年发现。这个反应是羟醛反应 (Chapter 26) 的一种修饰，只是烯醇盐不是由去质子形成的，而是通过共轭加成形成的。在 Chapter 25 中您一见到，共轭加成的烯醇盐产物可以被烷基化试剂捕获，而在 Baylis–Hillman 反应中，亲电试剂是一个醛，这个醛在反应一开始就存在，这个反应也仅需在室温下搅拌各组分即可完成。下面是典型例子。



反应开始于 (相对亲核的) DABCO 对丙烯酸乙酯的共轭加成。这会形成一个可以通过羟醛反应进攻乙醛的烯醇盐。

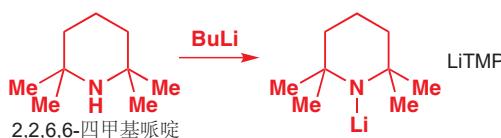


E1cB 消除通常紧跟着羟醛反应发生，并得到  $\alpha,\beta$ -不饱和产物。但在此情形中，DABCO 是比羟基好得多的离去基团，因此烯醇化后，DABCO 会通过 E1cB 消除失去，得到反映产物。DABCO 得到复原，它是一个催化剂。

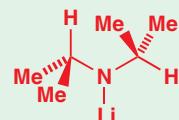


Baylis–Hillman 反应的一个缺点是它的速度：通常，需要反应数天。压力有助于加速反应，而作为催化剂，DABCO 大概是最好的。因为被“绑在后面”的烷基，它是具有亲核性的；但更重要的是，它相对较低的  $\text{pK}_a$  使之也是一个很好的离去基团，这意味着它很容易在最后一步中离去。如您之前所了解，好的亲核试剂通常是差的离去基团，但这有很多例外。DABCO 亲核性和离去能力的结合在此处是完美的。

环状胺中氮原子暴露的特性，意味着氮杂环会频繁出现于药物分子中，尤其是作用于中枢神经系统的药物（可卡因 cocaine、海洛因 heroin、吗啡 morphine 都包含氮杂环，可待因 codeine 和许多镇静剂，如 安定 Valium 也是如此）中。环还可用于支撑添加上的取代基，它们会阻碍氮的孤对电子。正如哌啶中的氮原子一直暴露，2,2,6,6-四甲基哌啶（TMP）中的氮原子则一直栖息于甲基的深处。TMP 的锂盐（LiTMP）是 LDA 的类似物——一种具有很大空阻的碱，并可以用在即使是 LDA 都失败了的选择性情形中。

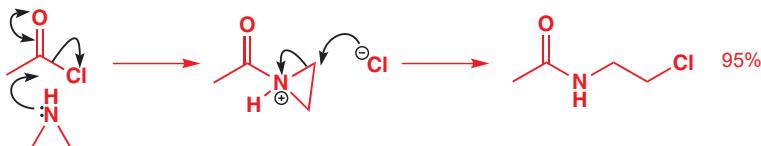


■ 在 LDA 中，其中一个或另一个异丙基常常会通过旋转，使得只有一个 C-H 基在 N-Li 键附近。但在 LiTMP 中，则不可避免地有四个 Me 基在 Li 附近。

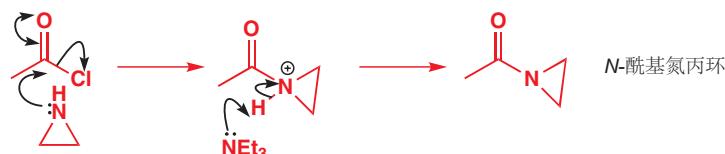


### 氮丙环：环张力促进开环

氮丙环（Aziridine）和氮丁环（azetidine）是稳定的，而易挥发的，它们是饱和氮杂环家族中的成员，氮丙环本身有一些有趣的化学。像吡咯烷和哌啶一样，氮丙环可以与酰氯反应而被酰基化，但产物是不稳定的。环会在氯离子，一个相对差的亲核试剂的进攻下打开，并得到开链的仲胺。



您可以将其看作非常类似于环氧开环（Chapter 19）——尤其是其中氧带正电荷的，质子化的环氧——的开环过程。正电荷对氮丙环开环是非常重要的，因为如果在碱性下完成这个反应，质子的移去会立即得到中性的酰基氮丙环，它是稳定的。

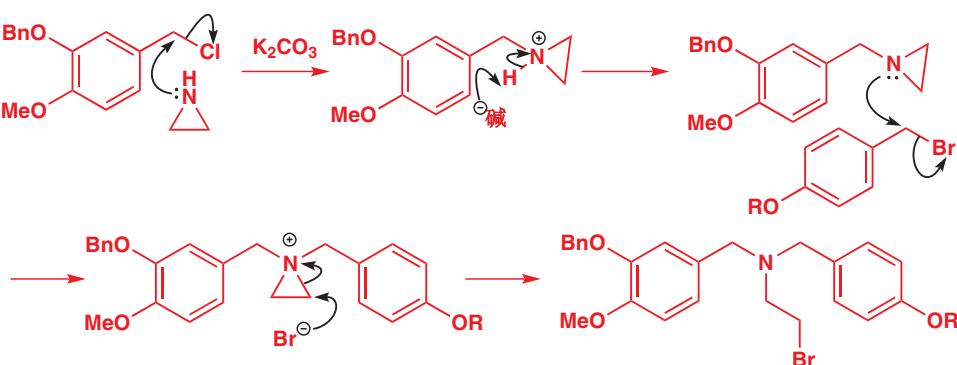


氮丙环的开环是一个制取更大的杂环的实用方法：任何会在氮上放正电荷的事物，都会通过质子化或如下所示的烷基化，将 N 转变为一个更好的离去基团，进而促进开环。氮丙环在碱性中的烷基化会如您所料地得到 N-取代的氮丙环，但再次烷基化，则会产生一个带正电的氮丙环𬭸盐（aziridinium salt），继而立即开环得到有用的溴代胺。

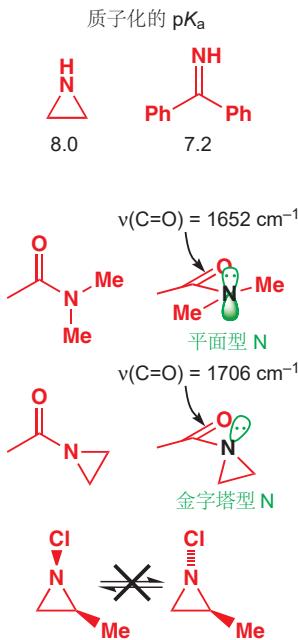
### 饱和杂环的系统命名法

氮丙环/吖丙啶 aziridine、氮丁环/吖丁啶 azetidine 的名称来源于一个逻辑合理的命名法体系，此体系通过下列规则得到一个由三部分组成的杂环名称：(a) 杂原子（“az-”=氮，“ox-”=氧，“thi-”=硫），(b) 环的大小（“-ir-”丙=3，来源于 tri；“-et-”丁=4，来源于 tetra；“-ol-”戊=5；6 没用代称；“-ep-”己=7，来源于 hepta；“-oc-”庚=8，来源于 octa；等），和 (c) 饱和度（“-ene”或“-ine”代表不饱和，“-idine”或“-ane”代表饱和）。由此可推知 az-ir-idine, az-et-idine, di-ox-ol-ane (二噁烷)，和 ox-ir-ane (环氧乙烷) 的名称。

■ 这个情形的产物是两种天然产物，sandaverine 和 corgoine 的合成的中间体。



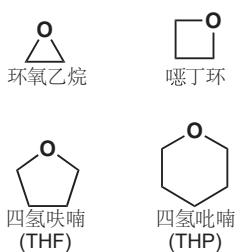
我们刚刚提及了氮丙环的质子化，您可能会联想到我们之前所谈论的，氮杂环和它们的非环状对应物的亲核性和碱性的对比，并由此想到氮丙环会比吡咯烷更具亲核性，而碱性大约相同。嗯，这是错的。将烷基“绑在后面”的思路只适用于无环张力的五元环和六元环：对于小环，则有另一种效应取而代之。



氮丙环的碱性事实上比吡咯烷和哌啶弱得多：质子化的  $pK_a$  只有 8.0。这与包含一个  $sp^2$  杂化的氮原子的化合物的  $pK_a$  接近——例如侧边中的亚胺。这是因为，由于三元环，氮的孤对电子处在比典型亚胺中 s 成分更高的轨道中。这是我们之前，在 Chapter 18 中就讨论过的效应，如果您需要刷新记忆，那么请重新阅读 pp. 412–415；在那里，我们将三元环与炔烃做了比较，并阐释了，它们都可以相对容易地被去质子；阴离子的负电荷处在一个 s 成分较高的较低能轨道：和此处，氮丙环的孤对电子处在较低能轨道一样。

氮丙环的氮的孤对电子的 s 成分还有另一种影响。该孤电子与相邻的羰基相互作用得非常差，因此 N-酰基氮丙环，例如您在 p. 973 见过的一个，表现得完全不像酰胺。氮原子是金字塔型而不是平面型， $C=O$  键的伸缩频率 ( $1706 \text{ cm}^{-1}$ ) 也与酮 ( $1710 \text{ cm}^{-1}$ ) 更加接近，而不接近酰胺 ( $1650 \text{ cm}^{-1}$ )。

孤对电子的 s 成分还意味着，氮原子的翻转非常缓慢，相当像一个磷。通常氮不可能作为一个立体中心，因为翻转发生得太快了——(其中孤对电子处在 p 轨道的) 氮翻转的过渡态能量较低。但对于氮丙环，将孤电子放入 p 轨道需要大得多的活化能，因而这种氮可以是具有立体化学的 (stereogenic)。侧边栏中的 N-取代氮丙环的两种立体异构体可以得到分离。



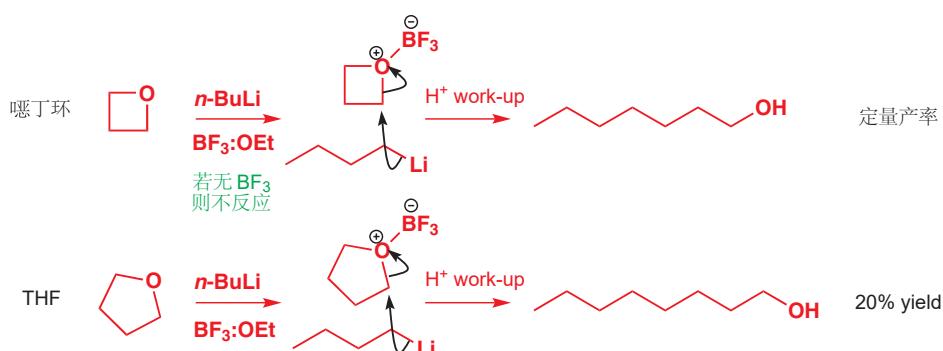
### 氧杂环

开环化学同样是氧杂环的特征，在此我们也无需再回顾有关环氧开环的内容。环氧尤其活泼，因为环张力的释放驱动了开环反应的发生。不过，通常，氧杂环，如环状醚，是相对不活泼的：醚是所有常见官能团中活性最低的一个。这也是 THF、二噁烷是重要溶剂的主要原因。第二个原因是，它们可以通过贡献孤对电子，稳定缺电子的金属阳离子（例如 Li）来溶解有机金属。环状醚是比非环状醚更好的给体（更亲核），与环状胺比非环状胺亲核性强的原因相同。

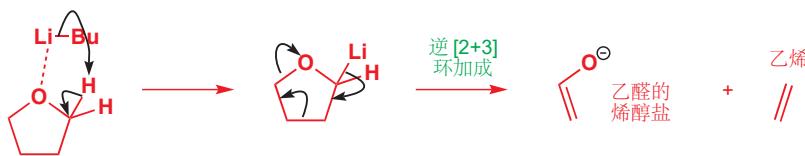
孤对电子与 Lewis 酸的相互作用，可以被利用来使醚更活泼。 $BF_3$  常被用于活化面对亲核进攻的环状醚；即使对于环氧，当用有机金属试剂做亲核试剂时，它也能提高速率和产率。 $n\text{-BuLi}$  在没有添加 Lewis 酸，如  $BF_3$  时，不会与噁丁环 (oxetane) 反应，这个反应会打开四元环，以定量的产率得到正庚醇。若无环张力帮助反应进行，以 THF 为对比，即使有 Lewis 酸，产率仍较低。

有关环氧在酸性和碱性环境下开环的内容已于 Chapter 19 中阐明。

■  $BF_3$  最容易以其与乙醚的络合物处理，写作  $BF_3\cdot OEt_2$  或  $BF_3\bullet OEt_2$ ，其中乙醚将其孤对电子贡献进硼的空 p 轨道。在相关的反应中， $HBr$ 、 $BBr_3$  或  $Me_3SiCl$  被用于活化苯酚的甲基和苯基醚面对亲核进攻。见 Chapters 15, p. 351 和 23, p. 551.



BuLi 和 THF 更常见 (然而却通常不想要) 的一个反应，并不是亲核进攻，而是去质子。您将会注意到，涉及 THF 中的 BuLi 的反应一贯在 0 °C 或更低的温度下进行——通常是 -78 °C. 这是因为，高于 0 °C 的温度，会使得 THF 的去质子化开始发生。被去质子了的 THF 是不稳定的，会经历一个我们称之为逆 [2 + 3] 环加成 (见 Chapter 34) 的反应分解。下面是其机理。产物是：(1) (碱性弱得多的) 乙醛的烯醇盐和 (2) 乙烯。前者倾向于聚合，后者通常 (其他情况见下面的文字框!) 从反应混合物中挥发出去。



### 出乎意料的乙基的情况

比利时的一些化学家曾在研究如下所示的有机金属的反应，以查明阴离子中心是否会进攻双键以形成一个五元环。这个反应是缓慢的，它们将有机锂在 THF 中，于 0 °C 下搅拌了 6 个小时。后处理后，他们没用发现五元环产物：而是得到了多一个乙基的化合物！它们发现，这个乙基事实上来源于 THF：有机锂并没有加成到自己分子中的双肩上，而是缓慢、低产率地加成了 THF 分解所得的乙烯上。



### THF 稳定型

THF 中的 *n*-BuLi (在 TMEDA 的存在下) 的半衰期在 20 °C 下是 40 分钟，0 °C 下是 5.5 小时，-20 °C 下是 2 天。乙醚中的 *n*-BuLi 的半衰期为 10 小时。有机锂的碱性越强，在 THF 中分解的速度就越快，*t*-BuLi 只能在 -78 °C 的 THF 中使用。在 -20 °C 下，*t*-BuLi 在 THF 中的半衰期仅为 45 分钟；同等温度的乙醚中，它的半衰期为 7.5 小时。

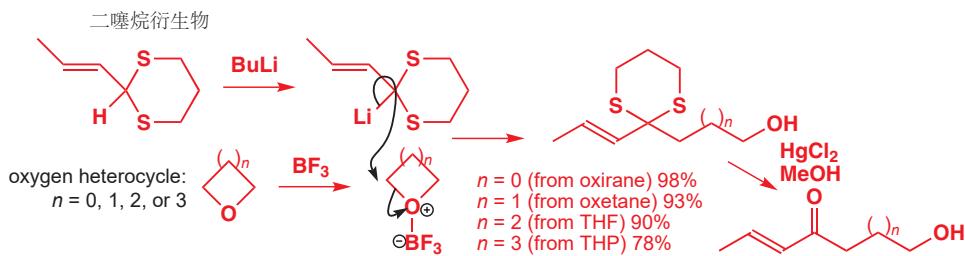
四氢吡喃衍生物最常见的用途，是被用作保护基：您在 Chapter 23 中遇到了这种情况。

### 硫杂环

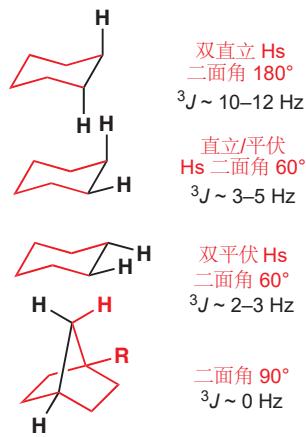
如您在 Chapter 27 中所了解，硫可稳定邻位的阴离子，这意味着，硫杂环比 THF 的去质子容易得多。其中最重要的一类，是包含两个硫原子的二噻烷 (dithiane)。二噻烷的去质子化发生在两个杂原子之间，您在 p. 661 已了解过一些由此产生的化学性质。下面的反应系列很好地说明了二噻烷化学，和氧杂环在  $\text{BF}_3$  存在下的开环反应。二噻烷衍生物被 BuLi 去质子，得到一个亲核性的有机锂，继而进攻亲电试剂——在  $\text{BF}_3$  存在下，甚至是氧杂环。即使亲电试剂是 THP，没用任何的环张力驱动反应发生，产物仍会以极好的产率形成。加成反应后，二噻烷环可以与 汞(II) 发生水解，以得到一个带有其他有用官能团的酮。



■ 二硫戊环 (Dithiolane), 二噻烷的五元环版本，不能用于这个反应，这是因为，虽然它很容易去质子，氮形成的阴离子会通过与 THF 相同的机理分解。

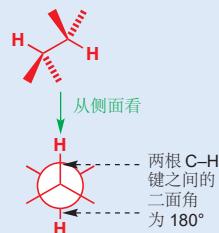


► 烯烃中的偶联已在 p. 293 描述；环己烷中的偶联在 p. 415。

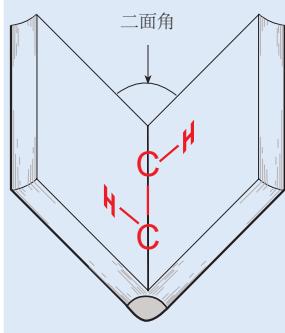


### 二面角

二面角在 Newman 投影式中十分清晰——二面角是两根 C–H 键投影在一个正交于 C–C 键的平面上所得的夹角。在 Newman 投影式中，纸面就是这个平面，此处该角为 180°。



另一种思考二面角的方式，是通过想象 C–C 键是一本部分打开的书的书脊。如果两根 C–H 键分别处在所翻开的这两页上，那么书页之间的角度就是二面角。



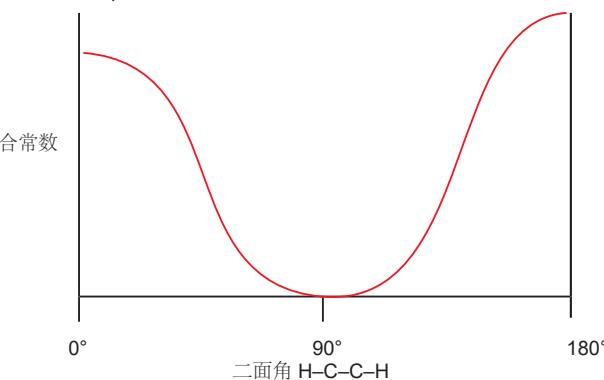
## 饱和杂环的构象

### 使用 NMR 研究构象：Karplus 关系

在 Chapters 13 和 18 中，我们阐释了 NMR 光谱中的偶合是沿键的（而不是沿空间的）效应——这也是为什么反式烯烃的偶合常数比顺式烯烃的大，也是为什么六元环中的 直立–直立偶合比 直立–平伏偶合 或 平伏–平伏 偶合大。现在我们需要针对您对于构象和偶合常数的关系的理解，建立更多细节，我们可以使用 NMR 来探测饱和环采取的构象。

环己烷中的偶合常数告诉我们，当涉及的 C–H 键平行得——换句话说就是当它们的二面角接近 180° 或 0° 时——最多时，偶合常数最大。简单环己烷中的 C–H 键只能有 60° 或 180° 的二面角，但通过对大量其他化合物中偶合常数的研究，我们可以绘制出偶合常数随二面角变化的规律。例如，在侧边的多环化合物中，黑色质子有一个接近 90° 的二面角，其偶合常数是 0 Hz。完整的对应关系是由 Karplus 在 1960s 研究得出的，被称为 Karplus 关系(relationship).  $J$  对二面角的图像的形式是最容易理解的。

Karplus 关系:  $J$ -二面角



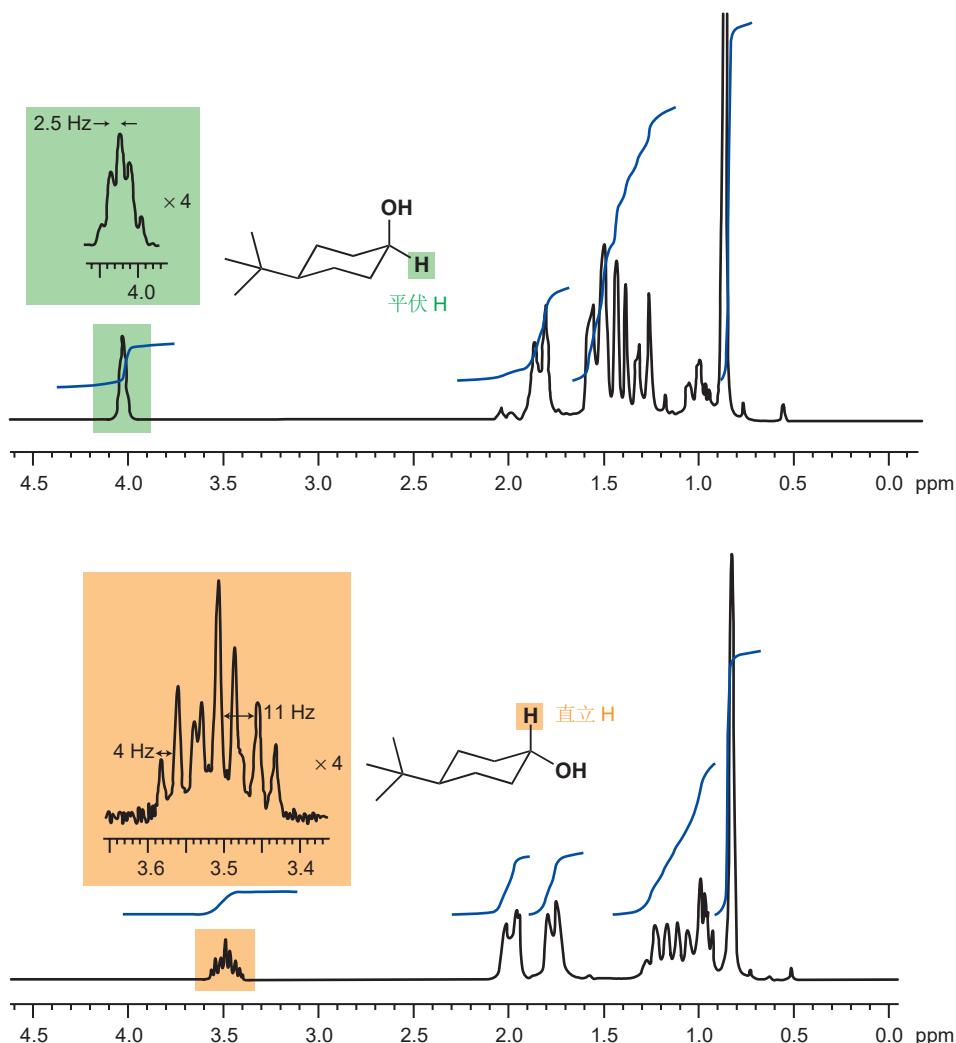
仔细审视上方的图表，并注意以下原则特征：

- 偶合的最大值出现于 180° 时，此时两根 C–H 键的轨道是完美地平行的（反式烯烃，或环己烷中反式双直立 C–H 键出现了这种情况）。
- 偶合在 0° 时几乎也一样大，此时两条轨道在同一平面但不平行（顺式烯烃的情况）。
- 当二面角是 90° 时，偶合为零——两条正交的轨道不会相互作用。
- 曲线在 0°, 90°, 和 180° 周围变平——这些区域中的化合物的  $J$  变化很小。
- 曲线在大约 60° 和 120° 处急剧倾斜——这些区域中的化合物，很小的角度变化都会引起较大的  $J$  变化。
- $J$  的数值会随着取代，环的大小等因素变化，但 Karplus 关系仍然可用——它可用提供相对数值。

NMR 可以确定构象，同时，它也可能确定构型。这通常发生于两个或更多的取代基处在环上时。下面是一个简单的例子：您在 Chapter 16 中已了解了 4-叔丁基环己酮的还原，可以通过对试剂的选择，控制生成顺式或反式的醇。



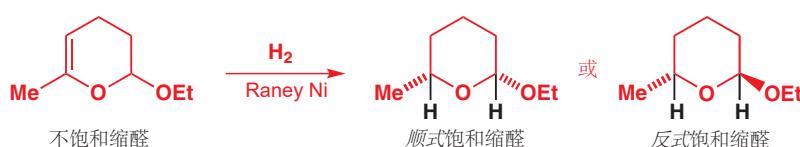
产物很容易区分，因为两种情况中，被标出的 H 在 NMR 光谱中出现的方式很不一样。其中一个以好的多重峰出现，而另一个则宽得多。



庞大的叔丁基往往处在平伏键，每个 OH 基都有两个完全相同的直立邻居和两个完全相同的平伏邻居（其中的一组已在 p. 796 底部的图表中示出——位点前方还有一组）。每个被标出的 H 都以三重峰的三重峰出现。在顺式醇中，两种偶合都很小（2.72 和 3.00 Hz），但在反式醇中，直立—直立偶合（11.1 Hz）比直立—平伏偶合（4.3 Hz）大得多。

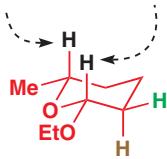
相同的思路可被用于研究饱和杂环体系的构象。对下面的不饱和缩醛氢化，会以单一异构体得到饱和化合物。但是是哪一个呢？两个取代基，Me 和 OEt，是顺式还是反式呢？

从这个观察中，您可以得出一个普遍性结论：NMR 信号的宽度大致等于它所有偶合的总和。在任何给定的化合物中，直立质子都会比平伏质子具有宽得多的信号。



两个黑色氢在 NMR 光谱上出现的方式揭示了答案，同样也显示了分子采取的构象。在 3.95 ppm 处（因而是与氧相连的氢）有一个 1H 信号，而且是双重四重峰。由于是四重峰，该氢必定是与

$\delta_{\text{H}} 3.95, 1\text{H}, \text{dq}$ ,  $J 9$  和  $6.5 \text{ Hz}$        $\delta_{\text{H}} 4.40, 1\text{H}, \text{dd}$ ,  $J 9$  和  $2 \text{ Hz}$



甲基相连的氢。四重峰的偶合常数  $J$  值是“正常的”  $6.5 \text{ Hz}$ . 二重峰偶合是  $9 \text{ Hz}$ , 若非直立-直立偶联, 这个值都太大了, 因此该氢是直立的。

在  $4.40 \text{ ppm}$  处(与两个氧相连)有另一个  $1\text{H}$  信号, 是一个二重二重峰信号,  $J = 9$  和  $2 \text{ Hz}$ . 它表现出一个 直立-直立 ( $9 \text{ Hz}$ ) 和一个 直立-平伏偶合, 这必定也是一个直立质子。我们现在知道了分子的构象。

两个黑色氢都是直立的, 因此两个取代基都是平伏的。这也意味着, 在此情况中, 它们是顺式的。但请注意, 这是因为它们在环的同一面, 即上面, 而不是因为它们都是平伏的! 在前方的质子有两个邻居——一个直立(棕色)  $\text{H}$ ,  $J = 9$ , 和一个平伏(绿色)  $\text{H}$ ,  $J = 2 \text{ Hz}$ . 所有这些都恰合 Karplus 关系所料。您可能注意到, 后面的  $\text{H}$  失去了于其平伏邻居的小偶合。毫无疑问, 它确实偶合了, 但在双重四重峰的八条线中, 小偶合的信号无法被注意到。小偶合很容易被忽视。

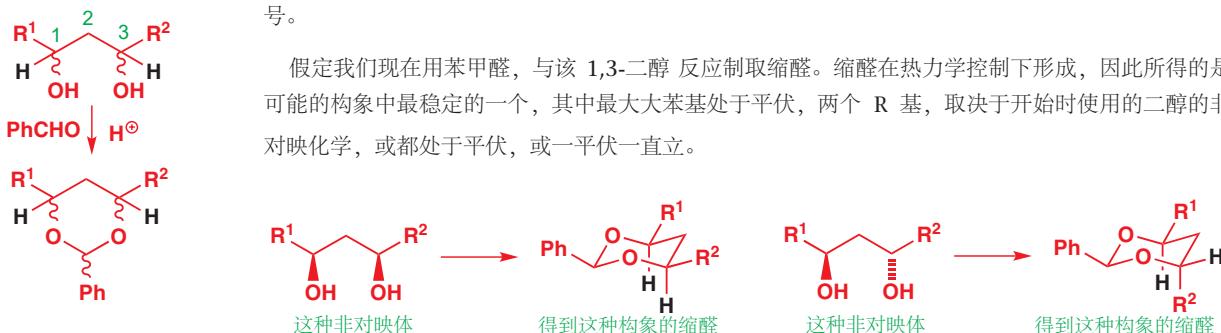


■ 此处  $\text{OEt}$  基由(通常有利的)平伏转变为直立的过程看起来可能奇怪, 我们将在下一节阐述。

当这种化合物被置于微酸性的乙醇中时, 它会转变为另一种异构体。反式化合物的 NMR 光谱同样非常有用。与甲基相连的质子几乎与前面相同, 但两个氧原子之间的质子则很不同。它位于  $5.29 \text{ ppm}$  处, 是一个宽度大约为  $5 \text{ Hz}$  的未被解决(unresolved)的信号。换句话说, 它没有较大的偶合, 因而必定是平伏质子。反式化合物的构象如侧边所示。

由于六元环中的偶合常数定义完善, 它可被用于确定所形成的杂环的立体化学。假设您有一个 1,3-二醇的非对映体, 并想要知道它是哪种。您可能会想要使用两种黑色质子的 NMR 偶合常数。但这样并不好, 因为该分子没有固定的构象。所有  $\sigma$  键的自由旋转, 意味着 Karplus 等式(equation)无法使用, 无论质子的立体化学如何, 所观察到的很有可能都是一个在大约  $6\text{--}7 \text{ Hz}$  处的时间平均信号。

假定我们现在用苯甲醛, 与该 1,3-二醇 反应制取缩醛。缩醛在热力学控制下形成, 因此所得的是可能的构象中最稳定的一个, 其中最大大苯基处于平伏, 两个  $\text{R}$  基, 取决于开始时使用的二醇的非对映化学, 或都处于平伏, 或一平伏一直立。

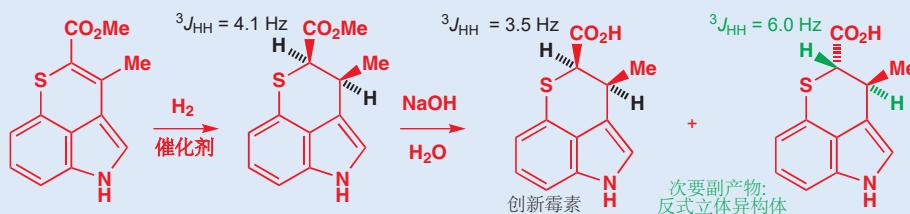
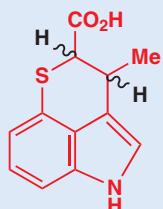


现在分子便有了固定的构象, 黑色  $\text{Hs}$  对相邻的  $\text{CH}_2$  基的偶合常数可以被确定——直立  $\text{H}$  会表现出一个大的  $J$  值, 平伏  $\text{H}$  只会表现出小的  $J$  值。

### 推断一种新抗生素的立体化学

只有完全饱和的六元环会是真正的椅式或船式。即使环中只有一根双键, 环也会部分地平面化: 此处, 我们会着眼于一个较平的例子。这是一种由中国研究者发现的独特抗生素, 被称作“创新霉素(chuangxinmycin)”(意思是“一种新的抗生素”, 其中“霉素 mycin”= 抗生素)。它的独特性在于, 它是一个含硫吲哚: 很少有天然产物包含这种结构, 并且没有其他的抗生素包含这种结构。

结构本身很容易阐明, 但两个黑色氢的立体化学并不十分明显。偶合常数( $^3J$ )是  $3.5 \text{ Hz}$ . 试图合成该化合物时, Kozikowski 将下面的烯烃酯氢化, 得到一个毋庸置疑的顺式产物 (氢化是顺式选择性的: 见 Chapter 23, p. 535).

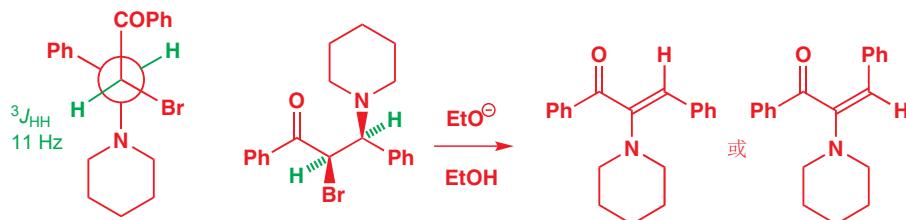


黑色氢的 $^3J$ 偶合是4.1 Hz, 与抗生素很像, 在碱的水溶液中将酯基水解, 主产物与天然的创新霉素完全相同。然而, 还存在次要产物, 即反式异构体,  $^3J = 6.0$  Hz。注意观察这个值比饱和六元环中的直立-直立偶合的10 Hz以上要小得多。环的平面化会减少二面角, 进而减小 $J$ 的大小。

偶合常数并不总能提供关于立体化学无歧义的信息, 下一节中, 我们将着眼于另一种技术, 可以不依赖于偶合地从NMR光谱中提取结构信息。

### 在偶合常数不起作用时确定立体化学: 核的欧沃豪斯效应

下面的化合物中绿色质子的偶合常数相当大, 位于11 Hz处——与环己烷中反式双直立偶合相当。Karplus关系会指出, 绿色质子和它们的键, 在大部分时间, 必定接近180°二面角排列, 由此我们可以推断出该化合物的构象, 及构型。而更困难的, 是确定由这个溴代胺与碱反应得到的消除产物的立体化学中的排列方式。这不是一个简单的问题, 因为消除还包含胺基的重排。产物是一个有两种可能的几何结构的烯烃。



通常, 我们会使用偶合常数确定烯烃的立体化学, 但在此处, 由于烯烃上只有一个质子, 这旧行不通了: 两种化合物都只会有一个单峰。这样的情形下, 我们可以利用NMR的一个奇异性质, 被称作核的欧沃豪斯效应(nuclear Overhauser effect, NOE)。NOE与偶合在所提供的信息上相当不同: NOE告诉我们哪些氢在空间上接近, 并不是如偶合常数揭示的, 在沿键关系上接近。

关于核的欧沃豪斯效应的缘起的细节超出了本书的范围, 但我们可以为您提供该效应的一个一般性思路。如您在Chapters 3和13中所了解的, 取得质子NMR光谱的时候, 射频电磁辐射的脉冲将质子的自旋振动到一个更高的能量状态。我们观察到的信号便是这些自旋跌落回它们的原始状态时所生成的。到目前为止, 我们一直假设, 跌落的过程是自发的, 如同悬崖上的石头会自发掉下来一样。但事实上并不是这样——有时需要“帮助”质子跌落回去——这个过程被称为弛豫(relaxation)。帮助其跌落的“某个事物”就是其他附近的磁活性核——通常是更多的质子。注意, 是相邻的——在空间上相邻, 而非沿键接近。对于质子, 弛豫往往很快, 附近质子的数目并不会对NMR光谱的外观产生影响。

虽然在正常的谱图中, 峰的强度是独立于附近的质子数目的, 但通过使用其描述超出本书讨论范围的方法, 根据附近的质子数目, 非常轻微地修改峰的强度是可能的。该方法的基础是特定的质子(或完全相同的质子的组)被选择性地照射(换句话说, 它们精确地被恰当的频率的辐射脉冲——而非正常NMR实验中所需的宽脉冲——振动到高能状态, 并保持在那里)。在实验条件下, 这使得原本依赖被照射的质子弛豫它们的质子, 在NMR光谱中以稍强的峰强度出现(可能只是百分之几)。这个效应被称作核的欧沃豪斯效应, 峰强度的增加是核的欧沃豪斯增强/因子(nuclear Overhauser enhancement)。二者都缩写为“NOE”。

► 关于如何使用偶合常数的大小确定烯烃几何结构的详细内容, 请见p. 293.

### 为什么您不能积分<sup>13</sup>C NMR光谱

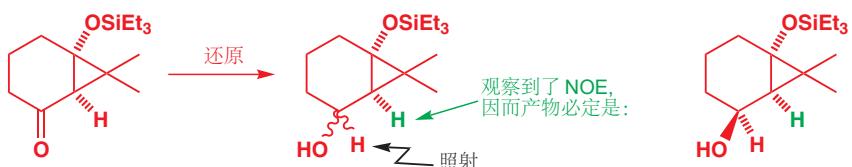
弛豫是您不能积分<sup>13</sup>C光谱的真实原因。<sup>13</sup>C的弛豫是缓慢的, 但在附近有很多质子的时候是很快的。这就是您经常会发现——CH<sub>3</sub>基在<sup>13</sup>C NMR光谱中表现出强信号, 而未连有质子的季碳, 则会表现出弱峰——的原因: 季碳只会缓慢地弛豫, 因此我们没用检测到强峰。让所有<sup>13</sup>C原子在脉冲之间有大量的时间弛豫, 可以得到更按比例的峰强度, 但代价是非常长的NMR采集时间。

在此阶段，您只需要意识到，NOE 实验中被照射的质子会引起在空间上与之邻近的其他质子峰强度的增强——无需偶合，并且 NOE 也不是一个沿键现相。这种效应随距离变长而迅速衰减：增强的程度正比于  $1/r^6$  (其中  $r$  是质子间的距离)，将两个质子移动到原来两倍远的距离的地方，一个质子对另一个质子的增强会减小到 64 分之一。NOE 光谱通常表现为差距：增强的光谱减去未增强的光谱，因此特定质子峰强度的小增强会立即被发现。

将 NOE 应用到刚刚的问题上，可以解决结构问题。照射哌啶环中与氮原子相邻的质子，发现烯烃质子的信号会在强度上有所增加，这说明这两组质子必定在空间上邻近。化合物是 *E* 烯烃。

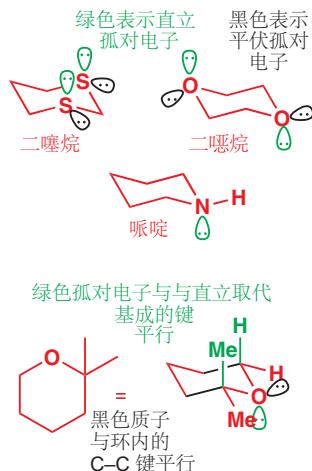


NOE 实验中的数据，在三维立体化学的确定上，很好地补充了从偶合常数得出的信息。用大位阻氢化物还原剂，还原下面的双环酮，会得到醇的一种非对映体，它是哪个呢？照射与 OH 相邻的质子，会导致绿色质子出现 NOE。这表明，两个质子在分子的同一侧，还原反应通过将氢负传递到酮的，与三元环中两个甲基相对的一面，发生。



偶合常数与 NOE 效应的结合经常被用于确定反应产物的立体化学。

### 环中的杂原子有直立和平伏的孤对电子



作为我们的首个近似，五元和六元杂环的构象遵循的规则，非常像我们在 Chapter 16 详细考察过的碳环化合物的构象。对于二𫫇烷，构象如侧边所示。由于硫原子韩愈孤对电子，它们也会占据直立和平伏位置。二𫫇烷和哌啶同样如此。

我们已将孤对电子，根据它是直立还是平伏，涂为绿色和黑色，您也可以考虑其他的涂色方式：例如将与在环中的 C–C 或 C–杂原子 键平行的孤对电子图为黑色，将与在环外的直立 C–H 键平行的质子涂为绿色，如果环带有取代基，这也相当于将与取代基成的键平行的质子涂为绿色。下面的取代的四氢吡喃可以说明这一点。注意观察，与杂原子相邻的平伏取代基既不与绿色孤对电子平行，又不与黑色孤对电子平行。

为什么这是重要的？有很多孤对电子在其中扮演角色的反应。例如，缩醛的水解，相邻的孤对电子对所形成的正电荷的稳定化作用会促进机理的消除步骤。让我们考虑，当缩醛是一个饱和杂环时，缩醛水解中发生的变化。由 Chapter 11，您会想到，此过程机理如下：



然而，当我们试图画出孤对电子的构象时，我们会遇到一个问题：它们都不与要断裂的 C–O 键重叠，因而它们也都不能向 C–O  $\sigma^*$  内贡献电子密度。另一种看待这个问题的方式，是说中间体锌离子——若要通过其中一对孤对电子成 C=O 双键——会极其扭曲。因而并不令人奇怪的是，这个缩醛的水解速率，相比于相似的，但氧的孤对电子与 C–O  $\sigma^*$  之间的重叠却是可行的缩醛的水解速率，要慢得多。右侧的缩醛比左侧的，水解速率快大约  $10^{10}$  倍。



您刚刚已看到了，轨道间的重叠控制着 NMR 偶合常数；轨道重叠重要的其他情形还有：

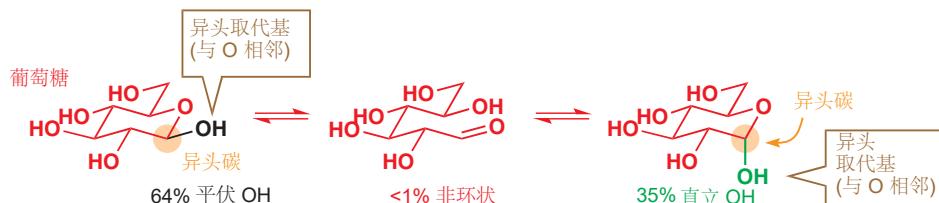
- E2 消除反应 (Chapter 17)
- 环状分子的反应 (Chapter 32)
- Felkin–Anh 过渡态构象 (Chapter 33)
- 碎片化和重排 (Chapter 36).

放在一起，这些因素，因为它们取决于轨道的取向，因而被称作立体电子效应。

### 一些饱和杂环的取代基倾向于处于直立：异头效应/端基异构效应

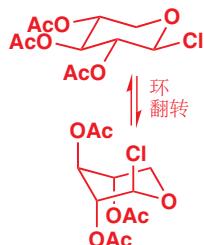
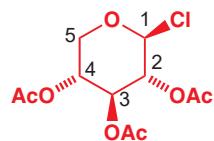
上述列表中，很多立体电子效应控制的都是反应性，但在本节中，我们将会处理立体电子效应影响结构——尤其是构象的方式。最重要的饱和氧杂环中，有一些是糖。葡萄糖是一种环状半缩醛——一个五取代的四氢吡喃——它在溶液中的主要构象如下所示。溶液中，有三分之二的葡萄糖以这个立体异构体存在，但半缩醛的形成和断裂是迅速的，它同时也进一步与占比三分之一的，羟基处在直立键的半缩醛平衡(开链形式占比<1%)。

我们在 Chapter 6, p. 137 介绍了葡萄糖的半缩醛结构。



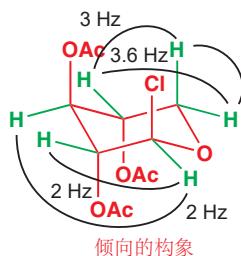
读过 Chapter 16 后，您不会对葡萄糖倾向于使其全部取代基处于平伏感到惊讶。对于其中四个，当然，别无选择：它们要不就全直立，要不就全平伏，这二者只需要通过环翻转即可转换。但对于第五个取代基，与环的氧相邻的羟基（被称作异头 anomeric 羟基），就可以通过半缩醛的断裂与重新形成使其能在直立和平伏间选择——即能够逆转它的构型。也许令人惊讶的是，这个羟基对于平伏的偏向性是如此小——只有 2:1. 更令人惊讶的是，对于大多数葡萄糖的衍生物，异头取代基倾向于处在直立而非平伏。





抛开葡萄糖，这个效应在其他取代的四氢吡喃中也同样有容身之地。下面的表格是侧边中的氯代化合物的 NMR 信号。这次只有两种可能的构象（由于它不是半缩醛，因而不可能有构型变化）——都已展示出来——由 NMR 光谱，您应当能推断出这个化合物究竟是哪种。

$\delta$	$J, \text{Hz}$		
5.78	1H	t	2.0
5.03	2H	m	H2, H3
4.86	1H	m	H4
4.37	1H	dd	12.9, 3.0
3.75	1H	ddd	12.9, 3.7, 0.6
2.10	9H	s	OAc $\times 3$



关键点是，即使邻位有负电性原子（倾向于减小偶合常数），直立-直立 偶合仍很大（如  $>8 \text{ Hz}$ ）。因此如果 H1 是一个直立质子，您会料到，它在 H2 处会有一个较大的偶合。但事实上没用——它与 H2 偶合的  $J$  仅为  $2.0 \text{ Hz}$ 。（另一个偶合是与 H3 的 W-偶合，同样是  $2.0 \text{ Hz}$ ：见 p. 296。）相似地，我们知道两个 H5 质子分享的  $12.9 \text{ Hz}$  偶合，必定是一个偕偶 ( $\beta J$ )。H5a、H5b 中的一个必定为直立，但与 H4 的两个偶合， $J$  都  $< 4 \text{ Hz}$ ，因此 H4 不能是直立的。由此证据，我们不得不得出结论，H1 和 H4 是（因而 H2 和 H3 也是）平伏的，因此该化合物必定主要以全直立构象存在。（与 H5b 的  $0.6 \text{ Hz}$  偶合也是一个 W-偶合，并且说明 H5b 是平伏质子，H5a 因而是直立质子。）这种对直立的倾向性被称作异头效应/端基异构效应 (anomeric effect)。

### ● 异头效应

一般来说，任何在 2 号位带有负电性取代基的四氢吡喃，都会倾向于使该取代基处于直立。这被称作异头效应。

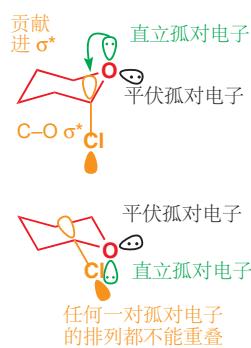


但这是为什么？这违反了我们在 Chapter 16 中所说的，关于直立取代基空阻更大，带有直立取代基的构象是不利的结论。关键同样在于立体电子效应，我们现在可以结合上一节末时，我们留给您的信息：消除反应仅在所涉及的两个轨道平行时才可发生。

酰胺比酮更稳定（更不活泼），是因为 N 的 p 轨道与羰基低能的 C=O  $\pi^*$  可以处于平行——它们可以重叠，电子密度可以由氮移动进 C=O 键，并弱化 C=O。（证据来源于酰胺 C=O 在其他事物中，IR 伸缩频率较低。）C-X 键也有低能的反键轨道——C-X  $\sigma^*$ ——因此我们会希望一个能类似地被邻位杂原子贡献电子进入其轨道而被稳定化的分子。以上方文字框中普遍化的四氢吡喃为例，比如 X=Cl 时。如侧边所示，当有一个氧孤对电子能与 C-Cl  $\sigma^*$  平行时，分子最稳定。

但只有氯处在直立时，才能这么办！还记得我们在前文曾指出：氧的平伏孤对电子只会与环中的键平行，因此唯一能帮助分子稳定化的，只有氧的直立孤对电子，这也要求 Cl 处在直立。只有直立构象从这种稳定化因素中受益，这便是异头效应的缘起。

我们如何表达这种稳定化？再次与酰胺的稳定化对比，您可能会想到，用弯曲箭头来表示它：对

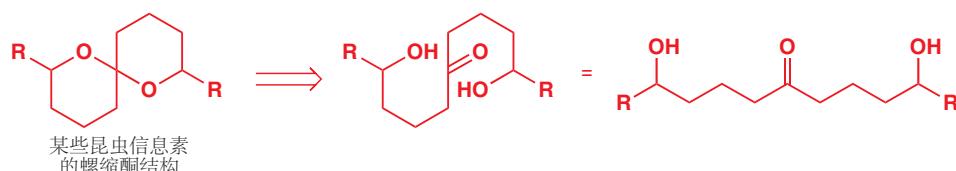


于酰胺来说，这很简单，因为您已经多次见过了。但对于杂环，这看起来有点奇怪：电子密度由 O 移至 Cl, C–Cl 键被弱化。如果这个过程继续进行，Cl<sup>-</sup> 就会离去。这也是我们在 p. 801 给您举出的缩醛所发生的事：只有直立 OAr 可以离去，因为该过程的要求与此处与氧孤对电子重叠的要求是相同的。我们现在考察的化合物的真实结构中，Cl 仍在那里：C–Cl 键是较弱的，并且还有一些离域到 Cl 上的氧的电子密度。这可以从晶体结构中看出：显出异头效应的晶体化合物在环外的键更长（因而被弱化），在环内的 C–O 键更短、更强。

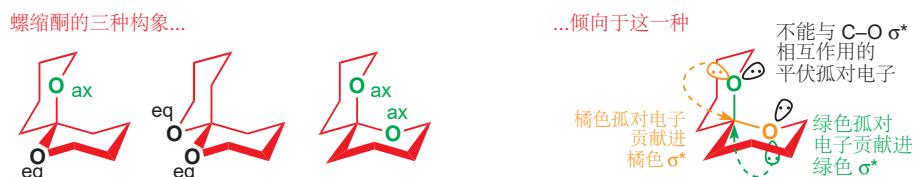


### 螺缩酮中的异头效应

现在既然您已了解了异头效应，您就应当将其列入您头脑中解释“意外”结果的可行方法的序列中。下面是一个例子。很多果蝇都拥有基于“螺缩酮（spiroketal）”结构的信息素，如下方我们忽略了立体化学的表达。您可以想象出，螺缩酮（即，由两个连接到单一原子上的环组成的，一种酮的缩醛）可由二羟基酮制得——并且，确实，这也是螺缩酮的合成非常常用的方法。但这是一个很差的表达，因为这些化合物是含有立体化学的，它们的立体化学还非常有趣。



让我们由最简单的例子开始，R=H 时（油橄榄实蝇的一种信息素）。一旦您将其中一个环画作它的椅式构象，另一个环的附着就会存在三种方式，如下所示。如果您认为它们看起来是相同的，那么请考虑每个 C–O 键的取向，即它相对于它不属于的环的取向：您可以使每个 C–O 处于直立或平伏，因而就有三种可能的排列方式（三种构象）了。



即使缩醛中心并不是一个手性中心，这也是一个手性化合物：没有含对称面的构象。

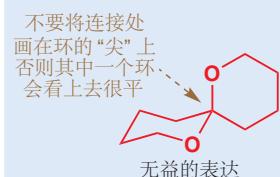
若不了解异头效应，您将很难预测哪种构象是有利的，并且，确实，您会认为得到的是全部三种的混合物。但 NMR 告诉我们，这种化合物完全以其中一种构象存在：最后一种构象，其中每个氧原子都在另一个环上处于直立。只有在这个构象中，两根 C–O 键才能都受益于异头效应——这常被称为双异头效应（double anomeric effect）。

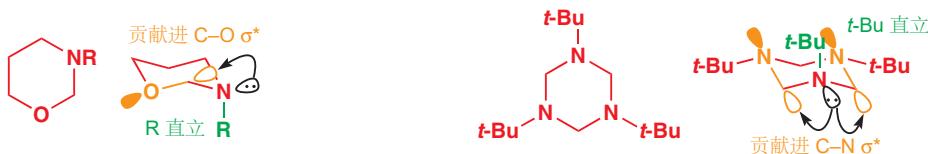
### 其他类型的化合物中的相关效应

异头效应的关键要求，是有一个带有孤对电子的杂原子（通常是 O, N, S）邻位于（处在能与之相互作用的位置上）一根低能的反键轨道——通常是一根 C–X σ\*（其中 X=卤素或 O）。C–X 键不必位于环中——例如下一页左侧的氮杂环，倾向于使其 R 基直立，这样氮就会得到一对处于平伏的孤电子。平伏孤对电子与环内的键，C–O 平行，因而这个构象是被一个 N 孤对电子/C–O σ\* 相互作用所稳定的。

### 关于螺缩酮绘制的提示

如果您试图画这些螺环缩醛，您很快就会发现，有一个能让它们看起来很好的技巧：螺碳原子不得不处在任何一个环的四个“端点”处，否则画完之后，其中一个环看上去就会像平面型的。





使右侧的 1,3,5-三嗪 含有三个处于直立的叔丁基，或许会有点困难（空阻太大），但它可以只使其中一个处于直立，这样也能从所得的可以与环中的两根 C=N  $\sigma^*$ s 重叠的平伏孤对电子中受益。

不仅在六元环中，填充与未填充的轨道间的立体电子效应相互作用，会使某些构象比其他的更为稳定。立体电子效应控制着很多类型的分子的构象。

- 任何包含与一个低能反键轨道反叠的孤对电子的构象，都会被立体电子效应稳定化。

我们会着眼于三种常见的，被立体电子效应所稳定的化合物：两个情形中，稳定化都专一于一种构象，我们可以用立体电子效应解释除此之外会成为意外的结果。



我们开始于一个非常简单的化合物，它简单到只有一种构象，因为它没有可旋转的键，它就是二氯甲烷。您可能会疑惑，为什么选择它，氯甲烷是一种活泼的亲电试剂，很容易参与取代反应中，但二氯甲烷却十分不活泼，可以被用作其他卤代烷发生取代反应的溶剂。您可能认为这是立体效应：确实，Cl 比 H 大。但  $\text{CH}_2\text{Cl}_2$  作为亲电试剂的活性，是要比氯乙烷和氯丙烷低得多的：因而必定有其他因素影响它的反应性。每个氯的一堆孤电子往往与另一根 C-Cl 键处于反叠式，这样就常常会有来源于这个效应的稳定化作用。

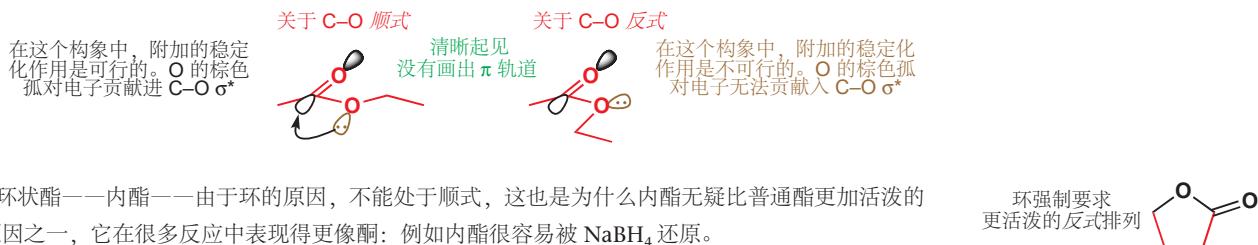
在显示出立体电子效应对构象的控制的非环状化合物中，分布最广泛的是缩醛。以甲醛和乙醇形成的简单缩醛为例：它的构象是什么？明显的建议是画出完全伸展的构象，每个基团都与另一个处在完全反叠式——这会是戊烷最低能的构象，但仅仅用 Os 替代  $\text{CH}_2\text{s}$  后，您会得到什么呢。

麻烦在于，在这个构象中，没有一对氧的孤电子有机会贡献进 C=O  $\sigma^*$  轨道。虽然将键从反叠式换成其他的，会在立体上产生影响，但从电子角度，分子更倾向于将其孤对电子放置得于 C=O 键反叠，因此键本身会彼此处于旁式（顺错式）。这被称作旁式效应/邻位交叉效应 (gauche effect)，但实际上，这只是导致异头效应出现于非环状体系中的立体电子效应的另一种方式。

最后，是一个您可能从没思考过，但却非常熟悉的例子。您现在已经很清楚，酰胺是平面型的，带有 C-N 半双键，叔酰胺有一个与氧顺式，一个与氧反式的烷基。那么酯会是怎么样呢？因为氧 p 轨道有电子贡献进羰基的  $\pi^*$ ，酯没有酰氯活泼，因此我们会认为它们也是平面型的，它们是这样。但对于一种酯，有两种可能的平面型构象：一种是 R 与氧顺式的，一种是 R 与氧反式的。倾向于哪种呢？



下面所画的是乙酸乙酯的两种构象。当乙基 ( $= R$ ) 与 O 处于顺式时, 不仅氧的一对孤电子可以与  $C=O \pi^*$  相互作用, 另一对孤电子也能贡献进  $C=O$  键的  $\sigma^*$  中。当 Et 和 O 处于反式时, 这都不可能了: 它们不再是反叠式的。酯基一般倾向于处于顺式构象, 即使在甲酸酯中, 烷基要处于一个很明显空阻较大的取向时也是如此。

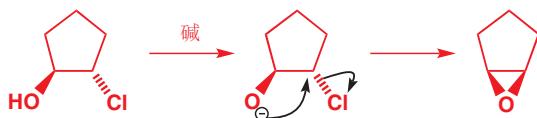


环状酯——内酯——由于环的原因, 不能处于顺式, 这也是为什么内酯无疑比普通酯更加活泼的原因之一, 它在很多反应中表现得更像酮: 例如内酯很容易被  $\text{NaBH}_4$  还原。

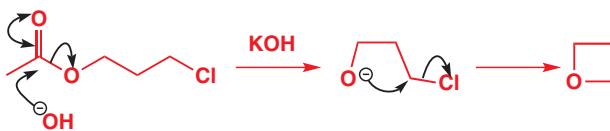
## 杂环的制取: 关环反应

我们已经讨论了饱和杂环的结构, 尤其是关于立体电子效应对构象对构象的控制, 在此之前, 我们还考察了一些它们的反应。现在, 我们将着眼于如何制取它们。迄今为止, 制取它们最重要的方法是使用关环反应 (ring-closing reactions), 因为我们经常可以在分子内取代反应或加成反应中, 用杂原子作为亲核试剂。当然, 关环反应是本章前文所述的开环反应的对立面, 我们可以由一个在两个方向都能很好地工作的反应开始: 关环形成环氧。您很清楚, 环氧可以由烯烃和  $m\text{-CPBA}$  形成, 但您也见过一些由分子内取代反应形成它们的例子, 如是。

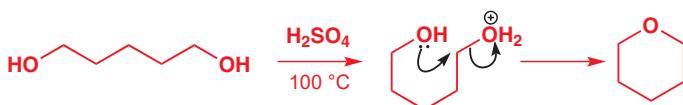
→  $m\text{-CPBA}$  环氧化反应已在 Chapter 19, p. 429 中讨论。



相同的方法也可被用于生成更大的环醚。例如噁丁环, 可以方便地由热氢氧化钾对乙酸 3-氯代丙酯的加成制得。这个反应的第一步是酯的水解。产生的烷氧基阴离子会经历一个分子内取代反应, 产出噁丁环。



早在 1890 年, 人们就已通过 1,5-戊二醇和硫酸的混合物, 在加热时发生的关环反应制备四氢吡喃了。



这些都是  $S_N2$  反应, 因此氮杂环可以以相同的方式被制备, 也不会令您惊讶。例如氮丙环本身在 1888 年的首次制备, 就是用 2-氯代乙胺完成的。相关的反应可被用于形成三、五, 和六元氮杂环, 但不能用于四元环的形成。事实上, 四元环一般是最难形成的。



为说明这一点，下表中绿色的一栏显示了由各种链长的溴代胺环化得到饱和氮杂环，包括三道七元环的相对速率（六元环形成 = 1）。

Reaction scheme showing the ring closure of a primary amine ( $\text{H}_2\ddot{\text{N}}-\text{Br}$ ) to form a saturated nitrogen heterocycle ( $\text{HN}_n$ ), catalyzed by base.

环的大小	产物	相对速率 <sup>a</sup>	速率评价
3		0.07	适中
4		0.0001	慢
5		100	非常快
6		1	快
7		0.002	慢
8		0.00015	非常慢

相对速率<sup>a</sup>相对于六元环形成反应；<sup>b</sup>E = CO<sub>2</sub>Et

乍一看，这些速率似乎是由随机数生成器产生的！似乎没有任何韵律、原因可言，也没有一致的趋势。为了让您相信这些数据是有意义的，我们还在黄色一栏给出了由取代的缩苹果酸酯发生分子内烷基化反应得到四到七元碳环的相对速率。虽然在两个情形中，数字很不一样，但起伏的次序是同样的；最后的一栏总结了相对速率。话句话说，如下是对环形成反应速率的大致指导（只是大致的——并非放之四海而皆准）。

### ● 饱和杂环形成反应的大致速率顺序

最快 5 > 6 > 3 > 7 > 4 > 8-10 最慢

■ 请回顾我们对于“小 (small)”，“正常 (normal)”，“中等 (medium)，和“大 (large)”环的定义，以及环张力 (ring strain) 的意思。您可以重新阅读 p. 366. 马上我们就会处理大环中发生的事情。

我们给部分数字涂了色，这是为了突显一个事实：这些看似没有逻辑的数字顺序，实际上隐含着两个相互叠加的趋势。由“正常”的环的大小 (5 和 6)，到“中等”的环的大小 (8 到 13)，形成反应的速率持续地下降。“小”(3 和 4) 环嵌入到了 6 之后的序列中。

导致这两个相互叠加的趋势的原因，是两个相反的因素。首先，小环形成缓慢，是因为它们的形成引入了环张力。环张力，即使在过渡态中也是存在的，这提高了其能量，并减缓反应的发生。三

元环形成反应的活化能非常高，这是环张力导致的，因而它还会随着环变大而减少。这解释了为什么三元和四元环不能直截了当地适配进序列中。

但如果反应仅仅取决于产物的张力，那么三元环的形成反应会是最慢的，而（基本上无张力的）六元环则会形成得最快。但是数据显示，四元环形成得比三元环慢，五元环又比六元环快。为了解释这一点，我们需要带您回顾一个我们在 Chapter 12 中给出过的方程

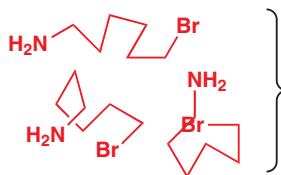
$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

反应的活化能垒  $\Delta G^\ddagger$  由两部分组成：活化焓  $\Delta H^\ddagger$ ，它告诉我们克服环张力，以及它们通常含有的排斥力，将原子组合在一起所需的能量；和活化熵  $\Delta S^\ddagger$ ，它告诉我们由扭来扭曲、随机旋转着的分子形成有序的过渡态的难易程度。

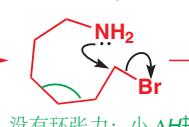
三、四元环形成反应的  $\Delta G^\ddagger$  大，是由于  $\Delta H^\ddagger$  大：将分子扭曲为有环张力的小环构象需要能量。五、六、和七元环的  $\Delta H^\ddagger$  较小：活化焓是我们刚刚引入的“环张力”因素的量化表达。第二个因素是一个取决于  $\Delta S^\ddagger$  的因素：要想使分子发生反应，需要强迫到什么程度才可使其有序。这样思考：长链的无序情况有很多种，要想让它的两端相遇并反应，则需要它不得不放弃很多自由。因此，对于中等和大环的形成反应， $\Delta S^\ddagger$  较大，且为负数，进而贡献了大的  $\Delta G^\ddagger$  并减缓了反应。另一方面，对于三元环，反应原子已经非常接近，几乎无需被强迫，即可发生环化：唯一需要的是绕着仅一根键旋转，以确保，如在上面的例子中，氨基处在进攻 C-B 键的  $\sigma^*$  的完美角度。三元环的  $\Delta S^\ddagger$  非常小，而  $\Delta H^\ddagger$  大， $T\Delta S^\ddagger$  的附加贡献很小，因而环化相对快速。四元环在两个因素中都是最糟糕的：形成四元环不但引入了环张力 ( $\Delta H^\ddagger$ ) 而且还需要对分子有序的强迫 ( $\Delta S^\ddagger$ )。它的形成非常缓慢，是这两者的结果。

### 环大小 5–7

#### 多种可能的构象



只有一种可以反映，因而  $\Delta S^\ddagger$  大



没有环张力：小  $\Delta H^\ddagger$

### 环张力 3 或 4

#### 少种可能的构象



环张力意味着大  $\Delta H^\ddagger$

可反应的构象是很少的几种构象之一，因而  $\Delta S^\ddagger$  小

结果如下文字框总结。

### ● 环的形成

- 三元环形成反应是快速的——产物有环张力，因此  $\Delta H^\ddagger$  大，但由于反应原子接近于自由旋转的链，可以弥补。
- 四元环形成反应是缓慢的——产物仍然有显著的环张力，但反应原子现在并不恰当地挨着彼此，因而不能弥补。
- 五元环形成反应通常是所有中最快的。环张力显著地减小，两端也仍没有离得太远。
- 六元环形成反应中没有环张力，但它也没有两端挨得近的优势。
- 由于  $\Delta S^\ddagger$  增加，七元及以上环形成得更加缓慢。

### 中等环和大环

对于七元以上的环，形成反应的速率保持较低，并开始趋于平稳；当到 10 或 11 元时，可能又会开始提升。由于环一边与另一边的 C-H 键之间的相互作用（跨环相互作用 transannular interactions），大约 8–13 元的“中等环/中环”也不同程度地承受着环张力，p. 368 (Chapter 16) 的图清楚地说明了这一点。这样的事在 8 和 9 元环中最糟糕，在 10 或 11 元环时开始减缓。对于 14 元及以上的环，没有跨环张力存在，关环的速率，在七元环左右也基本上保持恒定。14 元以上环的反应基本上与非环状化合物没什么区别。若要形成大环，在非常稀的溶液中发生反应，以防止分子间反应的进攻通常是有必要的。

跨环相互作用  
阻碍中环的形成

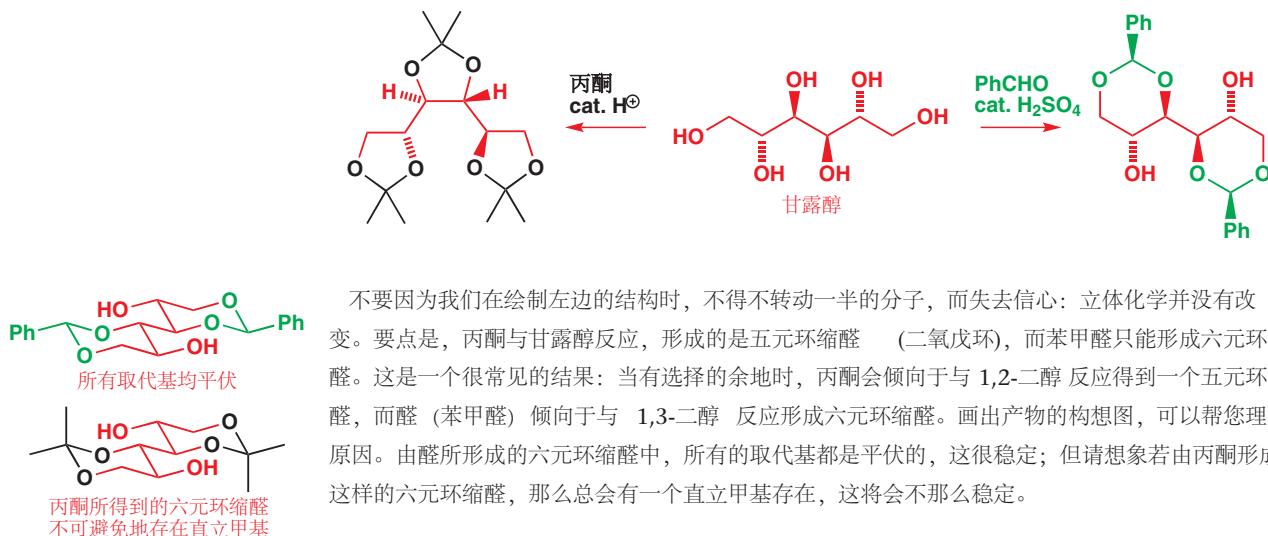


### 环尺寸的热力学控制

本节中，我们已讨论过了环形成的速率：换句话说，就是环形成反应的动力学。然而，有很多的环形成反应是在热力学，而非动力学控制下完成的。例如，您已经了解了，葡萄糖在溶液中主要以六元环的形式存在。它也可以以五元环的形式存在：但它没有这样做，是由于虽然五元环比六元环形成得快，但五元环通常没有六元环稳定（记得，六元环基本上是无张力的）。出于相似的热力学原因，虽然您能画出合理的结构，它也不以七元环的形式存在。



对环大小的控制，可以用于完成对糖中羟基的选择性保护，因而热力学控制在糖化学的其他方面也是重要的。对比下列两个反应。它们都是由同一起始原料，甘露醇（mannitol），形成的缩醛。

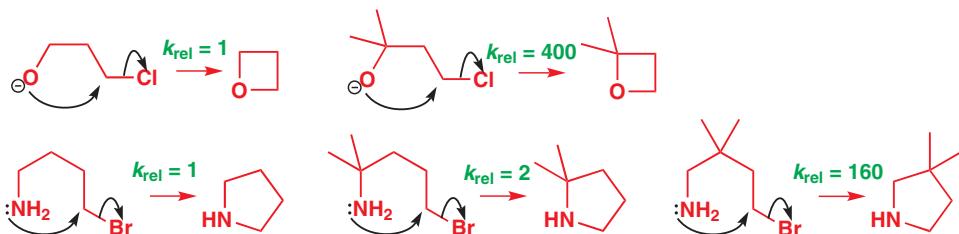


### 与 $\Delta S^\ddagger$ 竞争——Thorpe-Ingold 效应

环形成反应的速率不光受环大小的影响，还受欲形成的环上的取代基的影响。对比下列两种环氧形成反应的相对速率 ( $k_{\text{rel}}$ )。后者看起来受到了更大的空阻，但即便如此，它却比前者快数万倍！



在其他环形成反应中加入取代基，也可以使他们更快：下面的两个例子，产物是𫫇丁环和吡咯烷。

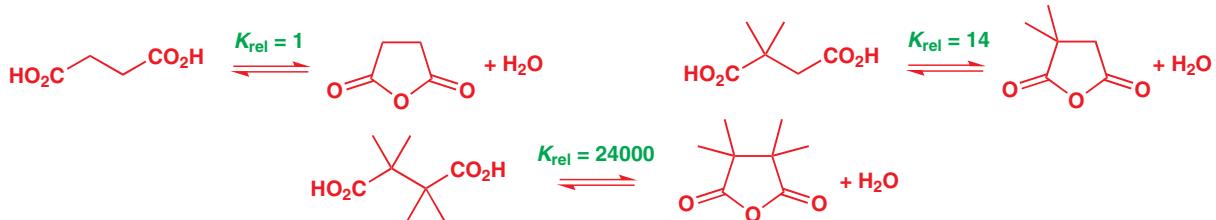


这种效应很普遍，以 1915 年首次发现它的化学家命名为 Thorpe-Ingold 效应 (effect) (索普-英格尔效应，也称偕二甲基效应)。

### ● Thorpe-Ingold 效应

Thorpe-Ingold 效应指通过环上的取代基，增加环形成反应的速率，和平衡常数。

如文字框中所述，受添加的取代基影响的不只有速率。下面是由一个 1,4-二羧酸 形成醛的反应的相对平衡常数 (非取代的酸，丁二酸被称作琥珀酸 succinic acid，平衡常数都以琥珀酸酐形成反应为 1 换算) 形成醛的反应的相对平衡常数。取代越多，意味着平衡中环化的产物就越多。Thorpe-Ingold 效应既是动力学的现象，又是热力学的现象。

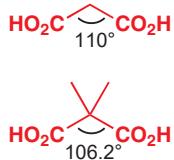


现在，我们需要解释一下为什么会这样。解释来源于两个部分，其中一部分——取决于欲形成的环——可能比另一部分更加重要。第一部分更适用于小环的形成，例如我们提供给您的第一个例子。

如果您测量碳原子链的键角，您会料到，它们接近于四面体角，109.5°。例如，1,3-二羧酸的晶体结构如侧边所示，其 C-C-C 键角为 110°。现在请想象在侧链上加入取代基。它们会排斥已经处在那里的碳原子，并强迫它们比先前离得更近，使键角轻微减小。X-射线晶体学 告诉我们，向 1,3-二羧酸 中添加两个甲基，可以将键角减小大约 4°。

我们可以假设，这一点在 p. 808 的环氧形成反应的醇起始原料中也是成立的 (这个化合物并不结晶，因而我们无法直接测量键角)。现在请考虑，当这两种醇在形成环氧时会发生什么。键角会变为大约 60°，对于未取代的，这个过程增加了大约 50° 的张力 (以二酸的情况做近似)，而对于已取代的，则只剩下 46°。甲基稍微地帮助了起始原料扭曲成环。

这部分论证只适用于小环。对于较大的环，我们需要另一种解释，这涉及熵。我们会使用吡咯形成反应作为例子。我们已经阐释了  $\Delta S^\ddagger$  (活化熵) 对环形成反应速率的影响：随着欲形成的环的扩大，达到过渡态需要失去更多的熵，这使  $\Delta G^\ddagger$  更不利。



但当起始原料取代基更多时，它初始的熵反正是较小了。取代基更多，就意味着起始原料不再能达到某些构象——上一页的右图中，绿色的弧线显示了，甲基阻碍着 N 和 CH<sub>2</sub>Br 取代基进入它的空间区域内旋转。在较少的这些构象中，有很多近似于过渡态的构象，由起始原料到过渡态也包含较小的熵减：ΔS<sup>‡</sup> 负值更小，因而 ΔG<sup>‡</sup> (= ΔH<sup>‡</sup> - TΔS<sup>‡</sup>) 负值更大，环形成得也更快了。同样的观点也适用于整个反应的 ΔS (起始原料和产物间的熵差)，因此即使在热力学控制下，增加的取代基也有利于关环反应。

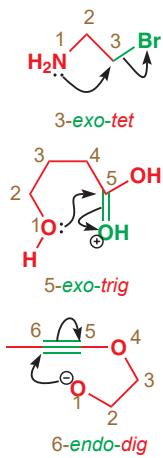
### Baldwin 规则

几乎所有我们讨论过的环化反应，都是分子内 S<sub>N</sub>2 反应，其中分子的一端做亲核试剂，取代掉另一端的离去基团。为了在不同大小的环之间进行有效而合理的比较，我们保留了这类反应。但您可以想象到，还有大量的其他方式可以用于饱和杂环的制取——例如对羰基的分子内取代反应，如下面的内酯化反应；或者氧阴离子对炔烃的分子内加成。

您在 Chapter 27, p. 683 见过相似的炔烃加成反应。



环化反应可以根据一个简单的体系分类，包括：(1) 欲形成的环的大小，(2) 环形成的同时，还断裂的键在新环的内部 (*endo*) 还是外部 (*exo*)，和 (3) 亲电试剂是 sp (对角型 *digonal*)，sp<sup>2</sup> (三角型)，还是 sp<sup>3</sup> (四面体型) 原子。以下三种环化反应便可根据此体系分类。



Interactive examples of Baldwin's rules

1. 欲形成的环是三元环；断裂的 C–Br 键在新环之外 (*exo*)；携带 Br 的 C 是四面体型 (sp<sup>3</sup>) 原子 (*tet*)。
2. 欲形成的环是五元环；断裂的 C=O 键在新环之外 (*exo*)；被进攻的 C 是三角型 (sp<sup>2</sup>) 原子 (*trig*)。
3. 欲形成的环是六元环；断裂的 C=C 键在新环内部 (*endo*)；被进攻的 C 是对角型 (sp) 原子 (*dig*)。

环化反应的分类很重要，但这并不是因为难以控制的维多利亚式渴望 (Victorian desire)，不是为了分类而分类，而是因为反应的分类决定了它是否可能成功。即使很多反应在纸上看起来很好，但并非所有的环化反应都能成功！描述哪些反应会发生的准则被称为 *Baldwin 规则* (*Baldwin's rules*)：它是一种经验规则，又由一些合理的立体电子效应因素支撑。根据这些规则，反应可以被划分为“有利”和“不利”。我们将逐步地处理这些参考准则，并在最后将它们总结到一个表格中。

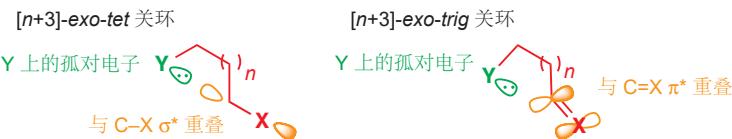
首先，我们可以接受 (由于我们已经在本章中讨论了很多这种类型的反应)：

- 所有 *exo-tet* (外型-四面体型) 环化反应都是有利的

然后，相似地 (您在本书中同样见过很多例子)：

- 任何 *exo-trig* (外型-三角型) 环化都是有利的

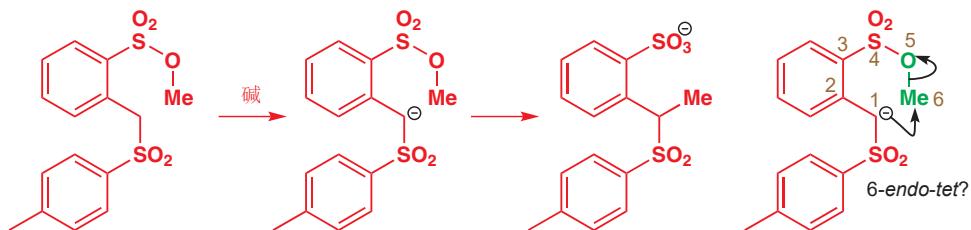
尽管我们已经讨论过，这类反应的速率不尽相同，但 *exo-tet* 环化反应是没有立体电子效应困难的：不考虑环的大小，孤对电子和 C–X  $\sigma^*$  (X 为离去基团) 是可以成功地重叠的。P. 809 列举的关环反应都属于这一分类。*exo-trig* 反应也是如此：亲核试剂的孤对电子很容易与 C=X  $\pi^*$  重叠，并形成新键。内酯形成反应，如 p. 810 所示的，就是一个例子。



*Endo-tet* 反应就相当不同了。首先：

● 5 和 6-*endo-tet* (内型-四面体型) 是不利的。

*Endo-tet* 反应事实上并不会制得一个环，但它们也是分类的一部分，我们将在此讨论。下面是一个看似与我们之前所说相矛盾的反应。右侧看似合理的机理中的箭头描述了一种 6-*endo-tet* 过程，其中断裂的 Me–O 键处于六元环过渡态 (即使环没有形成) 中。



Sir Jack Baldwin (杰克·鲍德温爵士) 教授曾在牛津工作；于 1976 年在麻省理工学院拟定了它的规则。它在生物合成 (生命体制造分子的方式) 方面研究广泛，尤其是与盘尼西林相关的内容，并将很多生物合成的思想运用在了实验室合成困难的解决上。Baldwin 规则与您将在 Chapters 34 和 35 了解的 Woodward–Hoffmann 规则有根本上的不同。

Woodward–Hoffmann 规则是由理论推导出来的，然后才是逐渐发现符合它们的例子。它们是不能违反的：一个似乎违背了 Woodward–Hoffmann 规则却可以发生的“禁阻的 (forbidden)”反应，一定是通过其他机理绕开的。Baldwin 规则的制定，依据的是对反应是否起作用的观察。这也是为什么我们的措辞，使用的是“有利”、“不利”，而非“允许”、“受阻”。

但 Eschenmoser 指出，尽管这个机理很有吸引力 (分子内反应通常在速率上超过所有其他可能发生的反应)，但它是错的。他将上方反应的起始原料，与下方所示的六氘代化合物混合在一起，并重新进行反应。如果反应在分子内发生，那么产物就要么不含氘，要么含有六个氘。但结果与之相反，产物混合物中，以上的两种都占大约 25%，并还有一种包含三个氘的产物，占 50%。因而产物不可能是分子内形成的，这种分布恰恰是分子间反应的预期结果。



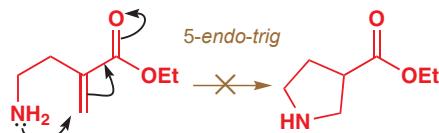
■ 这是一个交叉实验 (crossover experiment). 见 Chapter 39, p. 1038.

对于 *endo-trig*，它们是否反应取决于环的大小。

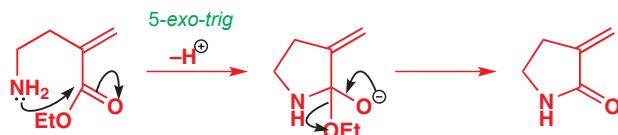
● 3-, 4-, 和 5-*endo-trig* (内型-三角型) 是不利的；6 和 7-*endo-trig* 是有利的。

*endo-trig* 中最重要的情形是不利的 5-*endo-trig* 反应，如果您在这一节中收获了某条信息，那么它应该是：5-*endo-trig* 反应是不利的。我们这样说的原因在于，5-*endo-trig* 环化反应在纸上看起来非常好，第一次见时，您也会对它们不能反应感到很奇怪。例如下面的分子内共轭加成反应，似乎是制取取代的吡咯烷的一种合理方法。

■ 胺通常善于共轭加成不饱和酯：见 Chapter 22.



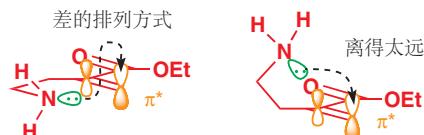
但这个反应是不会发生的：相反，胺会进攻羰基，并发送(有利的) 5-exo-trig 环化反应。



Interactive mechanism for 5-endo-trig vs 5-exo-trig

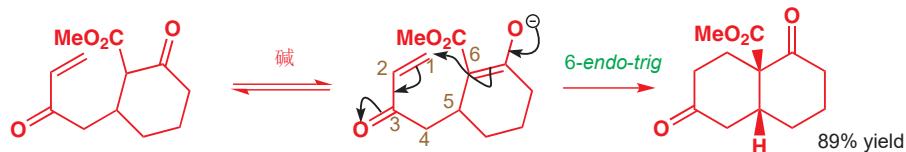
■ 有模型的情况下，这些内容很容易理解。如果您有一套分子模型，那么您应当为自己搭建这些分子。

为什么 5-*endo*-trig 这么糟呢？原因在于，氮的孤对电子在抵达 Michael 受体的  $\pi^*$  轨道并发生反应时出现了问题。只要氮位于亲电碳原子所处的平面上，那么反应一点问题都没有，但如果它扭曲处这个平面——如果它像与  $\pi^*$  轨道共轭，那么必须如此——就会离要反应的亚甲基很远。它就像被拴住的狗，刚好够不到骨头。



不过，如果链再长一些，狗便能吃到他的晚餐了。下面是一个很简单的 6-*endo*-trig，其中没有轨道重叠的问题。

Interactive mechanism for 6-endo-trig cyclization



### Baldwin 规则的例外

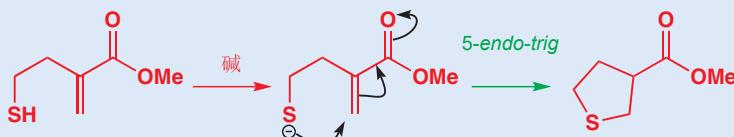
Baldwin 规则只是参考准则，当一个反应在热力学上很有利 (Baldwin 规则，当然描述的是反应的动力学有利性)，并且也没有其他可能的路径发生反应时，5-*endo*-trig 反应也是可以发生的。最引人注目的例子是您在本书很靠前的位置 (Chapter 11) 了解的反应：由羧基化

合物和乙二醇形成环状缩醛 (二氧戊烷) 的过程。我们无需再提供全部的机理，但您应当检查自己是否仍能写出来。有关于 Baldwin 规则的关键一步如绿色箭头所示。这是一个仍能工作的 5-*endo*-trig 反应！



事实上，阳离子经常违背 Baldwin 规则。其他定义明确的 Baldwin 规则的例外，还包括周环反应 (Chapters 34 和 35) 以及环中包含第三周期元素，如硫时的反应。这个 5-*endo*-trig 反应，是刚刚不

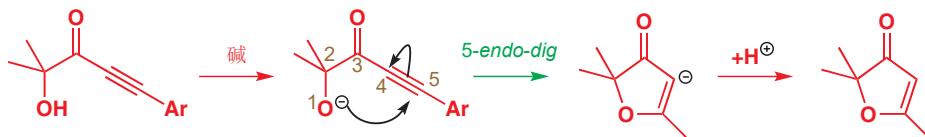
能工作的胺环化反应的硫替代品，但它是却工作得很好。C-S 键很长，硫的空 3d 轨道可能会在初始就与 C-C  $\pi$  轨道相互作用作用，进而起作用。



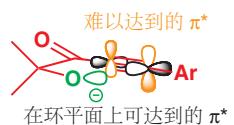
对于 *tet* 和 *trig* 环化反应，*exo* 都好于 *endo*；对于 *dig* 环化反应，则反之。

● 所有的 *endo-dig* (内型-对角型) 环化反应都是有利的。

从 5-*endo-trig* 到 5-*endo-dig*, 反应会变得简单得多: 即便是 4-*endo-dig* 反应都是可以工作的。下面是一个 5-*endo-dig* 的例子。



我们警告过您, 要提防 5-*endo-trig* 反应, 因为即使在纸面上看起来很好, 它们也是不利的。现在, 警告的内容正好颠倒! 我们希望您认可, 即使这些 *endo-dig* 反应在纸面上看起来很糟: 直线型的炔烃, 似乎会将亲电碳很好地置于亲核试剂可以达到的范围之外, 比 5-*endo-trig* 反应离得还要远。然而, 在 *endo-dig* 环化反应中重要的一点是, 炔烃有两个  $\pi^*$  轨道, 其中一个必然处在新环形成的平面上, 进而使亲核试剂更容易达到。

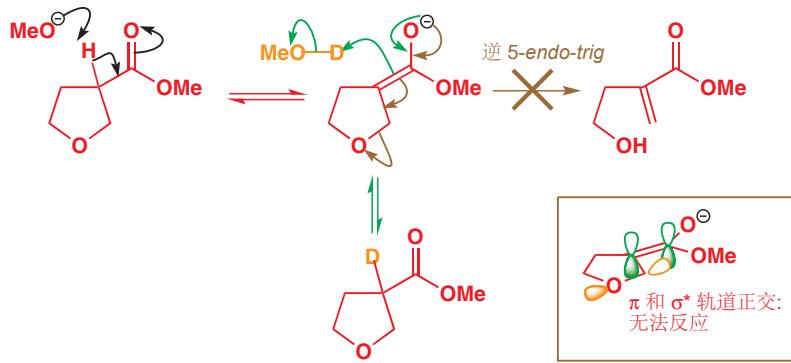


### ● 3 和 4-*exo-dig* 是不利的; 5 到 7-*exo-dig* 是有利的。

这些反应不是很重要, 我们不会展开讨论。

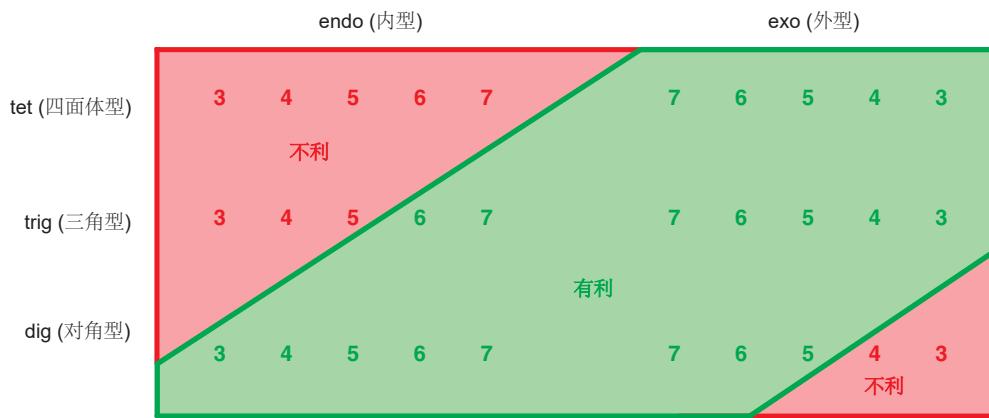
## Baldwin 规则和开环

Baldwin 规则之所以工作, 是因为它们基于: 是否容易达到过渡态所需的构象中的轨道重叠。但无论反应向前发生, 还是向后发生, 过渡态都是一样的——微观可逆性原理 the principle of microscopic reversibility (将在 Chapter 39 中进一步讨论) 提出, 如果一个反应通过某种特定的机理进行, 那么它的逆反应也必定以相反方向遵循相同的路径。因此 Baldwin 规则同样适用于开环反应。这是 5-*endo-trig* 的不利性真正的重要性之所在: 例如, 这个四氢呋喃酯, 看起来可以在碱中发生 E1cB 消除。但事实上, 当在氘代甲醇中用甲氧基阴离子处理它时, 只是将酯的  $\alpha$  质子交换为了氘, 这证明了烯醇盐在过程中得到了形成, 但并没有发生消除: 消除的过程是一个逆 5-*endo-trig* 过程, 因而是不利的。



当您思考一个开环反应时, 请想想它的逆反应, 并根据 Baldwin 规则评估它是否是有利的。

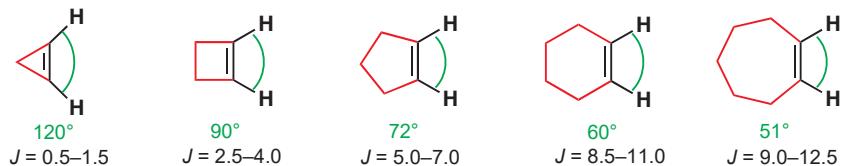
Baldwin 规则可以总结为一幅图表。您应当注意观察图表的大致轮廓, 并记牢, 笼统地讲, *endo-tet* 和 *endo-trig* 都是不利的; *exo-tet* 和 *exo-trig* 是有利的, 对于 *dig* 来说正好相反。然后您只需要记住这种概述的视角与其反例的分界线: 6-*endo-trig* 变为有利, 4-*exo-dig* 变为不利。然后, 如果您真的只能记一条, 那么请记住, 5-*endo-trig* 是不利的!



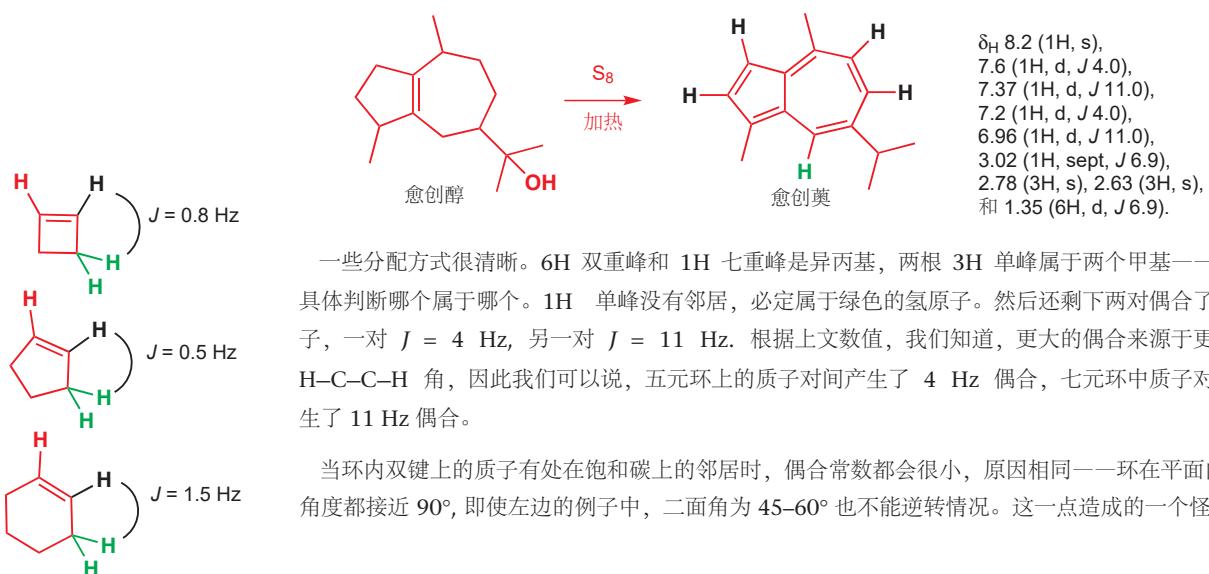
## 环的大小和 NMR

在 p. 796, 我们考虑了二面角的变化对偶合常数的影响。但二面角并不是唯一值得考虑的角度：我们还应当考虑两根 C–H 键在空间中展开的方式。我们之前类比过，二面角是我们俯视书脊时看到的角度——现在，我们想以正常方式看书页，与书脊成直角，和我们读书时一样。我们可以通过将二面角固定在  $0^\circ$  (C–H 键在同一平面内)，并着眼于一些环状烯烃中， $J$  随环的大小的变化情况，来说明我们的意思。

所示的角度，是在假设结构为平面正多边形的情况下计算得出的，偶合常数  $J$  的单位为 Hz.



氢原子之间的距离越宽，偶合常数就越小。记住，二面角是保持不变的 ( $0^\circ$ )——我们只是改变了平面中的角度。天然产物愈创醇 (guaiol) 与单质硫发生脱氢反应的产物，是一个激动人心的例子。从棕色，带有臭味的反应混合物中，可以蒸馏出一种深蓝色的油，愈创薁/愈创蓝油烃 (guaiaculene).



的结果是，红色和黑色氢之间的  $\beta$  偶合经常会与红色和绿色氢之间的烯丙基偶合 ( $\gamma$ ) 大小相同。马上就会有一个例子。

这种“扩散 (spreading out)”效应同样在简单饱和环中影响邻位偶合 ( $\beta$ )。任何其他环的构象都没有六元环的定义得如此清晰，但当我们从 6 向 5 向 4 向 3 移动时，仍然能注意到有用的趋势。简要来说，在五元环中，顺式和反式偶合基本上是相同的。而在四元和三元环中，顺式偶合比反式偶合大。但在所有情况下， $J$  的绝对数值都随环变小，以及 C–H 键更“扩散”而减小。确实，如我们所见，您可以说，小环中的任何偶合常数都较小。但我们还需要稍详细地考察几个例子。

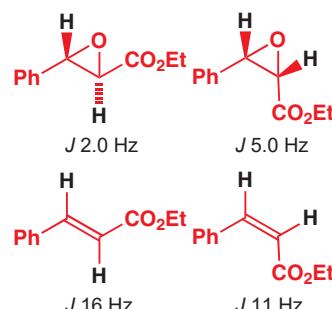
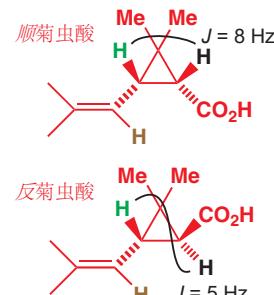
### 三元环

三元环不得不不是平面型的，所有键都是重叠的，因此顺式 Hs 的二面角为  $0^\circ$ ，反式 Hs 的二面角为  $109^\circ$ 。看看 p. 796 的 Karplus 曲线，我们期望顺式偶合更大，事实也正是这样。菊虫酸 (chrysanthemic acid) 是一个很好的例子，它是从匹菊属植物中发现的杀虫剂化合物的除虫菊酯 (pyrethrin) 基团。顺式和反式的菊虫酸都很重要，两个异构体中，环上绿色的质子与其在双键上棕色的邻居之间的偶合为 8 Hz。在顺式化合物中，绿色质子是一个三重峰，因此环中的顺式偶合也是 8 Hz；在反式化合物中，它是一个二重二重峰，还有一个，反式跨环到黑色 H 上的 5 Hz 偶合。

最重要的三元环是环氧。您在 Chapter 13 中了解过 (p. 295)，负电性原子会通过从传输偶合“信息”的键上吸取电子密度，从而减小偶合常数。这意味着，环氧的偶合非常小——打个比方，比与他们密切相关的烯烃的偶合小得多。对比图中的四种偶合常数：对于环氧，所有的耦合都很小，但顺式偶合比反式偶合大。在烯烃中，反式偶合更大 (Chapter 13, p. 293)。下表总结了烯烃、环氧，和环丙烷的偶合常数。

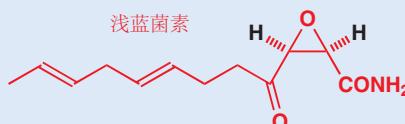
典型偶合常数  $J$ , Hz

立体化学	烯烃	环丙烷	环氧
顺式	10–12	8	5
反式	14–18	5	2

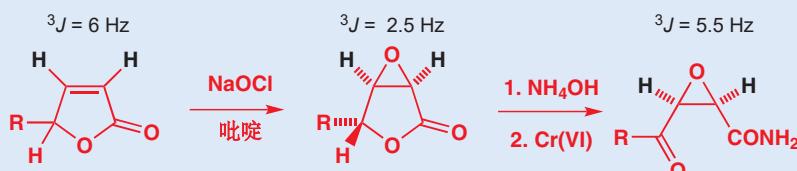


■ 环氧的偶合常数比烯烃小得多，这是因为(1) C–C 键比 C=C 键长，(2) 存在负电性元素，(3) 小环的“扩散”效应开始起作用。

### 浅蓝菌素

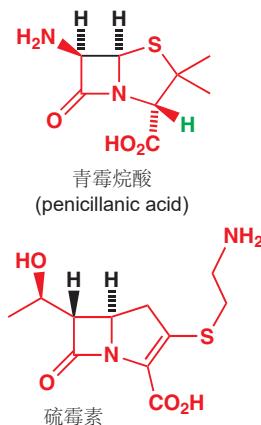


天然产物浅蓝菌素 (cerulenin) 是一种包含顺式环氧的抗生素。黑色氢之间的偶合常数为 5.5 Hz。这个化合物已由一种不饱和内酯经环氧化和开环反应制得。看看随着这个流程的进行，黑色氢之间的偶合常数会发生什么变化。



烯烃中的顺式偶合较小，这是因为它处在五元环中。在双环环氧中，黑色 Hs 既处在五元环，又处在三元环中，并且都与氧相连，因而偶合常数变得更小。得到浅蓝菌素后，它变得更大，这是因为五元环被打开了。

## 四元环



四元环中也存在相似的情况——顺式偶合比反式偶合大，但它们一般又都比较大的环中的小。侧边中的氨基酸，盘尼西林 (青霉素) 的骨架便是一个很好的例子。NMR 光谱包含三个位于中间区域的  $^1\text{H}$  信号。有一个位于  $\delta_{\text{H}} 4.15 \text{ ppm}$  的单峰，明显属于孤立的绿色质子；还有两个位于  $\delta_{\text{H}} 4.55$  和  $5.40 \text{ ppm}$  的双重峰，必定属于黑色质子。它们之间的偶合常数为数  $5 \text{ Hz}$ ，因而是顺式关系。

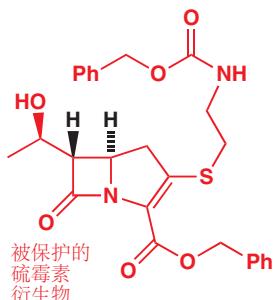
目前有大量已知的  $\beta$ -内酰胺类抗生素，其中一类在四元环上有相反的 (反式) 立体化学，典型成员是硫霉素 (thienamycin)。我么马上就会分析它的光谱，但请先看看它与上个结构，出去立体化学外的区别。硫原子现在位于五元环之外，羧基处在一根双键上 (在同一个环内的双键)，氨基离开了  $\beta$ -内酰胺环，原来的位置被羟烷基侧链取代。

再来看它的光谱，以及立体化学的关键问题，这是 Merck 所发现，并在它的原始文章中所说：

“硫霉素 (及其衍生物) 的  $^1\text{H}$  NMR... 显示，两个  $\beta$ -内酰胺 氢的邻位偶合常数较小， $J \leq 3 \text{ Hz}$ . 过去关于盘尼西林的经验... 说明， $\beta$ -内酰胺 氢的顺式相互关系往往与较大的偶合相勾连。” 我们刚刚也见过，盘尼西林的氢  $J \sim 5 \text{ Hz}$ .

在酰胺和羧酸上被保护了的硫霉素衍生物的 NMR 光谱如下所示。在阅读下文的解释之前，事实将它们解释清楚。您的目标是找到跨四元环的偶合常数。

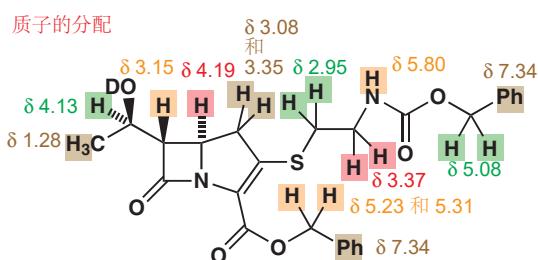
硫霉素衍生物在  $\text{CD}_3\text{OD}$  中的 NMR 光谱



位移 ( $\delta_{\text{H}}$ , ppm)	积分	多重峰	偶合常数 ( $J$ , Hz)
1.28	3H	d	6.5
2.95	2H	m	未解决
3.08	1H	dd	9, 18
3.15	1H	dd	2.5, 7
3.35	1H	dd	9, 18
3.37	2H	m	未解决
4.13	1H	dq	7, 6.5
4.19	1H	dt	2.5, 9
5.08	2H	s	—
5.23 和 5.31	2H	AB 体系 <sup>a</sup>	AB 体系 <sup>a</sup> : 12.5
5.80	1H	宽峰	—
7.34	10 H	多重峰	未解决

<sup>a</sup>有关 AB 体系的讨论见 p. 297.

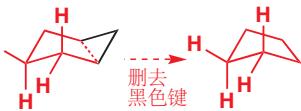
答案很简单，是  $2.5 \text{ Hz}$ . 位于  $3.15$  和  $4.19 \text{ ppm}$  处的信号是  $\beta$ -内酰胺 环上的质子， $9 \text{ Hz}$  额外的偶合是右侧质子与五元环中的  $\text{CH}_2$  间发生的。如果您详细研究这份光谱，您可能会担心  $12.5$  和 (尤其是)  $18 \text{ Hz}$  的偶合。它们是  $^{2}J$  (偕偶)，我们将在下一节中讨论。详细的分配方式如下所示。



我们应当强调，仅有 5 到 2.5 Hz 的偶合常数，不足以让我们分配跨四元环的立体化学，但，如果我们同时有两种，那么我们便有勇气提出，较大的偶合来源于顺式 Hs，较小的来源于反式 Hs.

## 五元环

您可以将五元环的构象，简单地想象为其中一个原子被删去的椅式环己烷构象。但这幅图太过简单化，因为五元环可以屈伸（而不是翻转），其中的任何碳原子都可以成为在平面外的那一个。所有氢原子都快速地交换着位置，NMR 光谱“看到的”是时间平均化结果。一般来说，这种大小的环中，顺式和反式偶合都在大约 8–9 Hz.



对于五元环中顺式和反式偶合的相似性，最好的说明，是一个正因此而被错误地推导出的结构。加拿大青霉酯 (Canadensolide) 是一种发现于青霉属 (*Penicillium*) 霉菌的抗真菌化合物。由 (高分辨率) 质谱法很容易推断出总结构，即  $C_{11}H_{14}O_4$  的分子式；红外光谱，显示了 (位于 1780 和  $1667 \text{ cm}^{-1}$ ) 一个共轭的五元环内酯，及质子 NMR 的一些方面。假设的结构如侧边所示。

环连接处的 Hs (以黑色和绿色显示) 的立体化学并不构成问题。由于两个五元环几乎不可能以反式方式耦合，因而它们当然是顺式的。环左侧的第三个立体中心，是该分子立体化学的不确定性所在。黑色和绿色 Hs 之间的偶合常数是 6.8 Hz，而绿色和棕色 Hs 间则为 4.5。它们的差异足够大，而是前者变为反式的吗？最初的研究者给出了肯定的回答。

当一些日本化学家以毫无以为的路线制取了这种化合物时，错误才得以显露。错误的化合物中的 NMR 光谱非常像加拿大青霉酯本身，但并不完全一样。尤其，绿色和棕色 Hs 的偶合为 1.5 Hz ——很不同！因此他们同样制取了另一种可能的非对映体，并发现这才与天然产物加拿大青霉酯完全相同。细节如侧边所示。

### 结构分析中邻位偶合的例子：黄曲霉素

我们可以将这一主题的很多要点汇聚在一种化合物的结构分析中，那就是可怕的黄曲霉素 (aflatoxin)。我们已在 Chapter 19 中提及过黄曲霉素：它们出现于霉菌中，包括长在一些食物上的霉菌，并会导致肝癌。这些慢性毒药是已知毒性最强的化合物之一。黄曲霉素 B<sub>1</sub> 便是一个例子，如侧边。五元环饱和碳原子上的四个红色氢以两个三重峰出现： $\delta_H$  2.61 (2H, t,  $J$  5 Hz) 和  $\delta_H$  3.42 (2H, t,  $J$  5 Hz)。顺式和反式偶合是相同的。在两个五元环状醚的连接处的黄色质子，是一个双重峰  $\delta_H$  6.89 (1H, d,  $J$  7 Hz)。这当然是与黑色质子的顺式偶合。黑色质子也有这种偶合，但却以三重峰的二重峰出现，其中有在 2.5 Hz 处的双重峰偶合： $\delta_H$  4.81 (1H, dt,  $J$  7, 2.5, 2.5 Hz)。这些小偶合只可能来源于两个绿色氢：<sup>3</sup>J 和 <sup>4</sup>J 偶合确实是相同的。

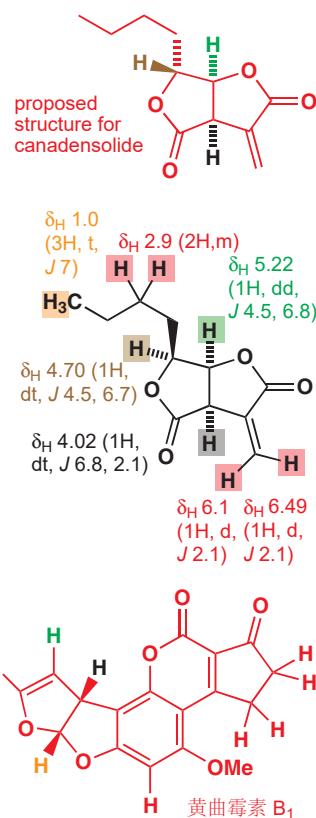
最后，还存在另一种奇怪的巧合——每个绿色氢都以 2.5 Hz 偶合的三重峰出现。显然，沿双键的顺式偶合也是 2.5 Hz。我们期望环戊烯中的顺式偶合很小 (p. 814 的奠中为 4 Hz)，但事实并不是这样——一定是因为负电性的氧原子进一步减小了数值。

## Geminal (<sup>2</sup>J) coupling

For coupling to be seen, the two hydrogen atoms in question must have different chemical shifts—identical protons do not couple. For <sup>2</sup>J, or geminal, couplings the two hydrogen atoms are on the same carbon atom, so in order to discuss geminal coupling we must first consider what leads the two hydrogens of a  $\text{CH}_2$  group to have different shifts.

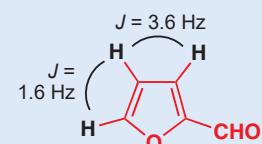
To introduce the topic, an example. It may seem to you that any six-membered ring might show different chemical shifts for axial and equatorial groups. But this doesn't happen. Consider the result of this Robinson annelation reaction.

→ 这个构象有时被称为“信封式”。见 Chapter 32, p. 834.

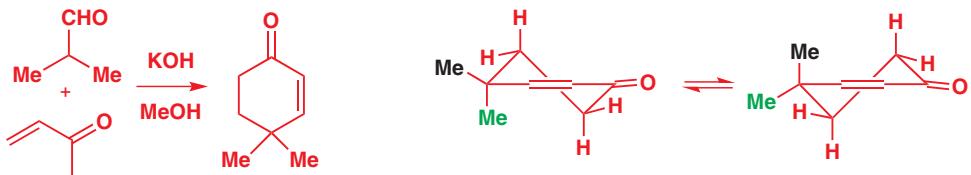


### Coupling in furans

The size of coupling constants in five-membered rings containing oxygen is illustrated clearly in furfuraldehyde (furan-2-aldehyde): note how small the couplings are.

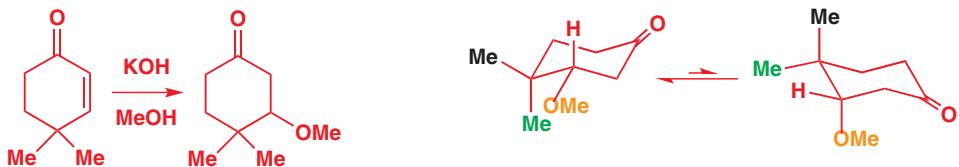


The Robinson annelation was introduced in Chapter 26, p. 638. The 'flattened chair' conformation of cyclohexenones shown here is described in detail in Chapter 32, p. 830.



The two methyl groups at C4 give rise to a single signal in the  $^{13}\text{C}$  NMR at 27.46 ppm. Even though one of them is (pseudo)axial and one (pseudo)equatorial, the molecule exists in solution as a rapidly equilibrating mixture of two conformations. The axial green methyl in the left-hand conformer becomes equatorial in the right-hand conformer, and vice versa for the black methyl group. The equilibrium position must be 50:50 and fast exchange averages the chemical shifts of the two methyl groups. The same is true for the  $\text{CH}_2$  groups around the back of the ring, which each appear as a triplet.

However, the enone is not the only product of this reaction. A methanol adduct is also formed by Michael addition of methanol to the conjugated enone. This product has two methyl signals at 26.1 and 34.7 ppm. If we examine the molecule by conformational analysis as we did for the first product we see a similar situation.

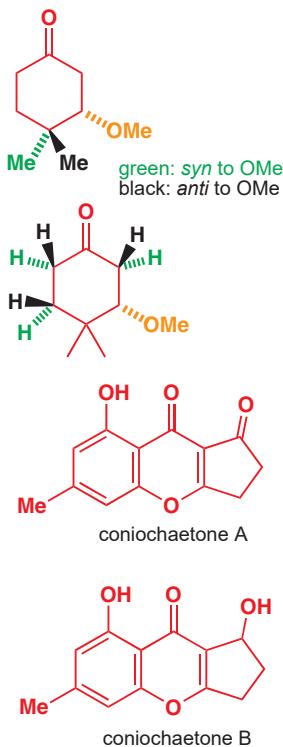


Similar but not the same. This time, the two conformations are not identical. One has the OMe group equatorial and the other has it axial. Even the two methyl groups do not entirely change places in the two conformations. True, the green methyl is axial on the left and equatorial on the right, but it has a gauche (dihedral angle 60°) relationship with the OMe group in *both* conformations. The black Me group is gauche to OMe on the left but anti-periplanar to the OMe group on the right. Averaging the two different conformations, in each of which the black and green methyl groups are different (that is, they don't just change places), does *not* lead to equalization of the two methyl groups.

Perhaps a simpler way to discover this is to use a configurational, rather than a conformational, diagram. The green methyl group is on the same face of the molecule as the MeO group, while the black methyl group is on the other face. No amount of ring flipping can make them the same. They are *diastereotopic*, a term we shall define shortly. And so are all three  $\text{CH}_2$  groups in the ring. The green Hs are on the same face of the molecule as the MeO group while the black Hs are on the other face.

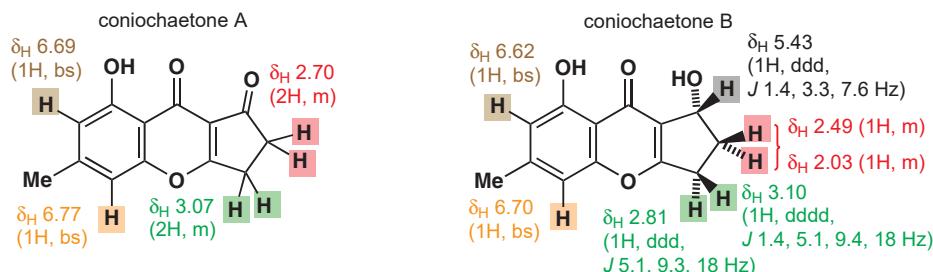
A proton NMR example confirms this, and here is one from an odd source. There are fungi that live on animal dung, called coprophilous fungi. They produce antifungal compounds, presumably to fight off competition! Anyway, in 1995 two new antifungal compounds were discovered in a fungus living on lemming dung. They were named coniochaetones A and B and their structures were deduced with the usual array of mass and NMR spectra. The proton spectra, run on a 600 MHz machine, are shown below, and they reveal considerable detail.

Some of the spectrum is essentially the same for the two compounds, but other parts are quite different. Coniochaetone A has a very simple spectrum, very easily assigned. Coniochaetone B is rather more interesting. The spectrum is much more complicated, even though it has only one more C–H (the grey one) than coniochaetone A. The reason is that addition of that H atom creates a stereogenic centre and makes the top and bottom faces of the molecule different. Each H in both  $\text{CH}_2$  groups becomes differentiated from its partner.



Coniochaetone A		Coniochaetone B	
$\delta_H$ , ppm	Coupling	$\delta_H$ , ppm	Coupling
2.41 (3H)	s	2.38 (3H)	s
2.70 (2H)	m	5.43 (1H)	ddd, $J$ 1.4, 3.3, 7.6 Hz
3.07 (2H)	m	2.49 (1H)	m
6.77 (1H)	broad s	2.03 (1H)	m
6.69 (1H)	broad s	3.10 (1H)	dddd, $J$ 1.4, 5.1, 9.4, 18 Hz
12.21 (1H) <sup>a</sup>	s	2.81 (1H)	ddd, $J$ 5.1, 9.3, 18 Hz
		6.70 (1H)	broad s
		6.62 (1H)	broad s
		12.25 (1H) <sup>a</sup>	s

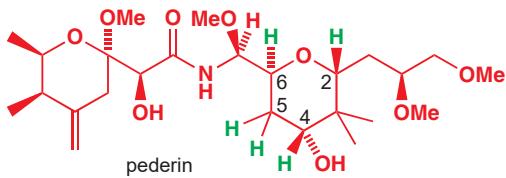
<sup>a</sup>Exchanges with D<sub>2</sub>O.



The green Hs are coupled to each other ( $J = 18$  Hz) and to each of the black Hs with a different coupling constant. One of the green hydrogens also shows a long-range ( $^4J = 1.4$  Hz) W-coupling to the red H. The black Hs are too complex to analyse, even at 600 MHz, but the different couplings to the red Hs are shown by the signal at 5.43 ppm.

### The size of the geminal coupling constant

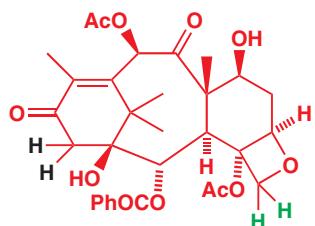
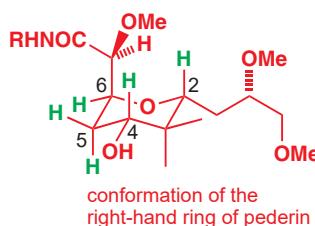
The 18 Hz geminal coupling constant between the green protons of coniochaetone B is large, but not unusually so for a geminal coupling. A more typical figure in a six-membered ring might be closer to 14 Hz, and we will see shortly why the value in coniochaetone B is bigger than this. The example below provides an opportunity to examine coupling constants in another example where NMR was essential for determining the structure. The compound is pederin, a toxic amide of the blister beetle *Paederus fuscipes*. After some incorrect early suggestions, the actual structure of the compound was eventually deduced as shown.



We are not going to discuss the full structure elucidation, but will concentrate on the stereochemistry of the right-hand ring. The five (green) protons on the ring gave the signals listed in the margin.

Three of the protons have shifts  $\delta_H$  3–4, and are obviously on carbons attached to oxygen atoms. The other two,  $\delta_H$  about 2, must be the diastereotopic pair at C5. The coupling of 12 Hz, which appears in both signals, must be the geminal coupling and the other couplings are found in the signals at  $\delta_H$  3.75 and 3.85. The signal at  $\delta_H$  3.75 has no other couplings and must be from C4 so that leaves  $\delta_H$  3.85 for the hydrogen atom at C6, which is also coupled to the hydrogen in

$\delta_H$
1.85 (1H, ddd, $J$ 5, 10, 12)
2.10 (1H, ddd, $J$ 3, 4, 12)
3.75 (1H, dd, $J$ 4, 10)
3.85 (1H, ddd, $J$ 3, 5, 8)
4.00 (1H dd, $J$ 3, 7)



► The effect of electronegative atoms on coupling was discussed in Chapter 13, p. 295.

the side chain. The 10 Hz coupling must be axial–axial—the others are all much smaller, meaning there is just the one axial–axial coupling. The left-hand side chain must therefore occupy an axial position as shown in the margin. This is perhaps a bit surprising—it's large and branched—but the molecule has no choice but to place one of the two side chains axial.

One of the most important compounds from the last 25 years is Taxol, the anti-cancer compound isolated from the bark of the Pacific yew tree. Taxol's structure has four rings—with eight, six (twice), and four members—and is too complex to analyse in detail, but the NMR spectrum of the closely related compound in the margin gives us the opportunity to illustrate how much geminal couplings in rings may vary and to analyse some of the factors which control this variation. The coupling between the black Hs is 20 Hz while that between the green Hs is just 6 Hz.

20 Hz is a very large coupling constant, even for geminal coupling, and the reason it is so big is the adjacent  $\pi$  bond. If a  $\text{CH}_2$  group is next to an alkene, aromatic ring,  $\text{C}=\text{O}$  group, CN group, or any other  $\pi$ -bonded functional group, it will have a larger geminal coupling constant. This effect also explains the large 18 Hz coupling in coniochaetone B (p. 819).

But why is the green coupling so small? The reason is the four-membered ring. You saw on p. 814 that vicinal couplings are small in small rings; the same is true of geminal couplings. Another factor comes into play here as well—the adjacent oxygen atom. Electronegative atoms always tend to reduce coupling constants.

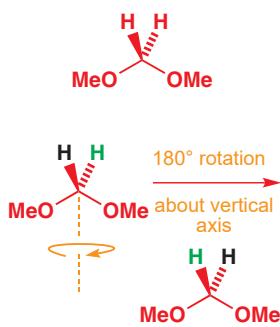
### ● The size of $^2J$ and $^3J$ coupling constants

We have now covered all of the important influences on the size of coupling constants. They are:

- dihedral angle:  $^3J$  greatest at  $180^\circ$  and  $0^\circ$ ; about 0 Hz at  $90^\circ$
- ring size, which leads to 'spreading out' of bonds and lower  $^2J$  and lower  $^3J$  in small rings
- electronegative atoms, which decrease  $^2J$  and  $^3J$  coupling constants between protons
- $\pi$  systems, which increase  $^2J$  coupling constants between protons.

## Diastereotopic groups

To understand this discussion, it is very important that you understand the ideas that we covered in Chapter 14. You may need to refresh your memory of the stereochemical points there before you read further.



You have now seen several examples where two protons attached to the same carbon are not the same, and it is time to examine more closely the appearance of these  $\text{CH}_2$  groups in NMR spectra. To do this, we shall have to discuss some aspects of symmetry that build on what you learned in Chapter 14. You will see that there are *three* possibilities for the symmetry associated with a  $\text{CH}_2$  group, and these three possibilities have an effect both on the chemistry of the molecule and on what its NMR spectrum will look like.

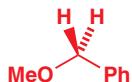
First, an example in which the two hydrogens are indeed the same. Although the molecule is of course achiral, we may draw one hydrogen coming towards us and one going away, but the two Hs are the same. This is easy to demonstrate. If we colour one H black and one green, and then rotate the molecule through  $180^\circ$ , the black H appears in the place of the green H and vice versa. The rotated molecule hasn't changed because the *other* two substituents (OMe here) are also the same.

If we had given out uncoloured models of this molecule with this book, and asked each reader to paint one H green and one H black, we would have no way at all of giving instructions about which to paint what colour. But it wouldn't matter because, even without these instructions, every reader would produce an identical model, whichever way they painted their Hs.

The correct description for this pair of hydrogen atoms is **homotopic**. They are the same (*homo*) topologically and cannot be distinguished by chemical reagents, enzymes, NMR machines, or human beings.

### ● Homotopic groups

Homotopic groups cannot be distinguished by any means whatsoever: they are chemically entirely identical.



What happens when the other two substituents are different? At first sight the situation does not seem to have changed. Surely the two hydrogens are still the same as one another?

In fact, they aren't—not quite. If we had given out uncoloured models of this molecule and just said 'paint one H green and one H black', we would not have got just one type of model. However, this time we *could* give instructions about which H we wanted which colour. To get the first of these two, we just need to say 'Take the MeO group in your *left* hand and the Ph group in your *right*, kink the carbon chain upwards. The hydrogen coming towards you is to be painted black.' All the models produced by readers would then be identical—as long as the readers knew their *left* from their *right*. This is a very important point: the green and black hydrogens in this molecule (unlike the first one) can be described only in phrases incorporating the words 'left' or 'right', and are distinguishable only by a system that knows its left from its right.

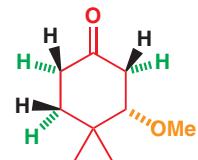
Human beings are such a system: so are enzymes and the asymmetric reagents you will meet in Chapter 41. But NMR machines are not. NMR machines cannot distinguish right and left—the NMR spectra of two enantiomers are identical, for example. There is no question of enantiomers in the molecule in question—it has a plane of symmetry and is achiral. Nonetheless, the relationship between these two hydrogens is rather like the relationship between enantiomers (the two possible ways of colouring the Hs are enantiomers—mirror images) and so they are called **enantiotopic**. Enantiotopic protons appear identical in the NMR spectrum.



### ● Enantiotopic groups

Enantiotopic groups can be distinguished by systems that can tell right from left, but are still magnetically equivalent and appear identical in the NMR spectrum.

The third situation usually arises when the molecule has a stereogenic centre. As an example we can take the Michael product from the beginning of this section. It is now very easy to distinguish the two hydrogens on each ring carbon atom and, if we want to give instructions on how to paint a model of this molecule, we can just say 'Make all the Hs on the same side of the ring as OMe green, and the ones on the opposite side to OMe black.' We do not need to use the words 'right' or 'left' in the instructions, and it is not necessary to know your right from your left to tell the two types of Hs apart. Ordinary chemical reagents and NMR machines can do it. These Hs are different in the way that diastereoisomers are different and they are **diastereotopic**. We expect them to have different chemical shifts in the proton NMR spectrum. The same is true of the methyl groups: they too are diastereotopic and we expect them to have different shifts.



### ● Diastereotopic groups

Diastereotopic groups are chemically different: they can be distinguished even by systems that cannot tell right from left, and they can appear at different chemical shifts in the NMR spectrum.

## How to tell if protons are homotopic, enantiotopic, or diastereotopic

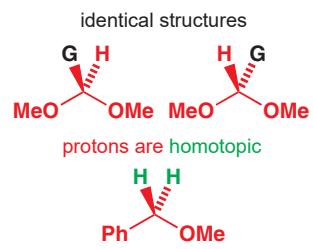
What we have said so far explains to you why homotopic and enantiotopic groups always appear identical in the NMR spectrum, but diastereotopic protons may not. Now we will give a quick guide to determining what sort of pair you are dealing with in a given molecule.

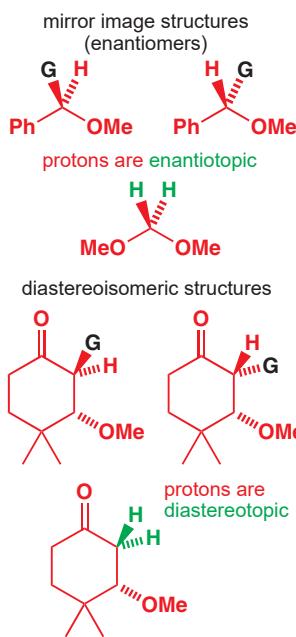
The key is to draw your molecule twice. In each drawing (or model if you prefer) replace one of the Hs (we'll assume we're looking at protons, but the argument works for other groups too—Me groups, for example) with an imaginary group 'G'. Write down the first structure you get, with stereochemistry shown. Next, write down the structure you get by replacing the other H with the group G. Now the more difficult bit: identify the stereochemical relationship between the two molecules you have drawn.

- If they are identical molecules, the protons are homotopic.
- If they are enantiomers, the protons are enantiotopic.
- If they are diastereoisomers, the protons are diastereotopic.

This is really just a simpler way of doing what we did with black and green above, but it is easy to do for any molecule. Take the first of our examples, and replace each H in turn by G. These two molecules are identical because just turning one over gives the other: the protons are homotopic.

■ NMR machines can tell the difference, but it does not follow that they *will*. There are many examples of protons that are different but have the same chemical shift (toluene, PhMe, shows a singlet in the NMR for all its aromatic protons even though they are of three different kinds). Sometimes diastereotopic protons have the same chemical shift, sometimes slightly different chemical shifts, and sometimes very different chemical shifts.





■ The shape of NMR signals where  $J$  and the chemical shift difference are of the same order of magnitude were discussed in Chapter 13. The arguments apply to any coupled protons of similar chemical shift—there we used disubstituted aromatic rings as the example—but are particularly relevant here.

■ It is not always easy to decide which proton gives rise to which signal in a diastereotopic AB system, although the information may be important in assigning stereochemistry. The size of other couplings, or the nuclear Overhauser effect (p. 799), may assist.

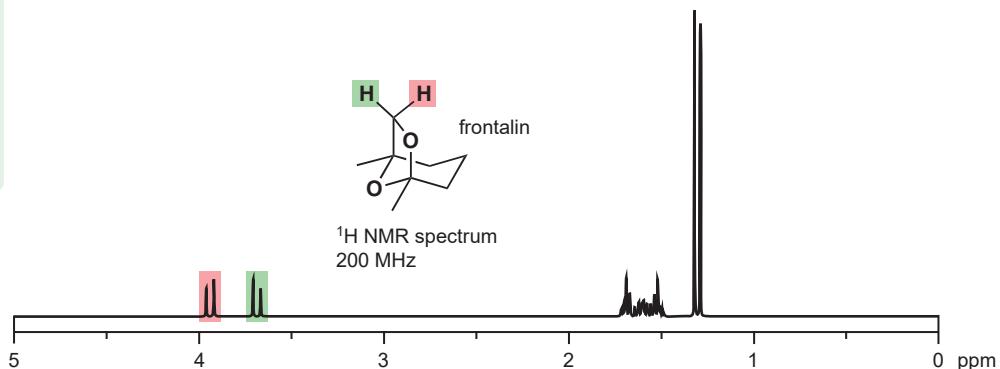
Now for the next example. The two molecules are not identical: to make one into the other you need to reflect in the plane of the paper, so they are enantiomers, and the Hs are *enantiotopic*. There is another term we must introduce you to in relation to this molecule, which will become useful in the next chapter, and that is ‘*prochiral*’. The molecule we started with here was not chiral—it had a plane of symmetry. But by changing just one of the Hs to a different group we have made it chiral. Molecules that are achiral but can become chiral through one simple change are called *prochiral*.

Now we will choose one of the three pairs of Hs in the cyclohexanone example. The starting molecule is, of course, now chiral, and the two molecules we get when we replace each H by G are now diastereoisomers: one has G and OMe *anti*, the other *syn*, and the pairs of hydrogens are *diastereotopic*. The same is true for the other CH<sub>2</sub> groups. Furthermore, the methyl groups attached to the ring will be diastereotopic too, and we expect them to appear as two 3H singlets.

### Spotting diastereotopic protons in the NMR spectrum

A CH<sub>2</sub> group with diastereotopic Hs isolated from any other Hs will give rise to two signals, one for each H, and they will couple to each other so that the complete signal is a pair of doublets. A typical geminal ( $^2J$ ) coupling constant is 14 Hz—relatively large. Because chemical shift differences ( $\Delta\delta$ ) between Hs on the same carbon atom tend to be small—usually less than 1 ppm—the signals have  $\Delta\delta \sim J$  and are distorted into a ‘roof-topped’ AB system.

Here is an example. The pheromone frontalin is a remarkable compound used by both insects and by elephants to attract a mate. Its structure and <sup>1</sup>H NMR spectrum are shown below.

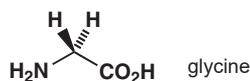


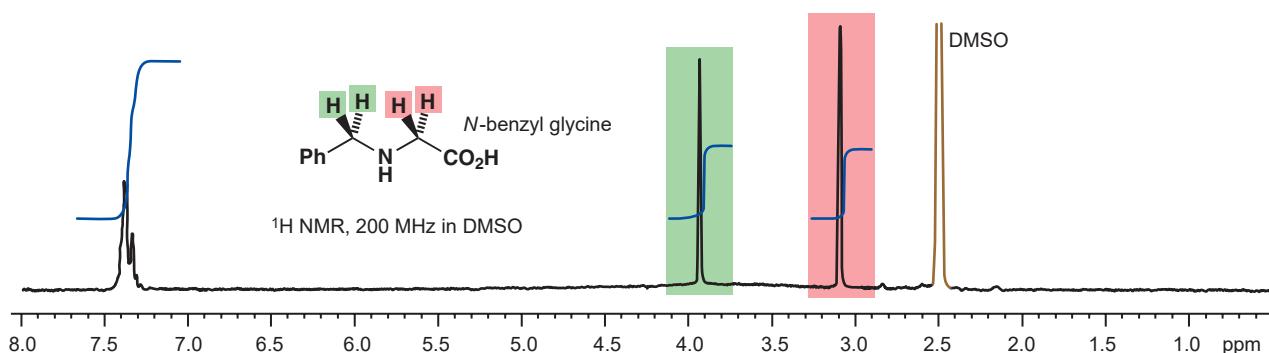
The red and green hydrogens are diastereotopic, and have no other couplings. They give the pair of doublets at 3.42 and 3.93 ppm., each with  $J$  7 Hz (an AB system) in the <sup>1</sup>H NMR. The coupling constant here is small for  $^2J$ —only 7 Hz—but that should not surprise you since we have a five-membered ring and a nearby oxygen atom.

The coupling constant in an AB system is easy to extract—it is the difference in Hz between the two lines highlighted same colour in the spectrum above. But the chemical shifts are not so easily measured. The chemical shift of each proton is at the weighted mean of the two lines—the more distorted the signal, the nearer the chemical shift to that of the larger inner line.

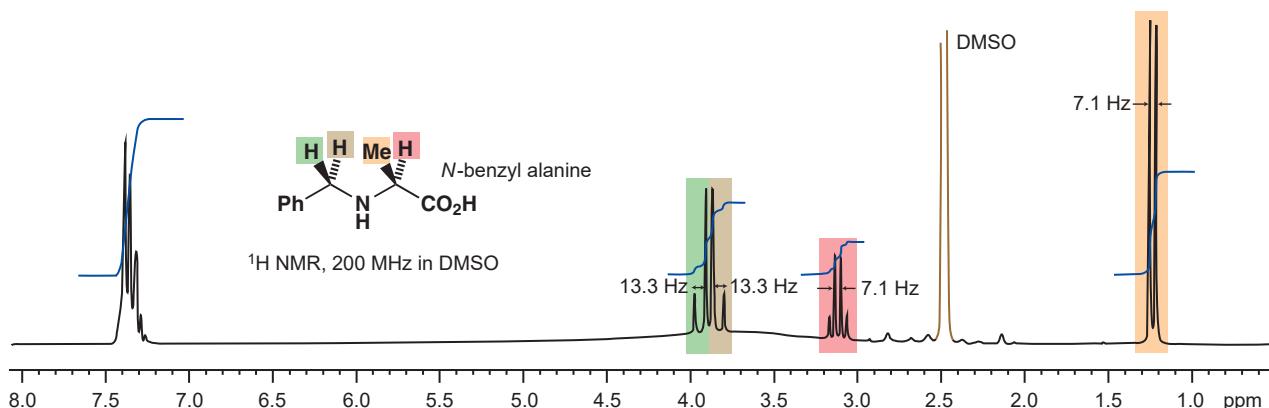
### Diastereotopic protons in acyclic compounds

The same principles apply to open-chain compounds, such as amino acids. All of the amino acids in proteins except glycine are chiral. Glycine has a CH<sub>2</sub> group that gives a singlet in the NMR spectrum as its Hs are enantiotopic. Similarly, the N-benzyl derivative of glycine has a second CH<sub>2</sub> group (NCH<sub>2</sub>Ph) that gives another singlet in the NMR spectrum as these Hs too are enantiotopic.





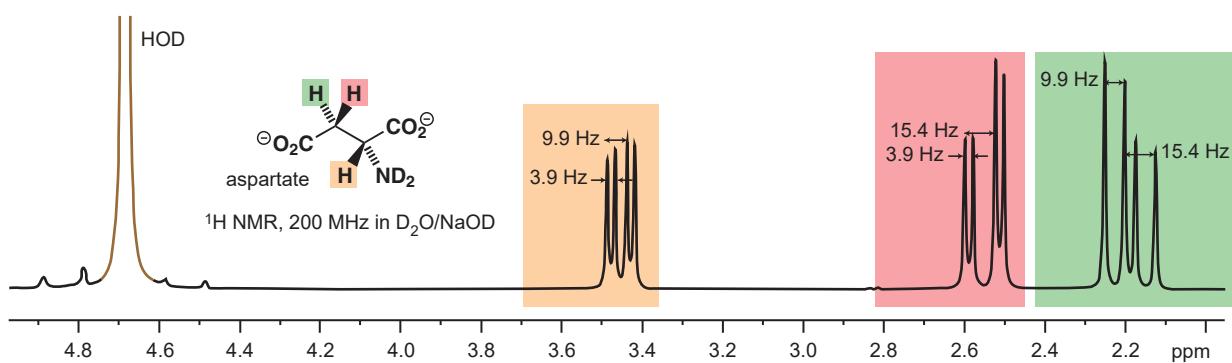
The plane of the paper is a plane of symmetry for both of the  $\text{CH}_2$  groups of *N*-benzyl glycine in the way it is drawn here. But for the other amino acids, which are all chiral, the symmetry is different. The  $^1\text{H}$  NMR spectrum of *N*-benzyl alanine is shown below. There is now no plane of symmetry, so the Hs of the  $\text{NCH}_2\text{Ph}$  group are diastereotopic. The  $\text{CH}_2$  group appears as an AB pattern.



In the way in which the molecule is drawn, the green H is on the same side as the Me group and the brown H on the other. It does not matter that there is free rotation in this molecule—the two diastereotopic protons are never in the same environment so even after averaging over all the conformations available to the molecule they always appear at different chemical shift. If a molecule is chiral, all  $\text{CH}_2$  groups in that molecule—however flexible it may be and however far they are from any chiral centre—are diastereotopic, and can potentially appear in the spectrum as an AB system.

It is more common to find diastereotopic  $\text{CH}_2$  groups with neighbours, and an example arises when aspartic acid is dissolved in  $\text{D}_2\text{O}$  with NaOD present. The  $\text{NH}_2$  protons are exchanged for deuterium atoms and do not show up in the spectrum—the molecule exists as its dianion.

For an illustration of diastereotopic  $\text{CH}_2$  groups which may or may not appear as AB systems, look back at the spectrum of thienamycin on p. 816. Compare the two  $\text{OCH}_2\text{Ph}$  groups: both have a diastereotopic  $\text{CH}_2$  pair, but one appears as a singlet and one as an AB system.



## 小结

We have covered a lot of ground in this chapter, and have used the huge topic of saturated heterocycles to explain a lot, not just about the reactivity and conformation of rings. Many of these explanations involved consideration of the alignment of orbitals—we called these stereoelectronic effects. The same analysis allowed us to make sense of the NMR spectra, and in particular the coupling constants, of cyclic molecules, both heterocyclic and carbocyclic. And by thinking about symmetry in these cyclic molecules we were also able to deduce the origins of symmetry-related features (such as diastereotopic protons) in the NMR spectra of acyclic compounds.

The next chapter is the fourth consecutive chapter to take rings as a theme. It will introduce you to practical ways of controlling stereochemistry in cyclic systems—the first step towards making molecules with a particular stereochemistry, which will continue in Chapter 33 and culminate in Chapter 41 on asymmetric synthesis.

## 延伸阅读

Another reminder: you will find it an advantage to have one of the short books on spectroscopic analysis to hand as they give explanations, comprehensive tables of data, and problems. We recommend D. H. Williams and Ian Fleming, *Spectroscopic Methods in Organic Chemistry*, McGraw-Hill, London, 6th edn, 2007.

For stereoelectronics, a short introduction is A. J. Kirby, *Stereoelectronic effects*, OUP, Oxford, 1996, and a longer book is P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon, London, 1983.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 环状分子中的立体选择性

## 联系

### 基础

- Stereochemistry ch14
- Conformational analysis ch16
- Saturated heterocycles and stereoelectronics ch31

### 目标

- Stereoselectivity in cyclic systems is easy to understand
- Flattened four-and five-membered rings are attacked *anti* to large substituents
- Flattened six-membered rings are attacked from an axial direction
- Bicyclic structures are attacked on the outside face
- Tethering together nucleophile and electrophile forces one stereochemical outcome
- Hydrogen bonding can reverse the normal stereochemical outcome of a reaction

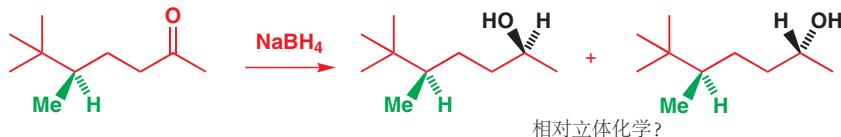
### 展望

- Diastereoselectivity ch33
- Pericyclic reactions ch34 & ch35
- Asymmetric synthesis ch41

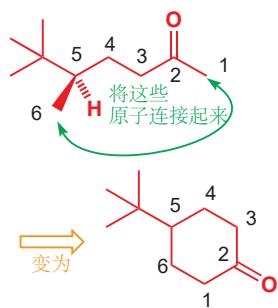
## 引入

在上一章中，我们考察了环状分子的 NMR 光谱反映它们的形状的方式——形状既指构象，又指构型。现在，我们的研究将超出简单的立体化学分析，而将开始阐释控制立体化学的方法。在 Chapter 27 中，我们花了一些时间研究了立体选择性控制的一个方面——双键几何结构的控制。但立体化学的内容比这多得多，在本章和下一章中，我们会阐释制取单一非对映体和单一对映体的方法。

我们将开始于环中的立体化学。不仅仅是因为环中的立体化学更容易理解，还是因为环中的立体化学行为表现得更好。假设您要把这个酮还原为其中一种对应的醇。



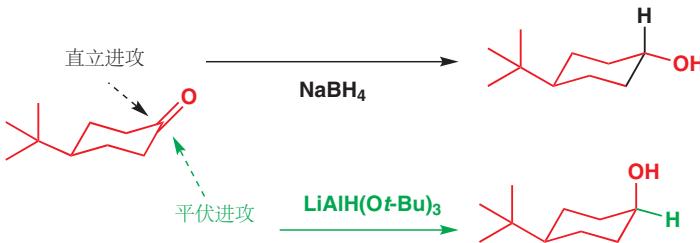
为了在新的立体化学中心（黑色显示）上实现立体选择性反应，绿色的立体化学中心会不得不以某种方式影响亲核试剂对 C=O 基进攻的方向。在一个具有高度灵活性的分子中，又是隔着三根键，这个要求太过苛刻。我们会认为两种非对映体以近似 50:50 混合物的方式存在。



如果您在 Chapter 16 中关于取代基对六元环构象的影响的记忆已经模糊，您现在应当刷新这段记忆。构想分析支撑了本章的大部分内容，您需要对它的概念和术语十分熟悉。

非环状化合物的立体选择性费用将在 Chapter 33 中处理。

然而，如果我们像侧边所示的，将分子连为一个环，那么事情就一瞬变得很不同了。(这当然不是一个化学反应，只是一个在思想中的过程！) 受必须处于平伏键的叔丁基决定，环状酮的构象被固定下来了。羰基的两面，因而明显很不同了，事实上，通过仔细地选择还原剂，可以做到根据意愿进攻任何一面，几乎专有地得到平伏醇或直立醇。如我们稍后会解释的 (p. 828)，大的试剂倾向于平伏着接近，小的试剂倾向于直立着接近，直立着接近会使新的 OH 基进入平伏位置。这些是立体选择性的反应，由于两种不同的结果之间是非对映体的关系，我们称它们为非对映选择性 (*diastereoselective*)。



这两种化合物之间关键的区别在于它们的构象。环状酮的六元环只有一种构象，从酮的两个面接近是非常不同的。在开链化合物中，绕着所有的 C-C 键旋转都是可行的，化合物也由非常多构象组成。在某一种构象中，可能对酮不同面的进攻是有选择性/倾向性的，但总和所有构象，平均选择性便会接近 1:1。当谈论立体选择性反应时，环状和非环状化合物具有天壤之别。

在本章中，我们会着眼于发生在环状化合物身上的反应，带有环状中间体的反应，以及带有环状过渡态的反应。我们还会调查，当两个 (或更多个) 环以一根键，或一个原子连接在一起时发生的变化。之前，您就已经详细地考察过关环反应 (Chapter 31, p. 805)，并且本章中涉及的很多反应也都是您在本书中已经遇到过的反应。我们的任务是揭示新的特征和微妙之处，并向您展示，如何运用这些反应来控制立体化学。

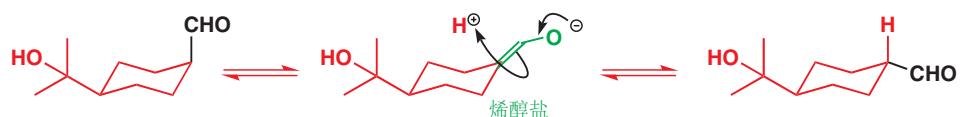
## 六元环中的立体化学控制

见于 Chapter 16，环己烯受益于界定明确的构想偏好。取代基可以选择直立或平伏取向，并通常更喜欢平伏取向，尤其当它们较大时。取代基采取平伏位置的强偏好，意味着，当非对映异构的环己烷通过例如烯醇化等过程发生平衡时，它们也许会高选择性地给出全平伏化合物。例如，下面这种良好的香水原料，会通过烯醇化失去价值。



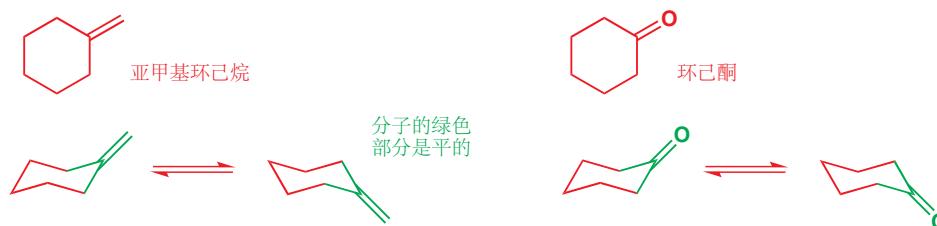
虽然在此处，这是一个缺点，但在其他情形中，平衡为更稳定的全直立构象会是立体化学控制非常有用的来源。见 p. 829 的例子。

平衡倾向于反式异构体 (在平衡混合物中 92% 地形成) 的原因是，两种取代基都处在更稳定的平伏构象中。



## 包含一个 $sp^2$ -杂环 碳原子的六元环: 环己酮

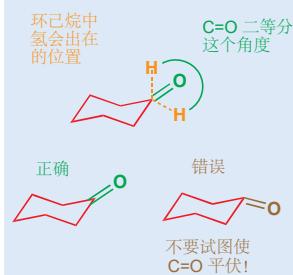
如果我们将六元环的反应感兴趣，那么我们会不得不考虑，当它们包含羰基或烯烃等活泼官能团时，构象上发生的变化——换句话说，就是向环中引入  $sp^2$  C 原子对其造成的影响。对于仅一个  $sp^2$  碳原子，简单的答案是没有影响——环中仅存在一个  $sp^2$  中心并不会对构象造成显著的改变。亚甲基环己烷 (methylenecyclohexene) 和环己酮的构象如下所示。



六元环所带有的，多于一个的  $sp^2$  C 原子是会使他们失去椅式构象的——当环内包含一根或多跟双键使，环会变平到某种程度，我们将在下一节中着眼于此。

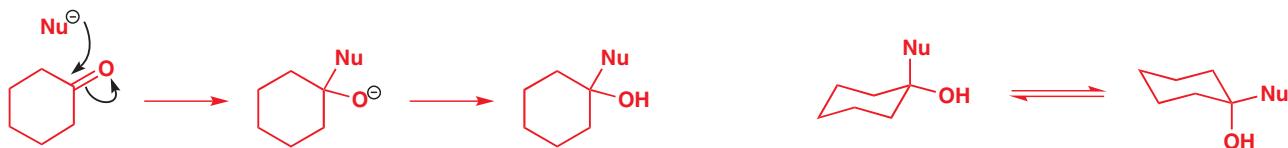
### 绘制环己酮

确保您将酮指向了正确的方向！它应该处于当碳原子是四面体型时，平伏和直立取代基之间二等分的位置。往往将羰基画在环的一个“尖儿”上是最好的：如果您选择画在中间的碳上，那么将它画对要难得多。



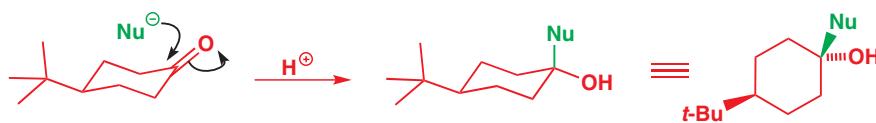
## 环己酮上的直立和平伏进攻都是可行的

那么，当环己酮被亲核试剂进攻时，会发生什么呢？对于环己酮本身，下面的反应会得到一种可以采取两种构象的产物，其中 Nu 直立还是平伏，取决于 Nu 与 OH 的相对大小。这个反应并未提供太多关于对  $C=O$  基的进攻本身的内容——例如，我们无法分辨  $Nu^-$  攻击  $C=O$  基的直立面，亦或平伏面。

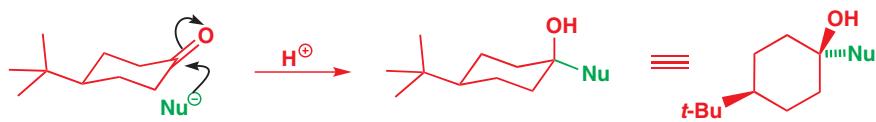


现在请思考对 4-叔丁基环己酮的亲核进攻。由于叔丁基锁住了环 ( $t\text{-Bu}$  绝不能直立)，Nu 是直立还是平伏完全取决于进攻  $C=O$  基的哪个面。进攻与叔丁基相同的面会得到亲核试剂平伏，亲核试剂平伏，羟基直立的结果；进攻另一面，则会得到亲核试剂直立，羟基平伏的结果。也就是说，亲核试剂的进攻方式可以是直立，也可以是平伏，这取决于它最终所处的位置。从图表中看得更清楚。

### 亲核试剂直立进攻

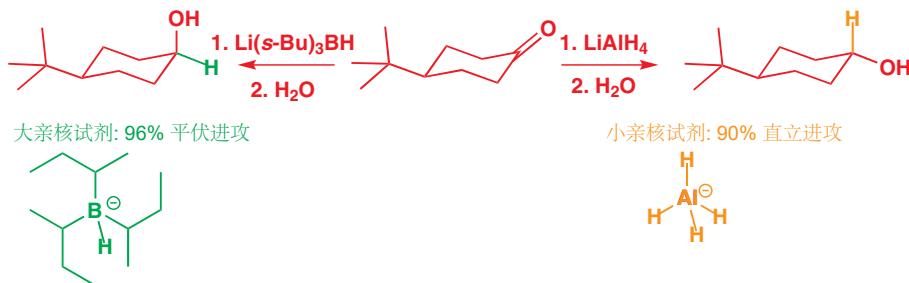


### 亲核试剂平伏进攻



现在我们会给出观察结果——并稍后试图解释。通常，较大的亲核试剂会平伏地进攻，较小的亲核试剂会直立地进攻。例如，4-叔丁基环己酮与  $\text{Et}_2\text{O}$  中氢化铝锂的还原反应，会得到 90% 的反式

醇：90% 的氢负直立地添加。 $\text{AlH}_4^-$  作为亲核试剂是很小的：要制取顺式醇，我们需要更大的亲核试剂——例如三仲丁基硼氢化锂，以“L-selectride®”为名称出售。它只会平伏地进攻，一般产出95% 的顺式醇。



以碳为中心的 (Carbon-centred) 亲核试剂都遵循相同的趋势——如下表所示，大小由纤细的乙炔基阴离子，经伯、仲有机金属，增加到 *t*-BuMgBr，直立选择性随之下降。 $\text{PhLi}$  表现得仿佛它很小，这是因为它的平面性。

亲核试剂	% 的产物产生于	
	直立进攻	平伏进攻
$\text{HC}\equiv\text{CLi}$	88	12
$\text{MeLi}$	35	65
$\text{PhLi}$	42	58
$\text{MeMgBr}$	41	59
$\text{EtMgBr}$	29	71
<i>i</i> -PrMgBr	18	82
<i>t</i> -BuMgBr	0	100

困难的部分来了——为什么会这样？这是一个答案并不真正确定的问题。直立进攻的接近方向比平伏进攻会受到更多的阻碍，这是肯定的，这也是大的亲核试剂倾向于平伏地进攻的原因。

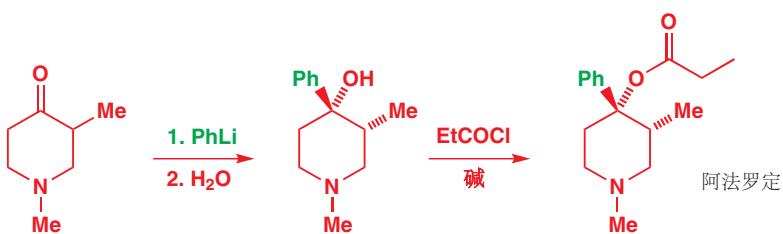
但如果是这样的话，为什么小亲核试剂又倾向于直立进攻呢？一定还有另一种因素有利于直立进攻，并在那些足够小，可以避免与其他直立氢发生很不好的相互作用的试剂上起作用。在过渡态中，正在形成的  $-\text{O}^-$  氧取代基会向直立方向或平伏方向移动。如同直立取代基没有平伏取代基有利一样，导致羟基直立的过渡态也不如导致它平伏的过渡态有利。

当化学家使用下面的反应制取药物阿法罗定 (alphaprodine) 时，他们发现靠近  $\text{C=O}$  邻位的甲基的平伏偏好，和对  $\text{C=O}$  基进攻的平伏偏好的结合，足够有利于其中一种非对映体的形成。下面是费用，起始原料和产物以构象图表达。

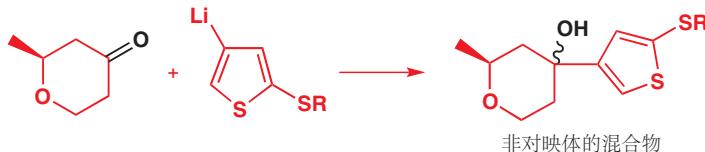
■ 还有人提出其他原因解释这个选择性，但它们超出了本书的讨论范围。



我们也可以用构型方式表示这个反应。这对于立体选择性的阐释并不那么好，但您应随时准备好将构象图转化为构型图。

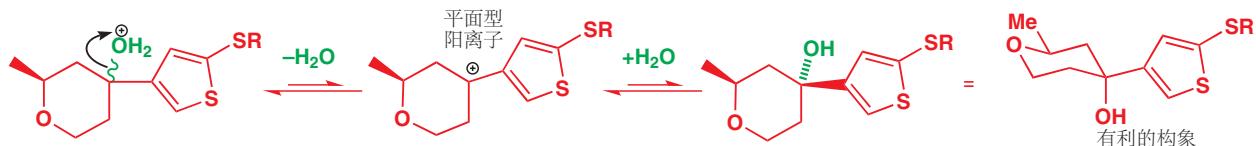


下一个反应中，立体选择性不是很好。捷利康 Zeneca (现为阿斯利康 AstraZeneca) 公布了一种药物的工业合成方法，即噻吩的锂化物对另一种杂环酮的加成，起初得到的是非对映体的混合物。



这样的混合物对于纯净药物的工业合成是不好的，但该化合物，可以在稀酸下，通过重复叔阳离子的  $S_N1$  形成，和被水的捕获产生平衡，进而使所需产物（其中 Me 和噻吩基都平伏，较稳定）以 92:8 占主要，再经过重结晶即可纯化。不需要的那种异构体可以在下一批平衡中再利用。

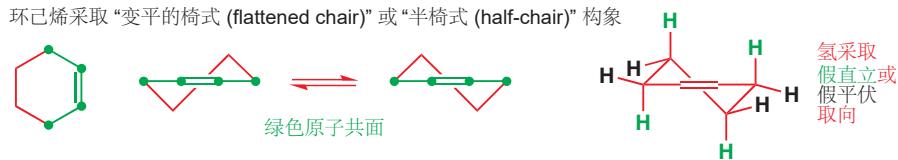
■ 请将这种策略与通过烯醇盐产生平衡的香水化合物合成方法对比，p. 826.



在这些反应中，我们唯一考虑的问题是分子对于——将取代基放在直立位点还是平伏位点上——这一问题的自由选择，因为反应的起始原料——酮或碳阳离子——所处的六元环，即便包含一个三角型( $sp^2$ )原子，仍然处在椅式构象上。

### 有两个及以上 $sp^2$ 碳原子的六元环：环己烯

环己烯，在环上包含两个碳原子，它不再采取椅式构象。环中至少四个原子要在同一平面内，表达这件事最好的方式如下图所示。四个共面的碳原子离您最近，剩下的两个碳原子，一个在平面上方，一个在平面下方。



环己烷本身在上面两种构象间迅速地翻转，能垒大约  $22 \text{ kJ mol}^{-1}$ ，大约是环己烷翻转能垒的一半。与环己烷一样，环己烯结构中饱和碳上的氢原子也采取两种位点类型，但它们的取向与环己烷并不完全一样，我们称它们为“假直立(pseudoaxial)”和“假平伏(pseudoequatorial)”。

### 环己烷仅接受直立进攻

这些带有多于一个三角型碳的六元环构象，很明显不是椅式构象，并且比椅式不稳定得多。任何能使它们恢复椅式的事件都会是高度有利的，这种反应的立体选择性更可能受过渡态的需要及生成

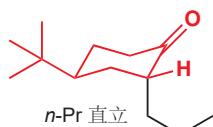
椅式产物而非船式产物的需要。这种偏好性凌驾于形成平伏取代产物的偏好性之上。(后文会分析，直立进攻符合该偏好性，) 直立进攻于是控制了环己烯(还有它们的环氧化物)、六元环状烯醇盐，及六元环状烯基酮反应的立体选择性。

### ● 环内三角型碳原子的数目决定了控制区立体选择性的因素

- 含有一个三角型( $sp^2$ )碳原子的六元环已经是椅式，既可以经历直立进攻，又可以经历平伏进攻。
- 含有两个及以上三角型碳原子的六元环并非椅式，为了形成椅式而非船式，需要经历直立进攻。最终产物无论是直立取代还是平伏取代，都有可能，也不是反应本身考虑的事情。

 Interactive mechanism for axial alkylation of cyclohexanone enamine

环己酮的烯醇盐、烯胺，和烯醇硅醚的烷基化反应，通常表现出直立进攻的倾向。4-叔丁基环己酮的烯胺，由于叔丁基的存在，构象是固定的，与  $n\text{-PrI}$  发生 90% 的直立烷基化，和仅 10% 的平伏烷基化。

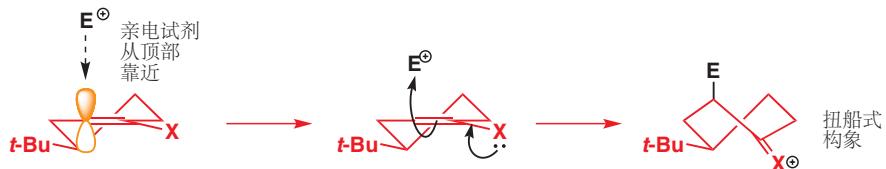


► Enolate equivalents were discussed in Chapter 25.

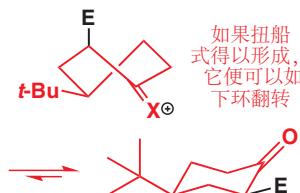


为了搞清楚这个结果的原因，我们需要着眼于烯胺中间体的构象。在此，我们会将其普遍化，绘制表达任何烯醇盐生物的结构，其中  $X$  可能为  $\text{OH}$ ,  $\text{O}^-$ ,  $\text{OSiMe}_3$ ,  $\text{NR}_2$ , 等等。环中的双键( $2 \times sp^2$  中心)意味着构象是部分变平的椅式，如上文叙述。我们将叔丁基放在了一个平伏位点上，因为如环己烷中一样，它太庞大，无法处于直立。这意味着只有一种待考虑的构象——如侧边所示。

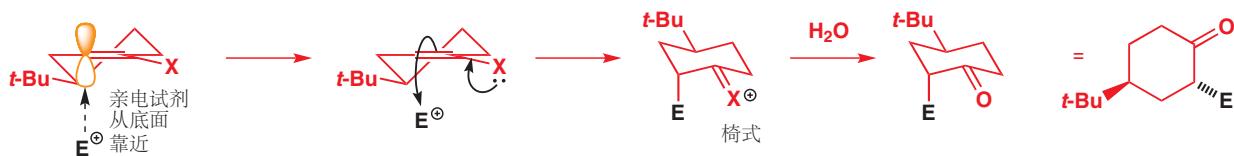
现在，亲电试剂必须进攻这个构象的  $\pi$  体系，为了做到这一点，它需要几乎处在平面的正上或正下方，因为只有这样，它才可以与烯醇位点上，橙色标出的  $p$  轨道相互作用。需要与  $\pi$  体系相互作用是环己烯和相关化合物发生直立取代的原因。分子的顶端看上去更欢迎进攻的到来，我们将先试试这种方式。



当亲电试剂与三角型碳原子成键时，该碳原子必定会变为四面体型，上述方式通过形成一根垂直向上的键完成这一过程。结果位于图中——环转变为一个扭船式(twist-boat)构象。当然，反应结束后，环还可以翻回椅式构象，新的取代基就将是平伏的了，但这些信息在反应的过渡态中是不存在的。我们可以说，分子并不“知道”它稍后可以形成椅式，也不知道在椅式中将会得到更好的平伏取代基：它唯独能看到的，是不稳定扭船式构象的形成，和导向它的高能过渡态(即动力学压倒热力学)。



从明显更受阻的底端进攻，会通过与亲电试剂形成垂直向下的键，而使三角型碳原子转变为四面体型。环直接变为椅式，其中亲电试剂位于直立位点。

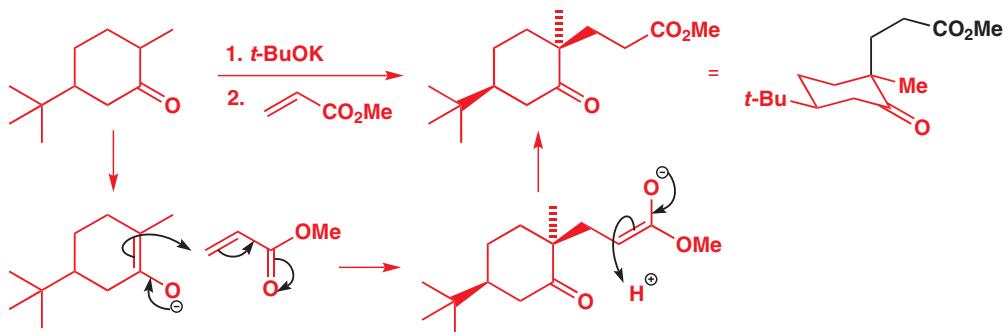


通过水解复原羰基 (如果必要的话——烯醇盐  $X^-$  还不是  $O^-$ )，环不必翻转：它已经处于椅式，叔丁基也处于平伏，新的取代基在椅式构象上直立。这是该反应观察到的产物。

理解在这里发生了什么对您来说是重要的。试剂不得不从直立方向进攻，来与  $p$  轨道相互作用。如果它从上方进攻，新的取代基会在不稳定的扭船式中处于直立。如果从下方进攻，新的取代基会在椅式中处于直立——的确，这并不如在椅式上平伏，但那并不是一个选项——它必须在什么东西上处于直立，而椅式又比扭船式好。因此这是所形成的产物。对于取代基，真是不幸，它并不能知道，如果它经受住了扭船式，那么稍后它便会在椅式上平伏——它选择在椅式上渡过整个一生，那么它必须满足于直立。

下面是一个不饱和羰基化合物做亲电试剂的例子：这个反应是一个 Michael 加成反应。这里的酮稍微有些不同——它也有叔丁基，但处在 3 号位上，Michael 加成中的反应中心也变为叔。但产物仍然是直立进攻。

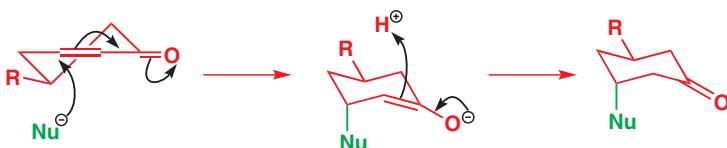
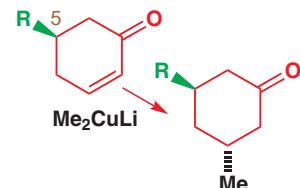
Such reactions were discussed in Chapter 25.



这个结果更令人印象深刻，因为大亲电试剂落在了环上与叔丁基相同的一侧，因此立体选择性的来源，并不是简单的——环的哪本空阻小——这样的思路。根据产物的构象图，它是名副其实的直立进攻。

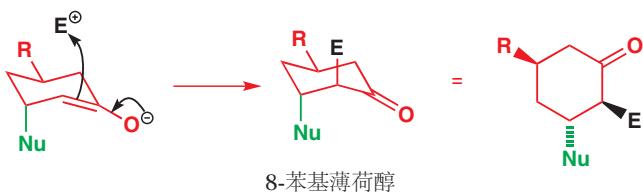
环己烯酮 (Cyclohexenones) 比环己烯更平，但方便起见，我们也将它化成环己烯的构象。侧边中对取代的环己烯酮的共轭加成得到反式产物。

这也是直接形成椅式 (而不是扭船式) 的直立进攻，亲核试剂由底端靠近。我们必须将环画作一个变平的椅式。

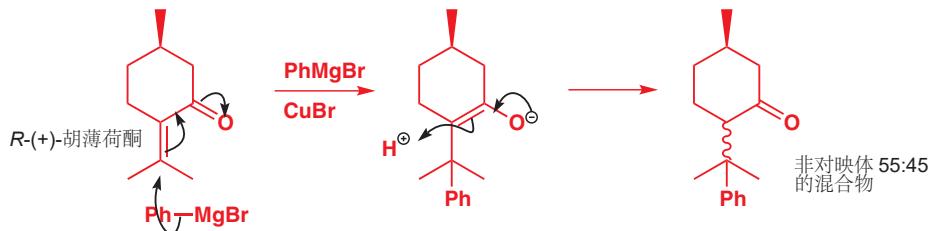


被我们选为例子的 5-烷基环己酮 会得到最好的结果。机理提出，烯醇盐中间体在上方 (还是直立加成) 被质子化，然而我们无法分别这一现象，因为产物在该点没有立体中心。但，如果我们用不同亲电试剂捕获烯醇盐的串联反应，产物由直立进攻得到的事实就会变得清晰了。

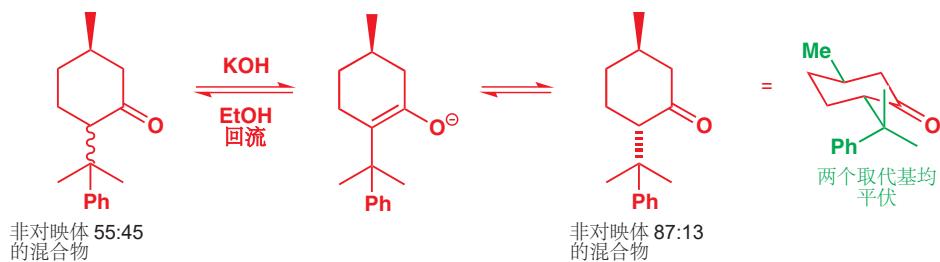
■ 注意：如果您以亲核试剂从较小空阻的一端靠近作为根据，也能得到正确的答案，但该原因是错的。



我们将以一种有用的手性分子的制备中用到的六元环构想控制结束本节，该分子是 8-苯基薄荷醇 (phenylmenthol)，来源于天然产物 (R)-(+)-胡薄荷酮 (也称蒲勒酮，长叶薄荷酮，pulegone)。第一步是一个铜促进的，对外环烯烃 (exocyclic alkene) 的共轭加成。烯醇盐中间体的质子化形成了新的立体中心，但却几乎没有立体选择性。



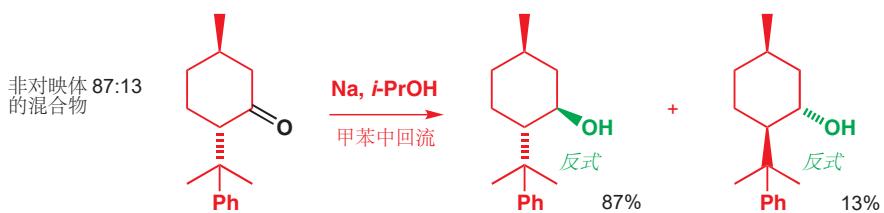
现在可以让热力学发挥实力。酮旁边的位点，可以通过烯醇盐发生差向异构化，并得到取代基均处于平伏的更稳定的异构体。这将非对映异构体的比例从 55:45 提高到 87:13。



现在，可选用一种小型的试剂将酮还原，并将氢氧根置于平伏（见 p. 826）——*i*-PrOH 中的 Na 便很好。这意味着所有的产物中，OH 都反式于挨着酮的大基团，非对映体混合物 87:13 的比例是相对于以 Me 为中心的相对构象而言的。

■ *i*-PrOH 中的 Na 是一种简单的单电子 Birch-类型还原剂(见 Chapter 23)。没有什么比电子更小的还原剂了!

■ 产物, 8-苯基薄荷醇, 可被用做手性助剂 (chiral auxiliary), 见 Chapter 41, p. 1113.



这些醇可以得到分离（它们当然可以，因为它们互为非对映体而非对映体），全平伏的主产物是有用的一个。这是一个既涉及热力学，又涉及动力学的构象控制过程，构象仅起源于六元环中的一个距离遥远的甲基，这是一个令人印象深刻的例子。

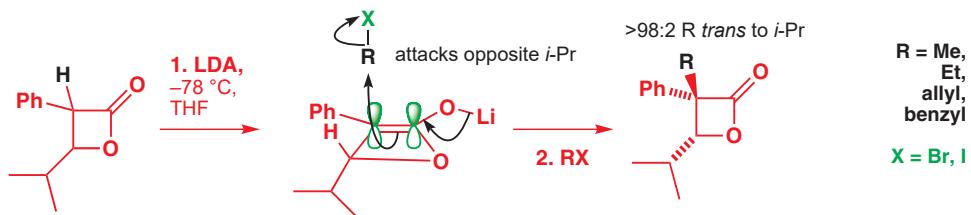
小环上的反应

The conformational principles which apply to rings other than six-membered ones are rather more sketchy because only six-membered rings adopt well-defined chair (or, for cyclohexenes, half-chair) conformations. But we can still give you some general guidelines and principles, and illustrate them with some important examples. We will look in detail at four- and five-membered rings.

→ We looked at the effect of ring size on NMR spectra and on rates of ring closure in Chapter 31, see pp. 814 and 805.

## Four-membered rings can be flat

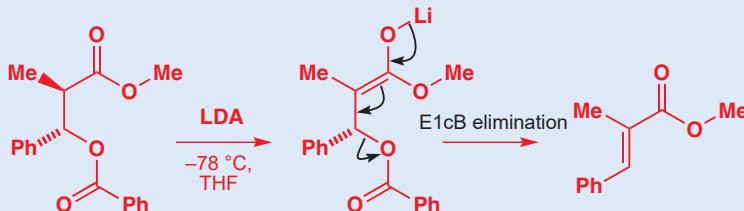
Saturated four-membered rings have a slightly bent conformation but four-membered lactones are flat. The enolates of these lactones can be made in the usual way with LDA at  $-78^{\circ}\text{C}$  and are stable at that temperature, and they react with electrophiles just as you saw in Chapter 25. If the  $\beta$ -lactone has a substituent already then there may be a choice as to which face of the enolate is attacked by an electrophile. In the example below, simple alkylation with a variety of alkyl halides gives essentially only one diastereoisomer of the product.



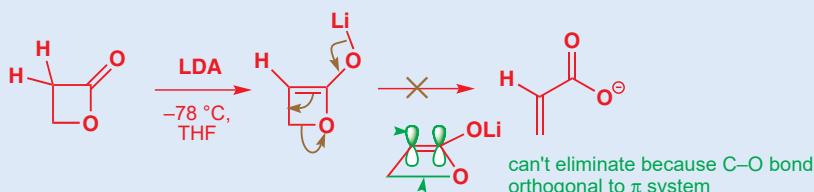
The enolate, as we have seen, is planar, and the phenyl group is in the plane (which is why it doesn't matter which of the two possible diastereoisomers of the starting material is used). The isopropyl group is the only thing out of the plane. The electrophile simply adds to the face of the enolate not blocked by the isopropyl group. This is a very simple case of a diastereoselective reaction.

### Lactone enolates

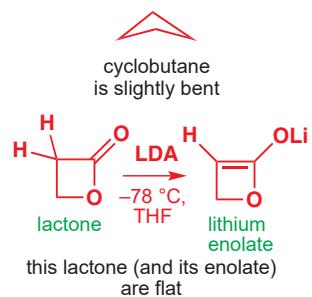
This lithium enolate works well even though it might be expected to be unstable because of a simple elimination reaction. In general, it is not possible to make open-chain lithium enolates with  $\beta$  oxygen substituents like this because they do undergo elimination.



But, in the four-membered ring, the p orbitals of the enolate and the C–O single bond are orthogonal (see diagram below) so that no interaction between them, and no elimination, can occur. In the terminology of Baldwin's rules (Chapter 31, p. 810) it would be a disfavoured 4-*endo*-trig reaction.



Reduction of substituted four-membered ring ketones is usually reasonably stereoselective. If the substituent is in the 3-position and small reagents like  $\text{NaBH}_4$  are used, the *cis* isomer is favoured. Like saturated four-membered rings, cyclobutanones are slightly puckered to reduce eclipsing interactions between hydrogen atoms on adjacent carbon atoms, but attack of the reducing agent still occurs from the direction away from the other substituent to give the *cis* product.

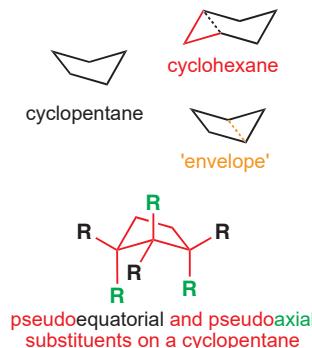


### Diastereoselective reactions of racemic compounds

The stereoselectivity we are discussing in this chapter is *diastereoselectivity*: we are not concerned with enantiomers and all of our discussions are equally valid whether the starting materials are racemic or enantiomerically pure. The product here, as in many other examples in the chapter, is racemic so we could write  $(\pm)$  underneath the structure. In this particular reaction, the starting material can be either of two diastereoisomers, but one of its chiral centres is lost on formation of the enolate.

### Five-membered ketones are flexible

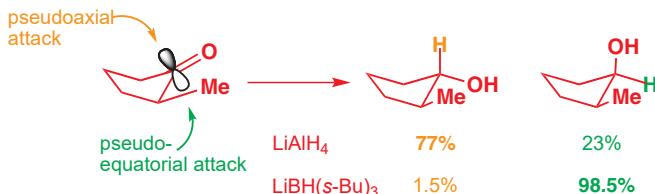
► We discussed this conformation and the consequences for NMR of its flexibility in Chapter 31, p. 817.



► We discussed the direction of attack on cyclohexanones on p. 826.

A saturated five-membered ring has a conformation often called an 'envelope'. It looks a bit like an opened envelope with one atom at the point of the flap. The arrangement closely matches what you get if you cut one atom out of a cyclohexane ring. At any one moment, one of the carbon atoms is at the point of the envelope but rapid ring flipping equilibrates all these conformers so that all five atoms are, on average, the same.

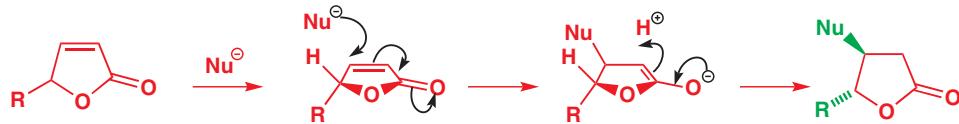
Substituted cyclopentanes can have substituents in pseudoaxial or pseudoequatorial positions (in other words, they are somewhat like the axial and equatorial positions in a cyclohexane), but rapid equilibration means that overall we have a very flexible and labile system. As a result, reduction of 2-substituted cyclopentanones may not be very stereoselective. What selectivity there is (about 3:1) in the reduction of 2-methylpentanone with  $\text{LiAlH}_4$  favours pseudoaxial attack in the conformation drawn, as is reasonable for a small nucleophile.



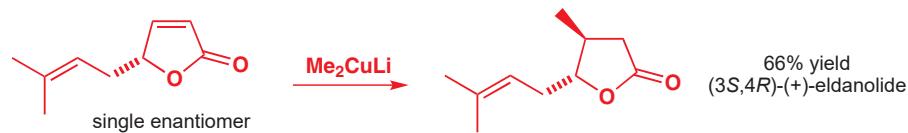
The use of a much more bulky reducing agent such as  $\text{LiBH}(s\text{-Bu})_3$  dramatically reverses and increases the stereoselectivity. Essentially only the *cis* compound is formed.

### Regard five-membered rings with two or more $\text{sp}^3$ carbons as flat

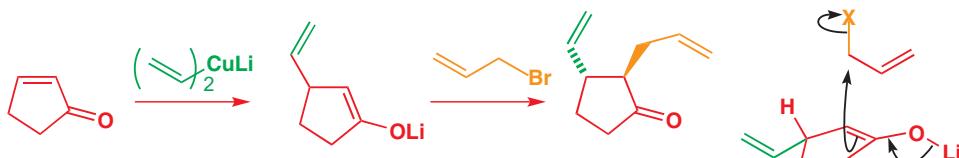
When there are two or three trigonal carbons in the ring, the ring is flatter and reactions such as enolate alkylation and conjugate addition give excellent stereoselectivity even with a simple cyclopentane ring. Unsaturated five-membered lactones (known as 'butenolides') give a very clear illustration of stereochemically controlled conjugate addition. There is only one possible stereogenic centre and the ring is almost planar so we expect nucleophilic attack to occur from the less hindered face. Cuprates are good nucleophiles for this reaction and here  $\text{Me}_2\text{CuLi}$  adds to the unsaturated lactone.



With a single enantiomer of the starting material below, the product is the single enantiomer of an insect pheromone.

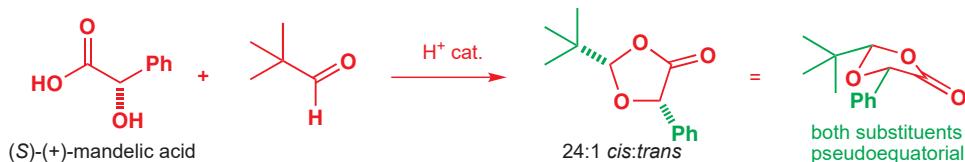


It is not even necessary to have a stereogenic centre in an unsaturated ring if we want to create stereochemistry. A tandem conjugate addition and alkylation creates two new stereogenic centres in one operation. The conjugate addition of a lithium cuprate makes a lithium enolate, which will react in turn with an alkyl halide. The product is usually *trans*.



The key step is the alkylation of the enolate intermediate. Enolates in five-membered rings are almost flat and the incoming orange allyl bromide prefers the less hindered face away from the recently added green vinyl group.

Our main example of enolate reactions in five-membered rings is one of some general importance. It illustrates how stereochemical information can be transmitted across a ring even though the original source of that information may be lost during the reaction. That may sound mysterious, but all will become clear. The first reaction is to make a five-membered cyclic acetal from an optically active hydroxy-acid. Our example shows (S)-(+)-mandelic acid reacting with *t*-BuCHO.

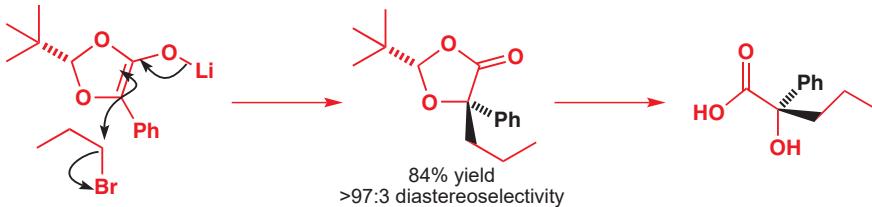


Acetal formation involves nucleophilic attack of the OH group on the aldehyde so there is no change at the stereogenic centre. The stereochemistry of the new (acetal) centre may surprise you—why should the *cis* isomer be so favoured? This is a conformational effect as both substituents can occupy pseudoequatorial positions.

Now, if we make the lithium enolate with LDA, the original stereogenic centre is destroyed as that carbon becomes trigonal and planar. The only stereogenic centre left is the newly introduced one at the acetal position.

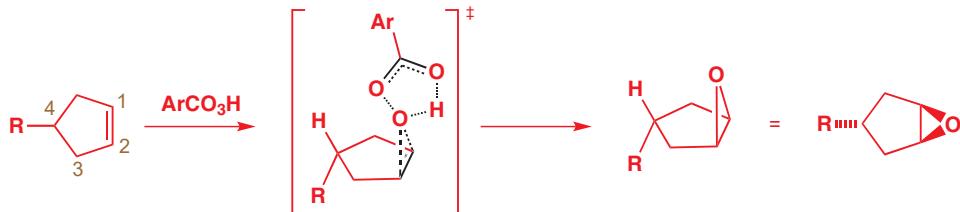


The ring is now essentially flat, owing to the C=C bond within it, and reaction of the enolate with an electrophile is again a simple matter of addition to the face of the enolate opposite to the *t*-butyl group.



If the acetal is now hydrolysed, the new stereogenic centre is revealed as an alkylated version of the starting material. It may appear that the alkylation has happened stereospecifically with retention, but what has really happened is that the new stereogenic centre in the acetal intermediate has relayed the stereochemical information through the reaction.

Five-membered rings also allow us to explore electrophilic attack on alkenes. A simple 4-substituted cyclopentene has two different faces—one on the same side as the substituent and one on the opposite side. Epoxidation with a peroxy-acid occurs preferentially on the less hindered face.



The conjugate addition forms a lithium enolate regiospecifically, and that was why you met this sequence in Chapter 25. We showed you a dramatic use of the stereoselectivity there as well, in a synthesis of a prostaglandin (p. 604).

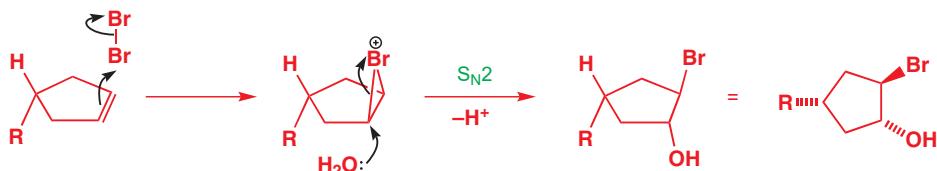
Check that you can write the mechanisms for acetal formation (Chapter 11). Acetal formation is under thermodynamic control so the product produced is the more stable.

► The mechanism of  $\text{RCO}_3\text{H}$  epoxidation was discussed on p. 430.

Note that this reaction is diastereoselective—but neither starting material nor products are chiral. Diastereoselectivity need have nothing to do with chirality!

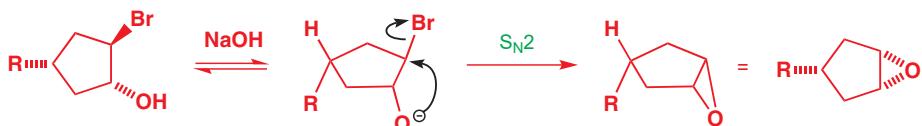
In the transition state (marked ♦) the peroxyacid prefers to be well away from R, even if R is only a methyl group (the selectivity is 76:24 with R=Me).

The opposite stereoselectivity can be achieved by bromination in water. The bromonium ion intermediate is formed stereoselectively on the less hindered side and the water is forced to attack stereospecifically in an S<sub>N</sub>2 reaction from the more hindered side.



You will spot that this reaction is no longer bimolecular because the nucleophile and leaving group are part of the same molecule. We still call it S<sub>N</sub>2 because the pathway of the mechanism is identical with a normal S<sub>N</sub>2 reaction. Substitution reactions were discussed in detail in Chapter 15.

Treatment of the product with base (NaOH) gives an epoxide by another S<sub>N</sub>2 reaction in which oxygen displaces bromide. This is again stereospecific and gives the epoxide on the same side as the R group.



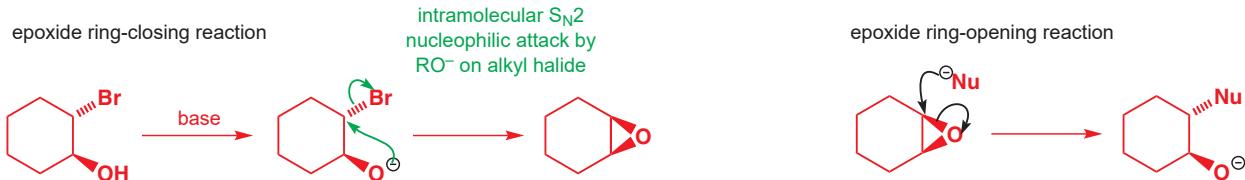
Two substituents on the *same side* of a five-membered ring combine to dictate approach from the other side by any reagent, and the two epoxides can be formed each with essentially 100% selectivity.

► N-Bromosuccinimide (NBS) acts as a source of electrophilic bromine: see Chapter 19, p. 441.



## Regiochemical control in cyclohexene epoxides

The two reactions above illustrate two important ways of making an epoxide. We are now going to look in a little more detail at what happens when epoxides are opened—a reaction that is essentially the reverse of the epoxide-closing reaction you have just seen. Here are both reactions with the epoxide fused to a cyclohexane ring:

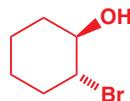


Epoxides can be formed from compounds containing an adjacent hydroxyl group and a leaving group by treatment with base. The epoxide formation is an intramolecular S<sub>N</sub>2 reaction, and as with any S<sub>N</sub>2 substitution, inter- or intramolecular, the incoming nucleophile must still attack into the σ\* orbital of the leaving group. And the only way that can happen, as you can see from the diagrams below, is (a) if the hydroxyl group and leaving group are *trans* to one another and (b) if the hydroxyl group and leaving group are both orientated axially. For the *trans* diastereoisomer, the groups can of course adopt either a diequatorial or a diaxial arrange-

ment (the diequatorial arrangement is favoured, as you saw in Chapter 16) but only the diaxial can react. The *cis* diastereoisomer cannot form an epoxide.

In Chapter 36 you will meet the alternative **rearrangement reactions** that occur if you try to force *cis* substituted compounds like these to react.

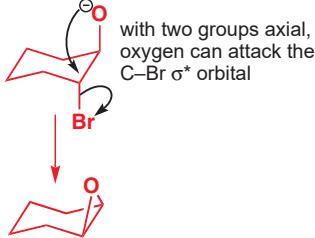
*trans*-2-bromocyclohexanol



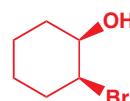
both groups equatorial



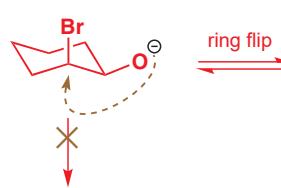
epoxide can't form because oxygen can't reach σ\* orbital



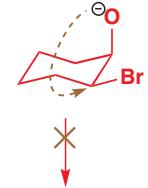
*cis*-2-bromocyclohexanol



Br axial, O<sup>−</sup> equatorial

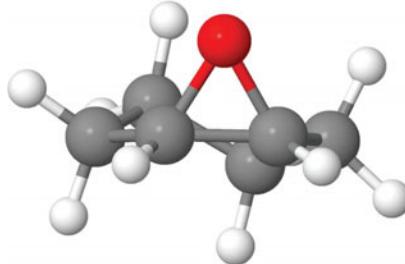


Br equatorial, O<sup>−</sup> axial



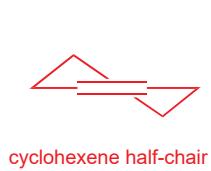
neither conformation can form an epoxide

How should we draw this epoxide fused to a six-membered ring? It is impossible for the CO bonds of the product epoxide ring to adopt perfectly axial and equatorial positions. If you make a model of cyclohexene oxide (as we can call this epoxide) you will see that the ring is a slightly deformed chair—in fact it is like the half-chair conformation of cyclohexene, in which four of the carbon atoms are in the same plane (you met this on p. 829).

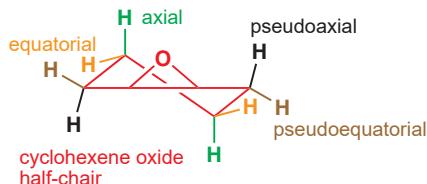


model of cyclohexene oxide

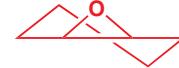
The usual way of drawing cyclohexene oxide is shown below: the distortion due to the three-membered ring changes the orientation of the axial and equatorial hydrogens next to the ring—they are **pseudoaxial** and **pseudoequatorial**. The hydrogens on the back of the ring (this part of the ring remains about the same as in the chair conformation) can be still considered as ‘normal’ axial and equatorial hydrogens.



cyclohexene half-chair

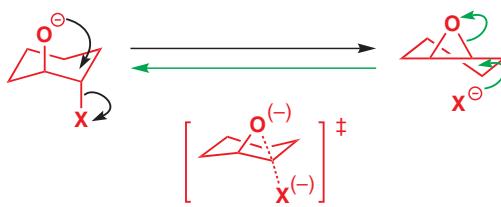


cyclohexene oxide half-chair



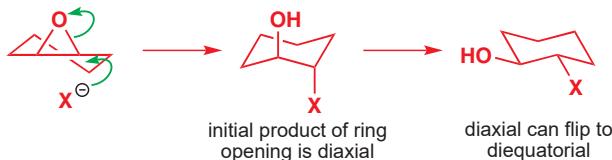
cyclohexene oxide half-chair showing skeleton only

You saw above that the epoxide-forming reaction is essentially the reverse of the epoxide-opening reaction. If we took a snapshot of the transition state for either reaction, we would not be able to tell whether it was the RO<sup>−</sup> that was attacking the C–X σ\* orbital to form the epoxide with X<sup>−</sup> as a leaving group, or a nucleophile X<sup>−</sup> attacking the C–O σ\* orbital of the epoxide to form a ring-opened alcohol. In other words, the transition state is the same for both reactions.



this transition state is the same for both formation and ring opening of the epoxide

Since ring closure is possible only when the starting material is diaxially substituted, this has to mean that ring opening is similarly possible only if the *product* is diaxial. This is a general principle: *ring opening of cyclohexene oxides always leads directly to diaxial products*. The diaxially substituted product may then subsequently flip to the diequatorial one, but it is always the one that is initially formed.



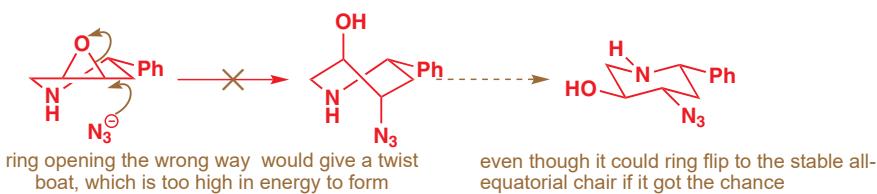
How do we know this to be true? If the ring bears a bulky substituent, ring flipping is impossible and the diaxial product has to stay diaxial. An example is nucleophilic attack of halide on the two epoxides shown below. The fact that the ring is a piperidine, rather than a cyclohexane, does not matter. The equatorial phenyl group fixes the conformation, and the regiochemistry of the epoxide opening with azide depends only on the relative stereochemistry of the starting material.



Points to note:

- The nucleophile must attack from the opposite side of the epoxide, allowing it to put electrons into the C–O  $\sigma^*$  orbital. This means that the nucleophile and hydroxyl group always end up *trans* in the product.
- The phenyl group locks the conformation of the epoxide. It stays equatorial, so we only have one epoxide conformation to consider in each case.
- In each case the epoxide opens only at the end that gives the diaxially substituted chair. Ring opening at the other end would still give a diaxially substituted product, but it is a diaxially substituted high-energy twist-boat conformation. The twist boat can, in fact, flip to give an all-equatorial product, but in a kinetically controlled

process such as this, it is the barrier to reaction that matters, not the stability of the final product.



### • Some general observations on stereo- and regioselectivity in six-membered rings:

- Six-membered rings which are not already a chair (such as cyclohexenes and cyclohexene oxides) react in such a way that they immediately become a chair.
- They do so by reacting from an axial direction: this may also dictate the *regioselectivity* of the reaction.
- Six-membered rings which are chairs already (such as cyclohexanones) remain a chair, and react from either the axial or equatorial direction according to the size of the attacking reagent.

## Stereoselectivity in bicyclic compounds

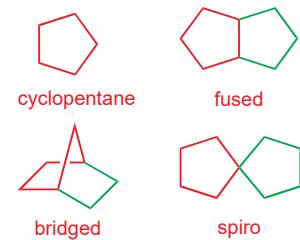
We have just looked at the way the reactivity of an epoxide gains additional subtleties when it is fused into a bicyclic structure with a six-membered ring. We're now going to look more generally at bicyclic compounds and their reactivity, and consider some features of their stereoselective reactions.

### Bridged bicyclic rings

There are broadly three kinds of bicyclic compounds. If we imagine adding a second five-membered ring to one already there, we could do this in a bridged, fused, or *spiro* fashion, as you see in the margin. Bridged bicyclic compounds are just what the name implies—a bridge of atom(s) is thrown across from one side of the ring to the other. Fused bicyclic compounds have one *bond* common to both rings, while *spiro* compounds have one *atom* common to both rings.

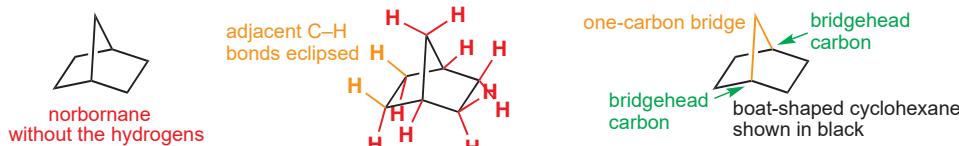
You will notice that these three types of bicyclic compounds with five-membered rings have different numbers of atoms added to a 'parent' five-membered ring. The bridged compound has two extra atoms, the fused compound three, and the spiro compound four. These are marked in green with the original five-membered ring in red. We shall consider stereoselectivity in each of these types of bicyclic ring systems, starting with bridged structures.

The bridged ring shown in the margin is known as norbornane: it's a simple but very important skeleton on which many other structures are based, and it's worth spending a moment learning how to draw it convincingly. The instructions in the box overleaf tell you how! Another way of looking at norbornane is as a six-membered ring held in a boat conformation by a one-carbon bridge. The bridge has to be axial at both bridgehead positions (or it wouldn't be able to form a ring) so the cyclohexane has no choice but to be a boat.



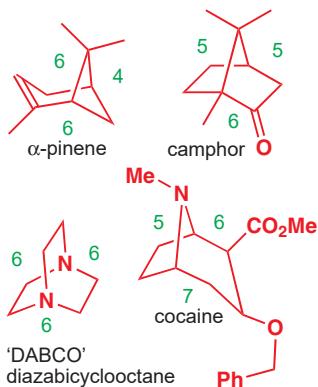
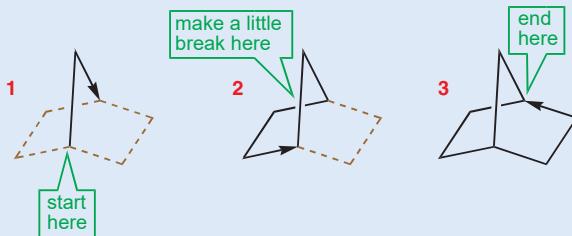
### Naming bicyclic compounds

As usual we shall not spend too long on nomenclature, but you may hear norbornane structures referred to as 'bicyclo[2.2.1]heptanes'. The 'bicyclo' and 'heptane' parts are self explanatory. The numbers (always separated by dots) refer to the lengths of the bridges linking the two bridgehead carbons. The other two compounds in the margin above are thus bicyclo[3.3.0]octane and spiro[4.4]nonane.



### How to draw norbornane structures

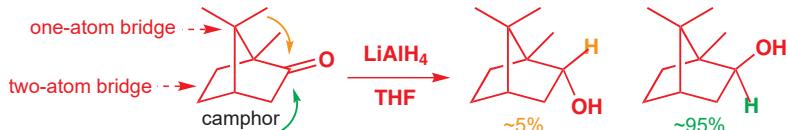
The easiest way to draw a convincing norbornane is to start with the bridge: draw a sort of skewed upwards chevron as shown in **1**. Then join the ends of the chevron with three bonds, as in **2**, making sure to break one of them as it passes behind the chevron, to give an impression of the three-dimensional shape of the molecule. Finally, link the second ring round to the right, **3**.



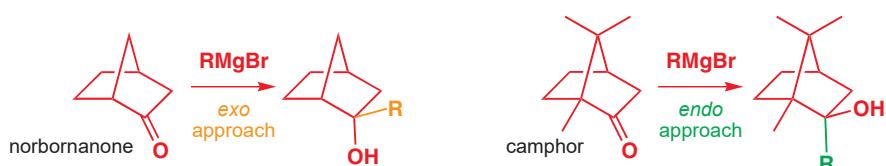
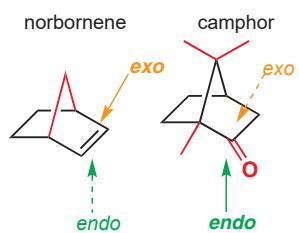
A selection of important bridged bicyclic compounds is shown in the margin. Bridged structures (sometimes called cage structures) are generally very rigid, spending most of their time in a single, well-defined conformation, and this rigidity is reflected in the stereochemistry of their reactions. For example, attack on norbornanone occurs predominantly from the side of the one-atom bridge (the green arrow) rather than the two-atom bridge (the orange arrow).



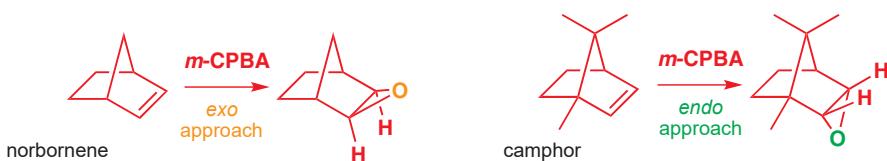
This selectivity is completely reversed in camphor because the one-atom bridge then carries two methyl groups. One of these must project over the line of approach of the hydride reducing agent.



The two methyl groups on the bridge of the camphor molecule are key features in stereo-selective reactions—take them away and the result often changes dramatically. This bicyclic system, with and without methyl groups, has been so widely used to establish stereochemical principles that the two faces of, say, the ketone group in camphor, or the C=C double bond in norbornene (the alkene derivative of norbornane) have been given the names *endo* and *exo*. These refer to inside (*endo*) and outside (*exo*) the boat-shaped six-membered ring shown in black. In general, reactions of norbornane-type structures occur from the less hindered *exo* face, but the methyl groups of camphor reverse this selectivity to favour *endo* attack:



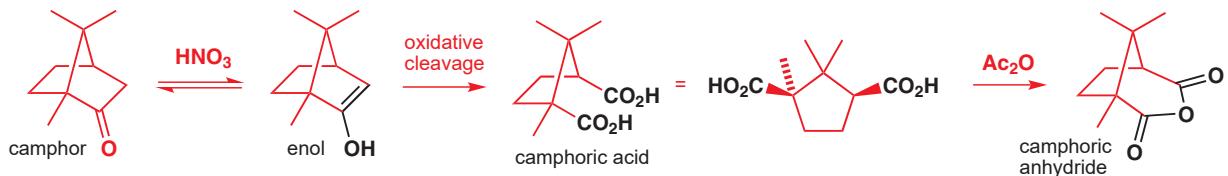
In a similar style, epoxidation of the two alkenes is totally stereoselective, occurring *exo* in norbornene and *endo* when methyl groups are present on the bridge. These stereoselectivities would be remarkable in a simple monocyclic compound, but in a rigid bridged bicyclic structure they are almost to be expected.



### Reactions that break open bridged molecules can preserve stereochemistry

Some powerful oxidizing agents are able to cleave C–C bonds. Oxidation of camphor with concentrated nitric acid cleaves a C–C bond adjacent to the C=O group and produces a diacid known as camphoric acid. The usual reagent is nitric acid ( $\text{HNO}_3$ ) and oxidation goes via camphor's enol.

► This is an unusual reaction; more common is cleavage of C=C bonds with ozone, as you saw in Chapter 19.

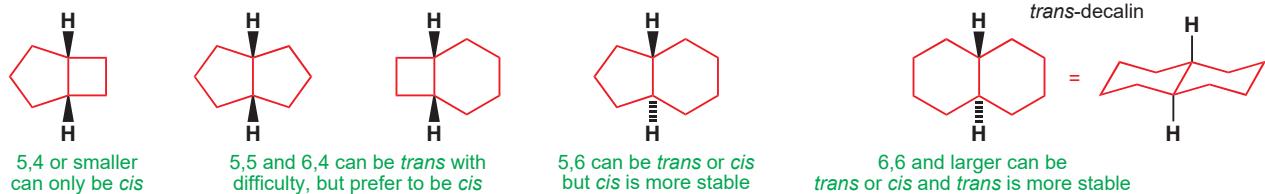


Because the bridge holds the molecule in a fixed conformation, the cleaved diacid has to have a specific stereochemistry. There is no change at the stereogenic centres, so the reaction must give retention of configuration. We can confidently write the structure of camphoric acid with *cis*- $\text{CO}_2\text{H}$  groups, but any doubt is dispelled by the ability of camphoric acid to form a bridged bicyclic anhydride.

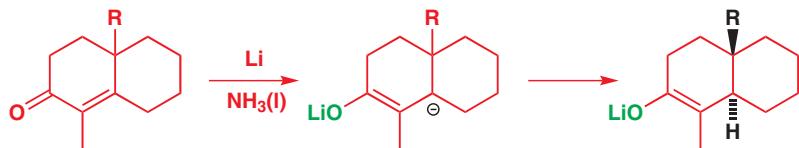
## Fused bicyclic compounds

### *trans*-Fused rings

The ring junction of a fused 6,5-membered ring system can have *cis* or *trans* stereochemistry, and so can any pair of larger rings. For smaller rings, *trans* 5,5- and 6,4-ring junctions can be made, with difficulty, but with smaller rings *trans* ring junctions are essentially impossible.

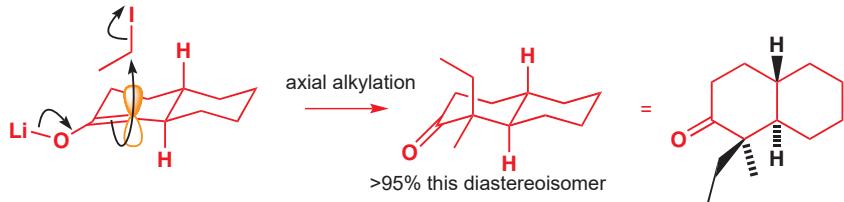


The *trans*-fused 6,6 systems—*trans*-decalins—have been very widely studied because they form an important part of the structure of steroids. Their conformation was discussed in Chapter 16: they prefer a *trans* ring junction as *trans*-decalins have all-chair conformations with every bond staggered from every other bond. We can show this by giving a 6,6 system the choice: reducing this enone with lithium metal gives a lithium enolate (Chapter 25). Protonation of this anion with the solvent (liquid ammonia) gives a *trans* ring junction.

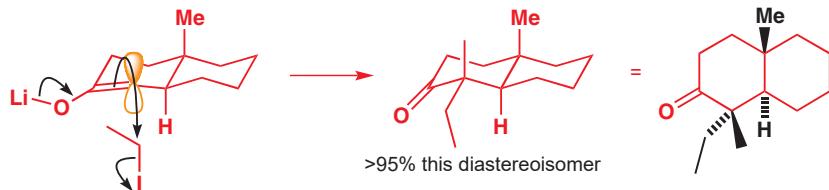


The lithium enolate remains and can be alkylated with an alkyl halide in the usual way. When there are hydrogen atoms at both ring junction positions, axial alkylation occurs just as you should now expect, and a new ketone with three stereogenic centres is formed with >95% stereoselectivity.

In this scheme, and the next, the methyl group attached at the yellow p orbital has been omitted for clarity.

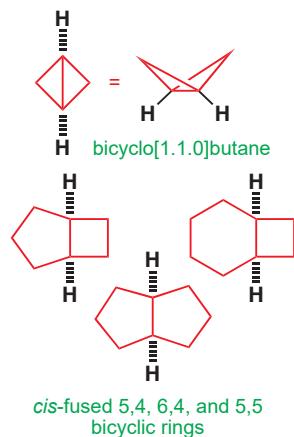


However, if there is anything else—even a methyl group—at the ring junction, so that axial approach would give a bad 1,3-diaxial interaction in the transition state, the usual stereoselectivity is overridden and the reaction switches to alkylation on the other face:



### cis-Fused rings

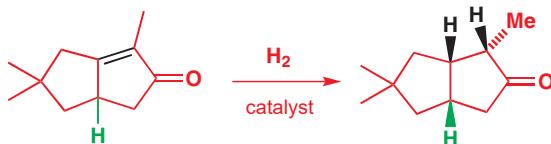
See the box on p. 839 for an explanation of the name bicyclo[1.1.0]butane.



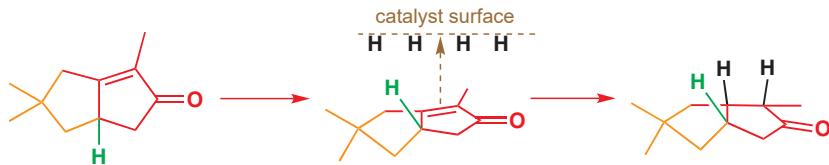
You met catalytic hydrogenation in Chapter 23. For a reminder of what **stereoselective** and **stereospecific** mean, see p. 396.

Almost any *cis*-fused junction from 3,3 upwards can be made. Even bicyclo[1.1.0]butane exists, although it is not very stable. *cis*-Fused 4,5, 4,6, and 5,5 systems are common and are much more stable than their *trans* isomers.

Any method of making such bicyclic compounds will therefore automatically form this stereochemistry. Consider this hydrogenation:

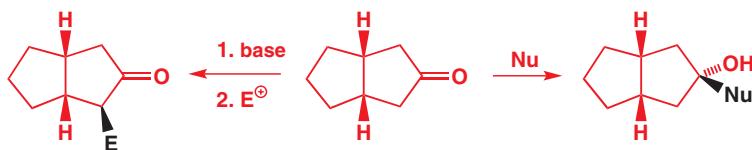


The two new hydrogen atoms (shown in black) must, of course, add *cis* to one another: this is a consequence of the stereospecificity of the reaction. What is interesting is that they have also added *cis* to the green hydrogen atom that was already there. This approach does give the more stable *cis* ring junction but the stereochemistry really arises because the other ring hinders approach to the other face of the alkene. Think of it in the way illustrated below: the alkene has two different faces. On one side there is the green hydrogen atom, and on the other the orange parts of the second ring. To get hydrogenated, the alkene must lie more or less flat on the catalyst surface and that is easier on the top face as drawn.

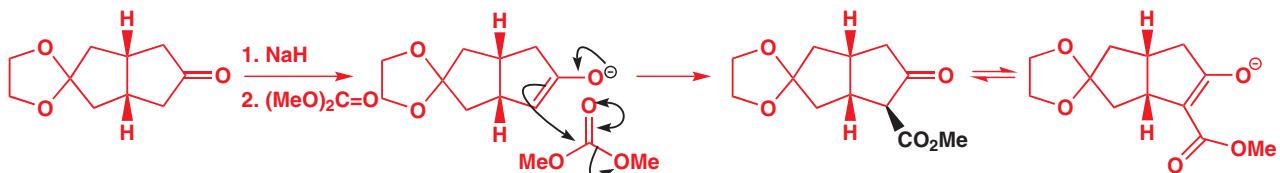


You can think of *cis*-fused rings as looking like a butterfly or an open book. The key to stereoselectivity in their reactions is that everything happens on the outside (on the cover of the book—the *exo* face). Nucleophiles add to carbonyl groups from the outside, enolates react with alkyl halides or Michael acceptors on the outside, and alkenes react with peroxyacids on the

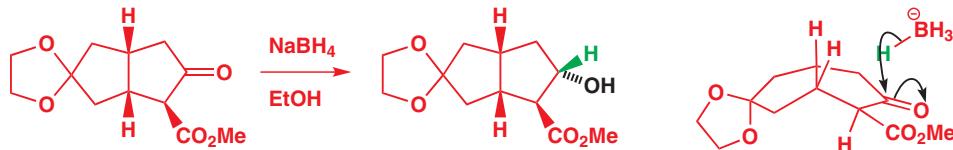
outside. Notice that this means the same side as the substituents at the ring junction. The rings are folded away from these ring-junction substituents, which are also on the outside.



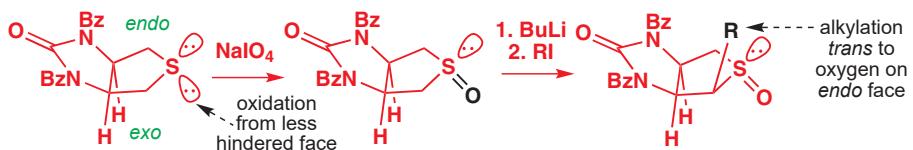
A real example comes in the acylation (Chapter 26) of the enolate from the keto-acetal below. The molecule is folded downwards and the enolate is essentially planar, so the outside face is the top face as drawn. Addition presumably occurs entirely from the outside, although the final stereochemistry of the product is controlled thermodynamically because of reversible enolization of the product, allowing the black ester group to adopt the less hindered outside position.



Reduction of the ketone product also occurs exclusively from the outside and this has the surprising effect of pushing the new OH group into the inside position. Attack from the inside is very hindered in this molecule because one of the acetal oxygen atoms is right on the flight path.

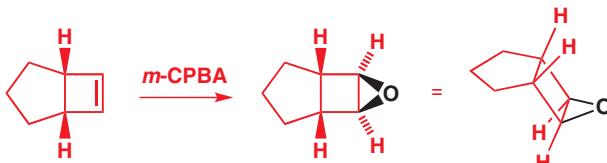


The important metabolite biotin has a *cis* bicyclic structure in which an alkyl chain lies on the more hindered face of the molecule, and any successful synthesis has to address this particular problem. You saw in Chapter 27 that sulfur stabilizes an adjacent anion, but the direct alkylation of the sulfide below is no good because the new alkyl group will go *exo*. Instead, the sulfide was oxidized to a sulfoxide from the *exo* face, giving an 8:1 ratio of *exo:endo* sulfoxides. Alkylation of the cyclic sulfoxide results in *trans* stereochemistry between the new alkyl group and the sulfoxide oxygen atom, forcing formation of the desired (*endo*) product. The synthesis is diastereoselective—but not enantioselective since there is no way of distinguishing the left and right sides of the symmetrical sulfoxide.



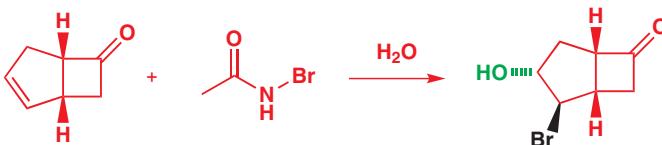
You will see in a moment more ways of forcing groups onto the inside face of bicyclic molecules.

A simple example of epoxidation occurs with a cyclobutene fused to a five-membered ring. This is a very rigid system and attack occurs exclusively from the outside to give a single epoxide in good yield.

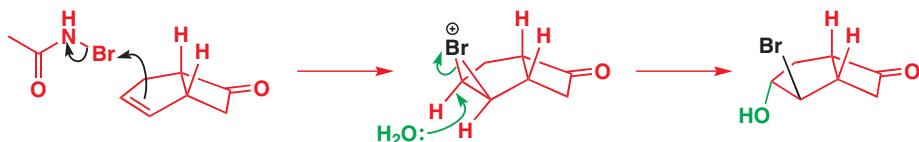


Epoxidation is stereospecific and *cis*—both new C–O bonds have to be on the same face of the old alkene. But Chapter 19 introduced you to several electrophilic additions to alkenes that were stereospecific and *trans*, many of them proceeding through a bromonium ion. If stereospecific *trans* addition occurs on a *cis*-fused bicyclic alkene, the electrophile will first add to the outside of the molecule, meaning the nucleophile will then be forced to add from the inside. A telling example occurs when the 5,4 fused unsaturated ketone below is treated with *N*-bromoacetamide in water.

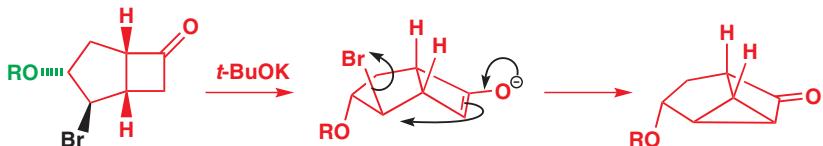
■ *N*-Bromoacetamide, like NBS (p. 836), simply provides Br<sub>2</sub> in low concentration.



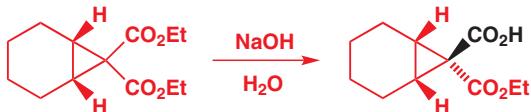
The bromonium ion is formed on the outside of the rigid structure and the water is then forced to add from the inside to get *trans* addition. As well as exhibiting stereospecificity (*trans* addition) and stereoselectivity (bromonium forms on outside), this reaction also exhibits regioselectivity in the attack of water on the bromonium ion. Water must come from inside, and it attacks the less hindered end of the bromonium ion.



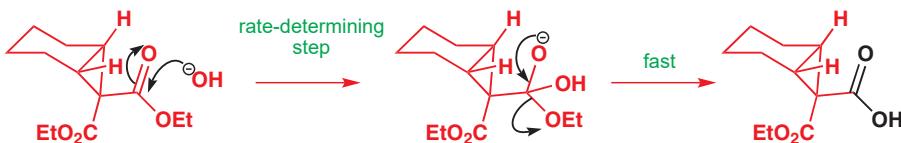
After protection of the OH group, treatment with base closes a three-membered ring to give a remarkably strained molecule. The ketone forms an enolate and the enolate attacks the alkyl bromide intramolecularly to close the third ring. This enolate is in just the right position to attack the C–Br bond from the back, precisely because of the folding of the molecule.



Inside/outside selectivity may allow the distinction between two otherwise similar functional groups. The *cis*-fused bicyclic diester below may look at first rather symmetrical but ester hydrolysis leaves one of the two esters alone while the other is converted to an acid.

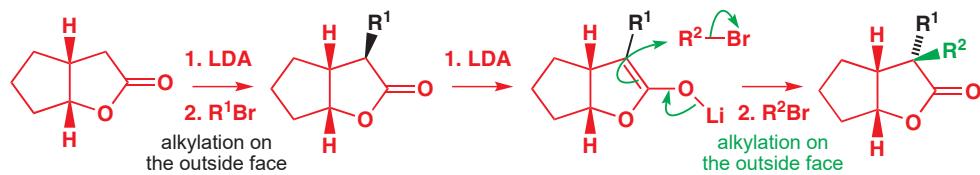


Only the outside ester—on the same side as the ring junction hydrogens—is hydrolysed. In the mechanism for ester hydrolysis, the rate-determining step is the attack by the hydroxide ion so the functional group *increases* in size in the rate-determining step. This will be much easier for the ester in the outside than for the one inside the half-open book.



The end result is again that the larger of the two groups is on the inside! There are other ways to do this too. If we alkylate the enolate of a bicyclic lactone, the alkyl group (black) goes on

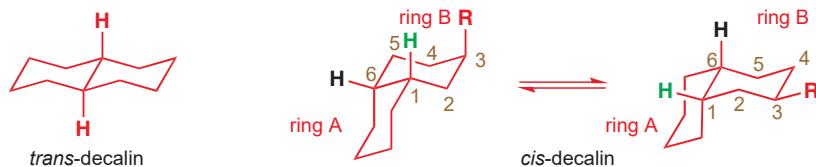
the outside as expected. But what will happen if we repeat the alkylation with a different alkyl group? The new enolate will be flat and the stereochemistry at the enolate carbon will be lost. When the new alkyl halide comes in, it will approach from the outside (green) and push the alkyl group already there into the inside.



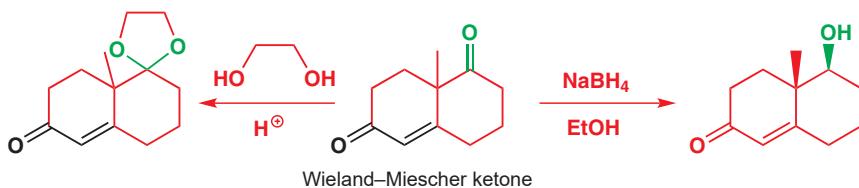
Should you wish to reverse the positions of the two groups, you simply add them in the reverse order. Whichever group is added first finishes on the inside; the other finishes on the outside.

### Reactions of *cis*-decalins

You saw in Chapter 16 that while *trans*-decalins are rigid, *cis*-decalins can flip rapidly between two all-chair conformations. During the flip, all substituents change their conformation. The substituent R is axial on ring B in the first conformation of *cis*-decalin shown below but equatorial in the second. The ring junction Hs are always axial on one ring and equatorial on the other. The green hydrogen is equatorial on ring A and axial on ring B in the first conformation and vice versa in the second. Of course, they are *cis* in both. Because R gets equatorial, the second conformation is preferred in this case.

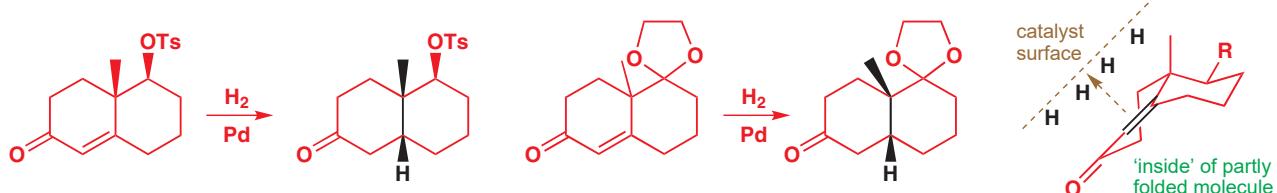


A standard reaction that gives substituted decalins is the Robinson annelation (Chapter 26). A Robinson annelation product available in quantity is the keto-enone known sometimes as the **Wieland–Miescher ketone** and used widely in steroid synthesis. The non-conjugated keto group can be protected or reduced without touching the more stable conjugated enone.

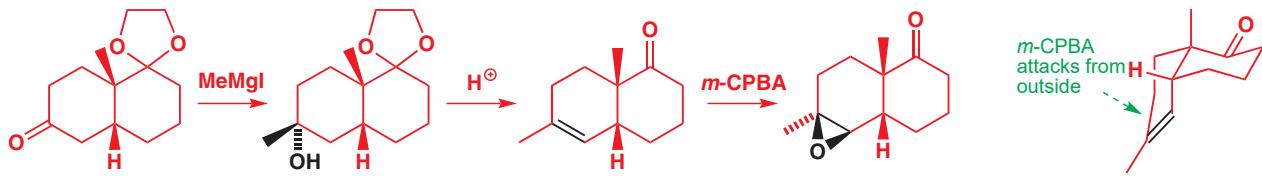


► The synthesis of this ketone can be found in Chapter 26, p. 638.

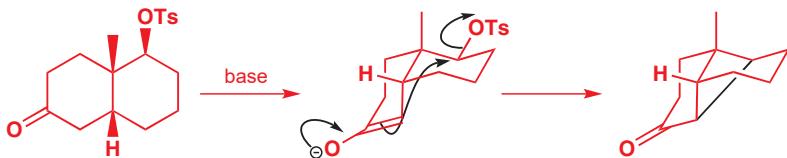
If either of these products is reduced with hydrogen and a Pd catalyst (the alcohol is first made into a tosylate), the *cis*-decalin is formed because the enone, although flattened, is already folded to some extent. A conformational drawing of either molecule shows that the top surface is better able to bind to the flat surface of the catalyst.



Each of these products shows interesting stereoselective reactions. The ketal can be converted into an alkene by Grignard addition and E1 elimination, and then epoxidized. Everything happens from the outside as expected, with the result that the methyl group is forced inside at the epoxidation stage.

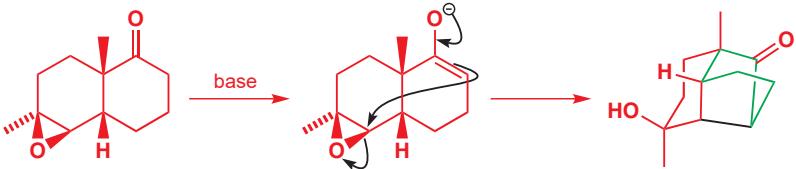


Treatment of the other product, the keto-tosylate, with base leads to an intramolecular enolate alkylation—a cyclization on the inside of the folded molecule that actually closes a four-membered ring. The reaction is easily seen in conformational terms and the product cannot readily be drawn in conventional diagrams.



A similar reaction happens on the epoxide to produce a beautiful cage structure. This time it is a five-membered ring that is formed, but the principle is the same—the molecule closes across the fold rather easily. The new stereogenic centres can only be formed with this configuration: no other stereoisomer would be a feasible structure.

■ Notice how the ring in green has to go into a boat conformation for cyclization to be possible. This is unfavourable but still better than any intermolecular reaction.



#### ● A summary of stereoselective reactions that occur on *cis*-fused rings

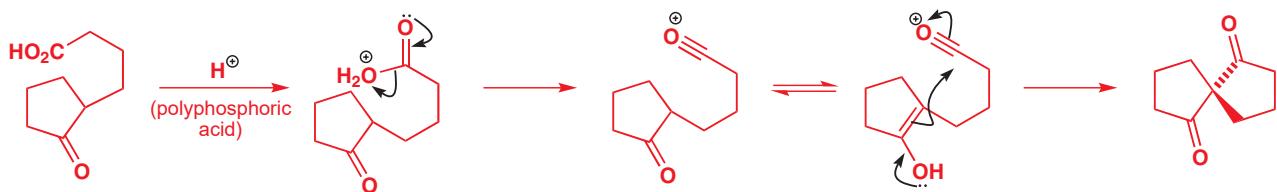
- 1 Reactions on the outside.
  - Nucleophilic additions to carbonyl groups in the ring.
  - Reactions of enolates of the same ketones with electrophiles: alkyl halides, aldols, Michael additions.
  - *cis*-Additions to cyclic alkenes: hydrogenation, hydroboration, epoxidation.
- 2 Reactions on the outside and then the inside.
  - *trans*-Additions to cyclic alkenes: bromination, epoxidation, and epoxide opening.
- 3 Reactions on the inside.
  - Bond formation across the ring(s).

## Spirocyclic compounds

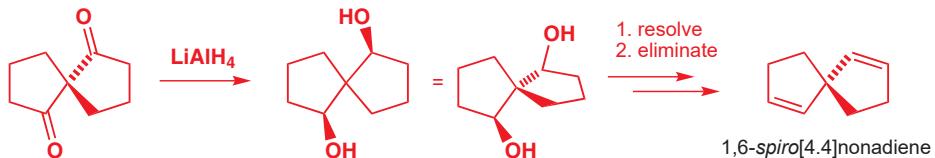


Spirocyclic rings meet at one single atom. This means that the two rings are orthogonal about the tetrahedral atom that is common to both. Even symmetrical-looking versions are unexpectedly chiral. The compound in the margin, for example, is not superimposable on its mirror image, and its symmetry is similar to that of an allene (see Chapter 14).

These sorts of compounds may look rather difficult to come by, but some simple ones are readily made. Cyclization of this keto-acid with polyphosphoric acid leads to a spirocyclic diketone. The *spiro* compound is formed because the more substituted enol is preferred in acid solution.



It is much more difficult to pass stereochemical information from one ring to the other in spirocyclic compounds because of the orthogonality of the rings. Still, some reactions are surprisingly stereoselective—one such is the reduction of the spirocyclic diketone that we made a moment ago. Treatment with  $\text{LiAlH}_4$  gives one diastereoisomer of the spirocyclic diol.



The diol can be resolved and used to make the very simple spiro-diene as a single enantiomer. The diene is chiral even though it has no chiral centre because it does not have a plane of symmetry.

In Chapter 14 we explained that planes of symmetry, not chiral centres, are the things to look for when deciding whether or not a compound is chiral.

## Reactions with cyclic intermediates or cyclic transition states

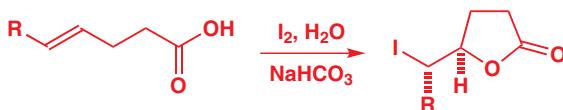
Rings are so good at controlling stereochemistry (as you have seen) that it's well worth introducing them where they are not really necessary in the final product, simply in order to enjoy those high levels of stereochemical control. In the rest of this chapter we shall consider the use of temporary rings in stereochemical control: these might be cyclic intermediates in a synthetic pathway, or cyclic reaction intermediates, or even merely cyclic transition states. All aid good stereocontrol. We shall concentrate on examples where the ring reverses the normal stereoselectivity so that some different result is possible.

### Tethered functional groups can reach only one side of the molecule

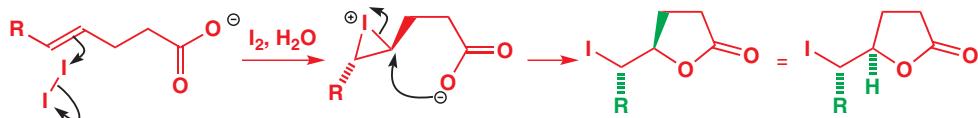
The proverbial donkey starved to death in the field with two heaps of hay because it could not decide which one to go for first. If the donkey had been tethered to a stake near one heap it would have been able to reach that heap alone and it could have feasted happily.

This principle can be applied to molecules. If a nucleophile is joined to the group it is to attack by a short chain of covalent bonds, it may be able to reach only one side. We can illustrate this idea with a reaction you met in Chapter 24: iodolactonization. To remind you, iodolactonization involves treating a non-conjugated unsaturated acid with iodine in aqueous  $\text{NaHCO}_3$ . The product is an iodolactone.

→ Iodolactonization is described on p. 569.



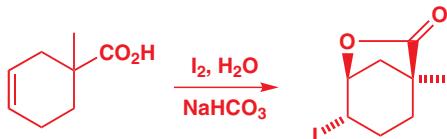
The cyclization reaction is a typical two-stage electrophilic addition to an alkene (Chapter 19) with attack by the nucleophile at the more substituted end of the intermediate iodonium ion. The ring opening is a stereospecific  $\text{S}_{\text{N}}2$  and the stereochemistry of the alkene will be reproduced in the product.



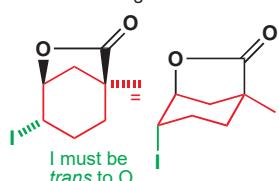
The starting acid contains an *E* alkene, giving a *trans* iodonium ion. Inversion occurs in the attack of the carboxylate anion on the iodonium ion and we have shown this by bringing the nucleophile in at 180° to the leaving group, with both bonds in the plane of the paper. A single diastereoisomer of the iodolactone results from a stereospecific reaction.

Things get more interesting again when the starting material is cyclic. The iodolactonization below gives only one diastereoisomer.

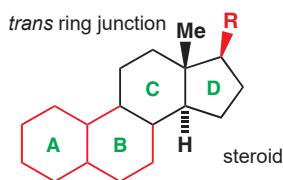
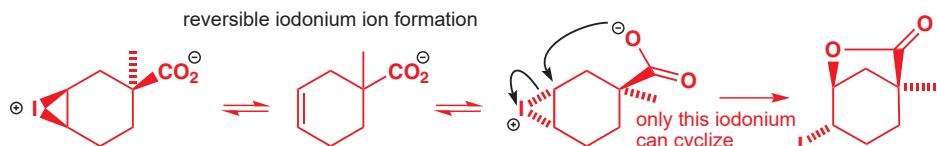
■ Chapter 34 describes how to make the unsaturated six-membered starting material.



bridge must be diaxial



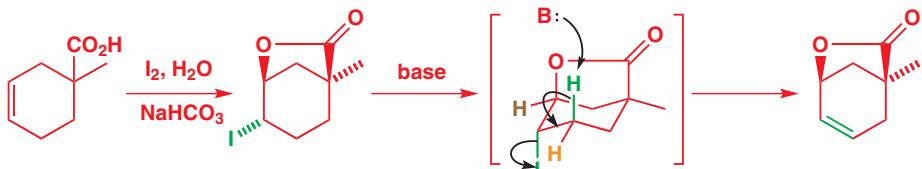
The relationship between the two stereogenic centres on the old alkene is not an issue—involution during opening of the iodonium ion means that the I and the O must lie *trans*. But during the cyclization the carboxylic acid can attack only the nearer side of what was the double bond—in other words the bridge in black has no choice but to be *cis* across the red six-membered ring. The reason for this is that, while formation of the iodonium ion is reversible, only the iodonium ion with the I and CO<sub>2</sub>H groups *trans* to each other can cyclize. Tethering the nucleophilic CO<sub>2</sub>H group to the alkene dictates the stereochemistry of the product.



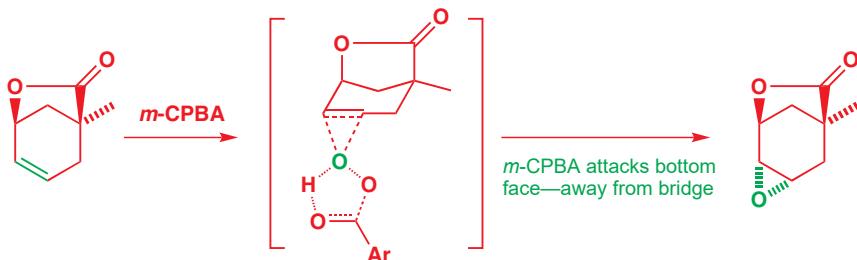
► The impossibility of bridgehead alkenes is mentioned in Chapter 17.

This reaction can be used to solve a general problem in the synthesis of steroids: the construction of a diketone with *trans*-fused 6,5 rings and a quaternary carbon atom at the ring junction. One solution to this problem uses the lactone just made.

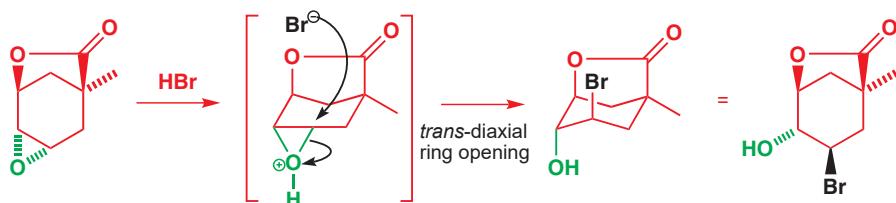
The lactone makes a good temporary tether because it can be hydrolysed or reduced to break the ring at the C–O bond and reveal new stereogenic centres on the old structure. In this sequence the lactone ring controls all the subsequent stereochemistry of the molecule in two ways: it fixes the conformation rigidly in one chair form—hence forcing the iodide to be axial—and it blocks one face of the ring. From the lactone above, an alkene is introduced by E2 reaction on the iodide. This stereospecific reaction requires an anti-periplanar H atom so it has to take the only available neighbouring axial hydrogen atom, shown in green. The brown and orange hydrogens are not anti-periplanar and anyway elimination with the brown one would produce a bridgehead alkene.



The resulting alkene has its top face blocked by the lactone bridge so epoxidation occurs entirely from the bottom face.



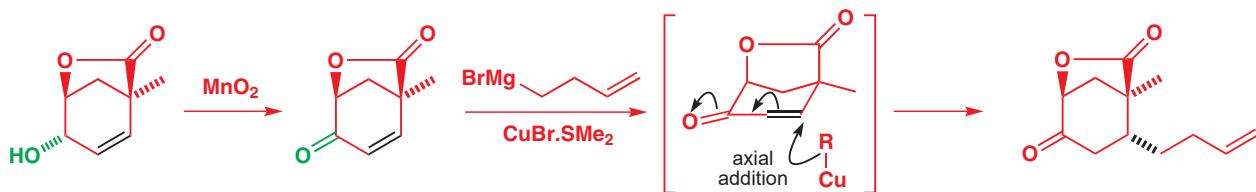
Now the epoxide is opened with HBr. Only the *trans* diaxial opening product is possible, so the bromide ion is forced to attack from the top face.



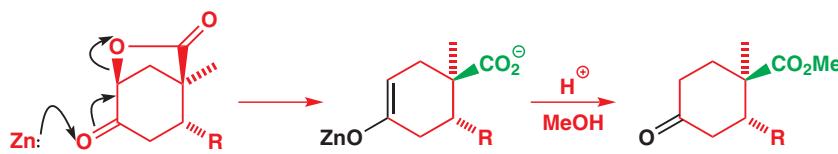
Do you see how the functional groups are being pushed round the ring? This process is extended further by a second elimination, after protection, which again seeks out the only neighbouring axial hydrogen.



The protecting silyl group is removed in acid, ready for the next important reaction: a Michael addition requiring the alcohol to be oxidized to a ketone. Allylic (or benzylic) alcohols can be oxidized by manganese dioxide, and with three atoms now trigonal the ring becomes even further flattened. But-3-enyl Grignard reagent is added with Cu(I) catalysis to make sure that conjugate addition occurs. Conjugate addition normally gives the axial product, as we saw earlier, and fortunately this is not the direction blocked by the bridge.

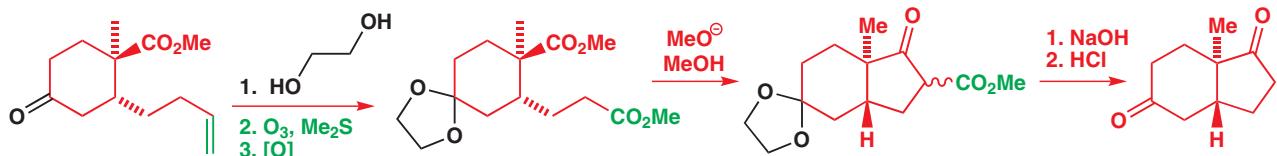


The bridge has now done its work and is removed by zinc metal reduction. This reaction removes leaving groups on the atoms next to carbonyl groups. In this case it is the axial carboxylate that is driven out by the zinc. The released carboxyl group is esterified.



This may look like a new reaction but think back to the Reformatsky reaction (Chapter 26, p 631). Both form zinc enolates from carbonyl compounds with adjacent leaving groups.

The last stages are shown below. The ketone is protected, and the alkene oxidized to a carbonyl group by ozonolysis (Chapter 19). The diester can be cyclized by a Claisen ester condensation (Chapter 26). The stereogenic centres in the ring are not affected by any of these reactions so a *trans* ring junction must result from this reaction. After ester hydrolysis, HCl decarboxylates the product and removes the protecting group.



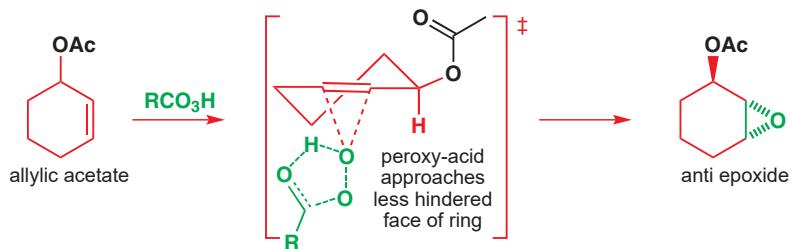
It is not easy to set up a *trans*-fused 5,6 system. In this sequence the molecule is effectively tricked into making the *trans* ring junction by the work done with the lactone tether.

### Cyclic transition states can reverse normal stereoselectivity

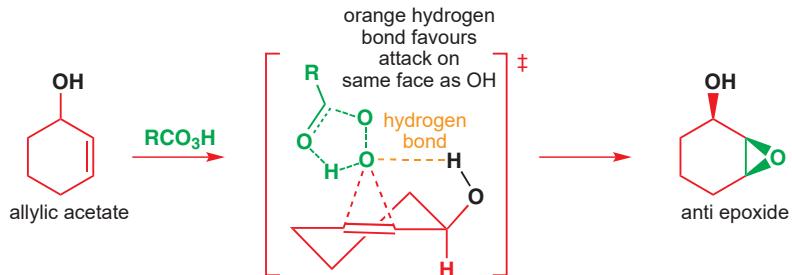
Formation of a ring in an intermediate is a means of enforcing a certain stereochemistry—the example you have seen made use of a lactone. But even transient formation of a ring in a cyclic transition state can be enough to control stereochemistry highly effectively. You will see further examples in the next chapter, but here we just present one type of reaction with this property: epoxidation.

Of course epoxidation reactions *form* rings, and you have seen examples of epoxidations with *m*-CPBA even in this chapter (p. 848) of alkenes such as cyclohexene. We pointed out in Chapter 19 that epoxidation is stereospecific because both new C–O bonds form to the same face of the alkene.

If we block one face of the ring with a substituent—even quite a small one, such as an acetate group—epoxidation becomes stereoselective for the face *anti* to the substituent already there.



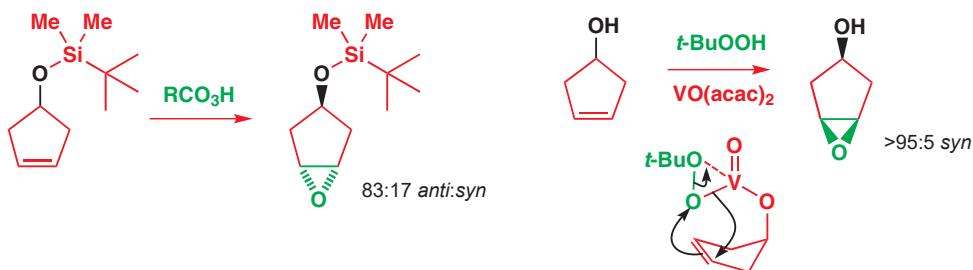
But there is one important exception to this rule, when the substituent is a hydroxyl group. When an allylic alcohol is epoxidized, the peroxy-acid attacks the face of the alkene *syn* to the hydroxyl group, even when that face is more crowded. For cyclohexenol the ratio of *syn* epoxide to *anti* epoxide is 24:1 with *m*-CPBA and it rises to 50:1 with  $\text{CF}_3\text{CO}_3\text{H}$ .



The reason is shown in the transition state: the OH group can hydrogen bond, through the H of the alcohol, to the peroxy-acid, stabilizing the transition state when the epoxidation is occurring *syn*. This hydrogen bond means that peroxy-acid epoxidations of alkenes with adjacent hydroxyl groups are much faster than epoxidations of simple alkenes, even when no stereochemistry is involved.

Peroxy-acids work for epoxidizing allylic alcohols *syn* to the OH group, but another reagent is better when the OH group is further from the alkene. 4-Hydroxycyclopentene, for example, can be converted into either diastereomer of the epoxide. If the alcohol is protected with a large group such as TBDMS (*t*-butyl-dimethylsilyl), it becomes a simple blocking group and the epoxide is formed on the opposite face of the alkene. The selectivity is reasonable (83:17) given that the blocking group is quite distant. But if the OH group is not blocked at all but left free, and the epoxidation reagent is the vanadium complex  $\text{VO}(\text{acac})_2$  combined with *t*-BuOOH, the *syn* epoxide is formed instead. The vanadyl group chelates reagent and alcohol, and delivers the reactive oxygen atom to the same face of the alkene as shown.

▶ See p. 430 for this discussion.



In both epoxidation examples, the stereoselectivity is due to the cyclic nature of the transition state: the fact that there is a hydrogen bond or O–metal bond ‘delivering’ the reagent to one face of the alkene. Effectively we have moved on from the tethered *nucleophiles* of the last section to (transiently) tethered *reagents*. This is a very important concept, and we revisit it in the next chapter: cyclic transition states are the key to getting good stereoselectivity in reactions of acyclic compounds.

### VO(acac)<sub>2</sub>

Vanadyl (acac)<sub>2</sub> is a square pyramidal complex of two molecules of the enolate of ‘acac’ (acetyl acetone, pentan-2,4-dione) and the vanadyl (V=O) dication. It can easily accept another ligand to form an octahedral complex so there is plenty of room for the alcohol to add and for the t-BuOOH to displace one of the ‘acac’ ligands to give some complex with the essential ingredients for the reaction here.

## To summarize...

Diastereoselectivity in rings generally follows a few simple principles:

- Flattened three-, four-, or five-membered rings, especially ones with two or more trigonal carbons in the ring, are generally attacked from the less hindered face.
- Flattened six-membered rings with two or more trigonal carbons in the ring (that is, which are not already a chair—so six-membered rings with one trigonal C atom don’t count here) react in such a way that the product becomes an axially substituted chair.
- Bicyclic compounds react on the outside face.
- Reaction on the more hindered face can be encouraged by: (1) tethered nucleophiles or (2) cyclic transition states (tethered reagents).

Diastereoselectivity in compounds without rings is different: it is less well controlled because there are many more conformations available to the molecule. But even in acyclic compounds rings can still be important, and some of the best diastereoselectivities arise when there is a ring formed temporarily in the transition state of the reaction. With or without cyclic transition states, in some cases we have good prospects of predicting which diastereoisomer will be the major reaction product, or explaining the diastereoselectivity if we already know this. That is the subject of the next chapter.

■ Another reaction in which an allylic alcohol is extremely effective at delivering a reagent via a cyclic transition state is the cyclopropanation reaction known as the Simmons–Smith reaction, described on p. 1017.

## Further reading

Oxford Primers by A. J. Kirby, *Stereoelectronic effects*, OUP, Oxford, 1996, and M. Grossel, *Alicyclic Chemistry*, OUP, Oxford, 1997 are relevant. The most comprehensive text is E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley Interscience, New York, 1994.

The elegant work of Jeffrey Aubé, describing the selective formation of substituted piperidines by control of their conformation, is in *Angew. Chem. Int. Ed.* 2011, **50**, 2734.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book’s Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 33

## 非对映选择性

### 联系

#### → 基础

- Nucleophilic attack on the C=O group [ch6](#)
- Stereochemistry [ch14](#)
- Conformation [ch16](#)
- Controlling alkene stereochemistry [ch27](#)
- Stereoelectronics [ch31](#)
- Stereochemistry in rings [ch32](#)

#### 目标

- How to make single diastereoisomers from geometrical isomers
- How to predict and explain reactions of chiral carbonyl compounds
- How chelation to metal ions can alter stereoselectivity
- How to predict and explain the reactions of chiral alkenes
- Stereoselective aldol reactions
- Using naturally derived compounds to make single enantiomers

#### → 展望

- Asymmetric synthesis [ch41](#)
- Organic chemistry of life [ch42](#)
- Organic chemistry today [ch43](#)

## Looking back

You have had two chapters in a row about stereochemistry: this is the third, and it is time for us to bring together some ideas from earlier in the book. We aim firstly to help you grasp some important general concepts and secondly to introduce some principles in connection with stereoselective reactions in acyclic systems. But, first, some revision.

We introduced the stereochemistry of structures in Chapter 14. We told you about two types of stereoisomers.

### ● Enantiomers and diastereoisomers

- **Enantiomers**—stereoisomers that are mirror images of one another.
- **Diastereoisomers**—stereoisomers that are not mirror images of one another.

In this chapter we shall talk about how to make compounds as single *diastereoisomers*. Making single *enantiomers* is treated in Chapter 41. Chapter 32 was also about making single diastereoisomers, and we hope that, having read that chapter, you are used to thinking stereochemically. We shall meet two different ways of making single diastereoisomers.

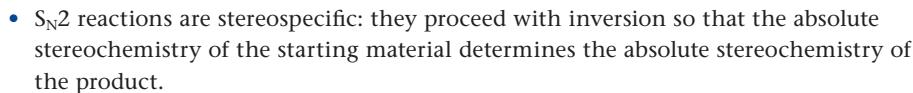
### ● Reactions that make single diastereoisomers

- **Stereospecific reactions**—reactions where the mechanism means that the stereochemistry of the starting material determines the stereochemistry of the product and there is no choice involved.
- **Stereoselective reactions**—reactions where one stereoisomer of product is formed predominantly because the reaction has a choice of pathways, and one pathway is more favourable than the other.

These terms were introduced in Chapter 17 in connection with elimination reactions, and many of the reactions we mention will be familiar from earlier chapters (particularly Chapters 15–19, 25, and 26). A common misapprehension is that stereospecific means merely very stereoselective. It doesn't—the two terms describe quite different properties of the stereochemistry of a reaction. For the purposes of making a single diastereoisomer, you can think of stereospecific reactions as ones which simply exchange different forms of stereochemical 'currency' (double bond geometry and three-dimensional relative stereochemistry, for example) while stereoselective reactions create additional new stereochemical value.

### Making single diastereoisomers using stereospecific reactions of alkenes

The essence of the definition we have just stated is much easier to grasp with some familiar examples. Here are two.



► This is discussed in Chapter 15, p. 344.



- E2 reactions are stereospecific: they proceed through an anti-periplanar transition state, with the relative stereochemistry of the starting material determining the geometry of the product.

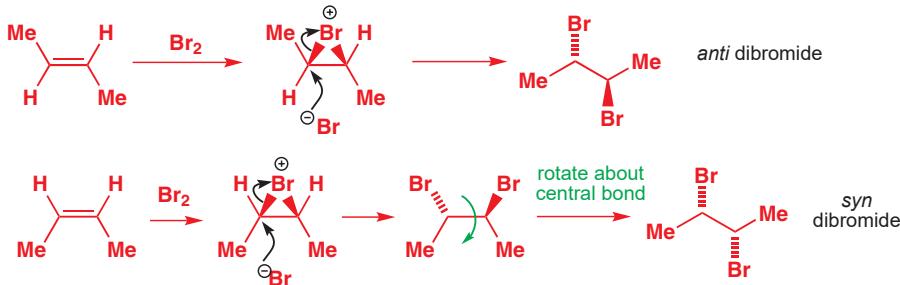
► This is discussed in Chapter 17, p. 395.



Both of these examples are interesting because they show how, once we have some stereochemistry in a molecule, we can change the functional groups but keep the stereochemistry—this is the essence of a stereospecific reaction. In the second example, we change the bromide to a double bond, but we keep the stereochemistry (or 'stereochemical information') because the geometry of the double bond tells us which bromide we started with.

This is a good place to begin if we want to make single diastereoisomers because we can reverse this type of reaction: instead of making a single geometry of alkene from a single diastereoisomer, we make a single diastereoisomer from a single geometry of double bond. Here is an example of this—again, one you have already met (Chapter 19). Electrophilic addition of bromine to alkenes is stereospecific and leads to *anti* addition across a double bond. So if we want the *anti* dibromide we choose to start with the *trans* double bond; if we want the *syn* dibromide we start with the *cis* double bond. The geometry of the starting material determines the relative stereochemistry of the product.

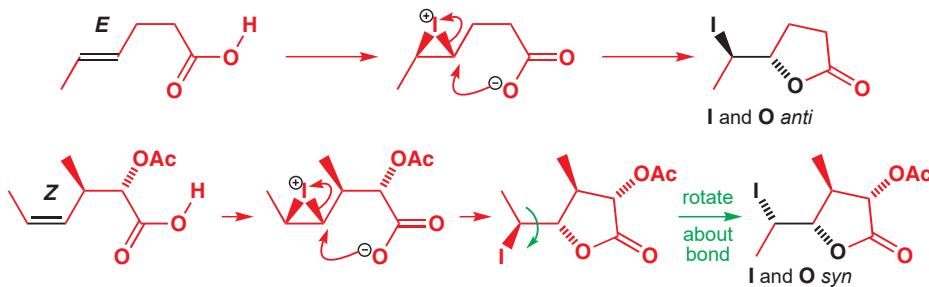
► Chapter 27 described the methods available for controlling the geometry of double bonds.



► Interactive mechanism for stereospecific *anti* addition to alkenes

Iodolactonization has a similar mechanism; notice how in these two examples the geometry of the double bond in the starting material defines the relative stereochemistry highlighted in black in the product.

There are two more stereogenic centres in the second example here and, although they do not affect the relative stereochemistry shown in black, they do affect how those two new stereogenic centres relate to the two that are already present in the starting material. We discuss how later in the chapter.



For a stereospecific alkene transformation, choose the right geometry of the starting material to get the right diastereoisomer of the product. Don't try to follow any 'rules' over this—just work through the mechanism.

Now for some examples with epoxides. Epoxides are very important because they can be formed stereospecifically from alkenes: *cis* alkenes give *cis* (or *syn*) epoxides and *trans* alkenes give *trans* (or *anti*) epoxides.

Formation and reaction of epoxides are described in Chapter 19, p. 429 and Chapter 15, p. 351.



Epoxides also react stereospecifically because the ring-opening reaction is an  $S_N2$  reaction. A single diastereoisomer of epoxide gives a single diastereoisomer of product.



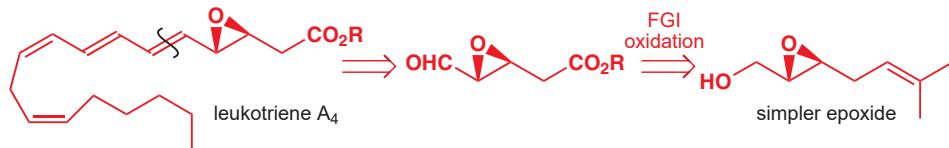
### Leukotrienes

Leukotrienes are metabolites of arachidonic acid related to prostaglandins and thromboxanes. They are made in nature (and often in the laboratory) by oxidation of alkenes. The letter (e.g. A) gives the general structure and the subscript number the number of alkenes. They are unstable and control localized physiological phenomena such as blood clotting and inflammation.

Leukotrienes are important molecules that regulate cell and tissue biology. Leukotriene  $C_4$  ( $LTC_4$ ) is a single diastereoisomer with an *anti* 1,2 S,O functional group relationship. In nature, this single diastereoisomer is made by an epoxide opening: since the opening is  $S_N2$  the epoxide must start off *anti* and, indeed, the epoxide precursor is another leukotriene,  $LTA_4$ .

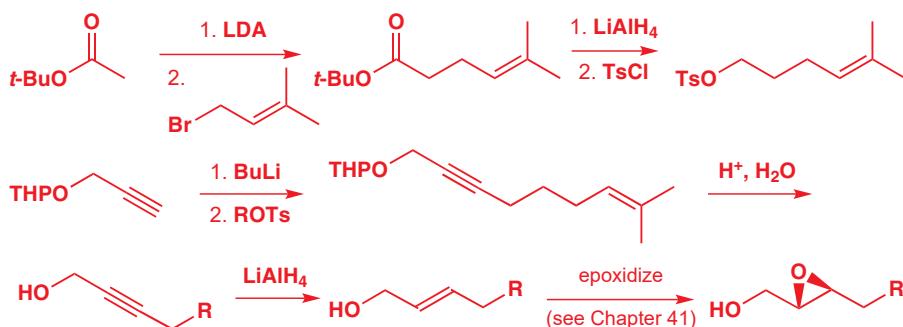


When Corey was making these compounds in the early 1980s he needed to be sure that the relative stereochemistry of  $LTC_4$  would be correctly controlled, and to do this he had to make a *trans* epoxide. Disconnecting  $LTA_4$  led back to a simpler epoxide.



The *trans* allylic alcohol needed to make this compound was made using one of the methods we introduced in Chapter 27: reduction of an alkynyl alcohol with  $LiAlH_4$ . Here is the full synthesis: alkylation of an ester enolate with prenyl bromide gives a new ester, which itself is turned into an alkylating agent by reduction and tosylation. The alkyne is introduced as its lithium derivative with the alcohol protected as a THP acetal. Hydrolysis of the acetal with

aqueous acid gives the hydroxy-alkyne needed for reduction to the *E* double bond, which is then epoxidized.

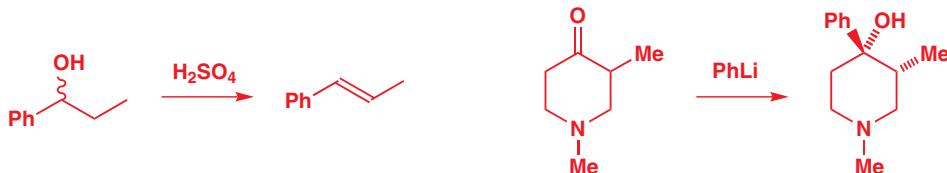


► The epoxide was, in fact, made as a single enantiomer using the Sharpless epoxidation, which we will describe in Chapter 41.

### Stereoselective reactions

For most of the rest of the chapter we shall discuss stereoselective reactions. You have already met several examples and we start with a summary of the most important methods.

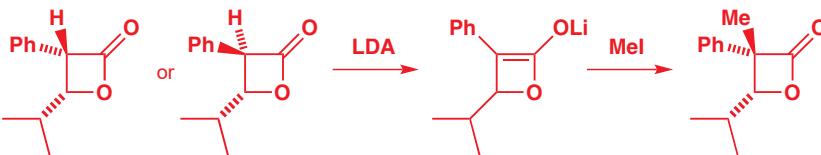
- E1 reactions are stereoselective: they form predominantly the more stable alkene.
- Nucleophilic attack on six-membered ring ketones is stereoselective: small nucleophiles attack axially and large ones equatorially.



► Chapter 17, p. 391 and Chapter 32, p. 829.



- Alkylation of cyclic enolates is stereoselective, with reaction taking place on the less hindered face (four- or five-membered rings) or via axial attack (six-membered rings).



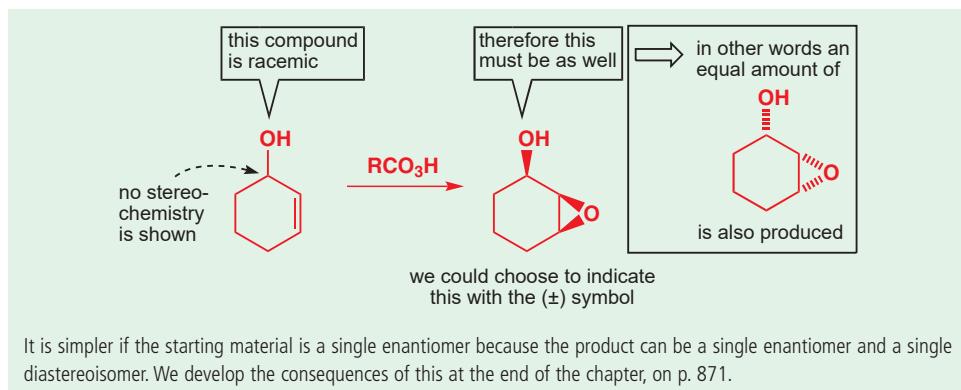
► Chapter 32, pp. 833 and 850.

- Epoxidation of cyclic alkenes is stereoselective, with reaction taking place on the less hindered face, or directed by hydrogen bonding to a hydroxyl group.



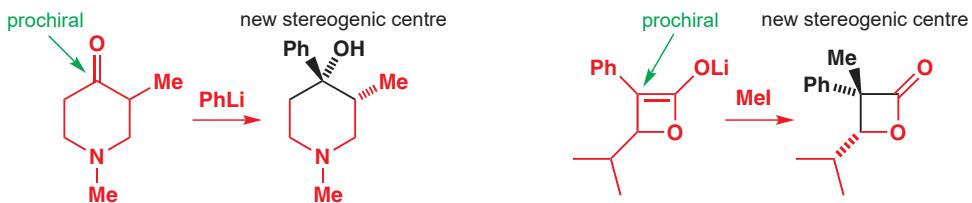
#### ■ A comment on structural drawings of single diastereoisomers

In the two reactions just above, a racemic starting material gives a racemic product as a single diastereoisomer. It is easy to draw a racemic compound with just one stereogenic centre—we just avoid showing stereochemistry. But in the products we *have* to show relative stereochemistry because we need to indicate which diastereoisomer is formed. There is no way of doing this except by arbitrarily choosing one enantiomer and drawing that. If there is a danger of confusion, we might sometimes write '(±)' under the structure.

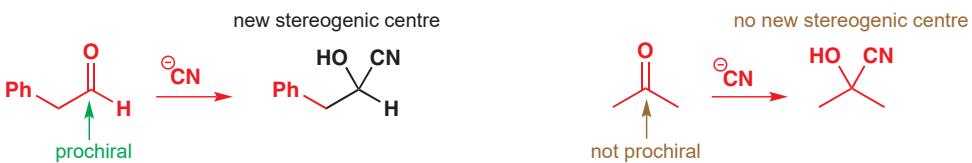


## Prochirality

Take another look at the reactions in the chapter so far—in particular those that give single diastereoisomers (rather than single enantiomers or geometrical isomers), in other words, those that are diastereoselective. They all involve the creation of a new, tetrahedral stereogenic centre at a carbon that was planar and trigonal. This leads us to our first new definition. Trigonal carbons that aren't stereogenic (or chiral) centres but can be made into them are called *prochiral*.



At the very start of Chapter 15 we introduced stereochemistry by thinking about the reactions of two sorts of carbonyl compounds. They are shown again here: the first has a prochiral carbonyl group. The second, on the other hand, is not prochiral because no stereogenic centre is created when the compound reacts.



A tetrahedral carbon atom can be prochiral too—if it carries two identical groups (and so is not a chiral centre) but replacement of one of them leads to a new chiral centre, then the carbon is prochiral.

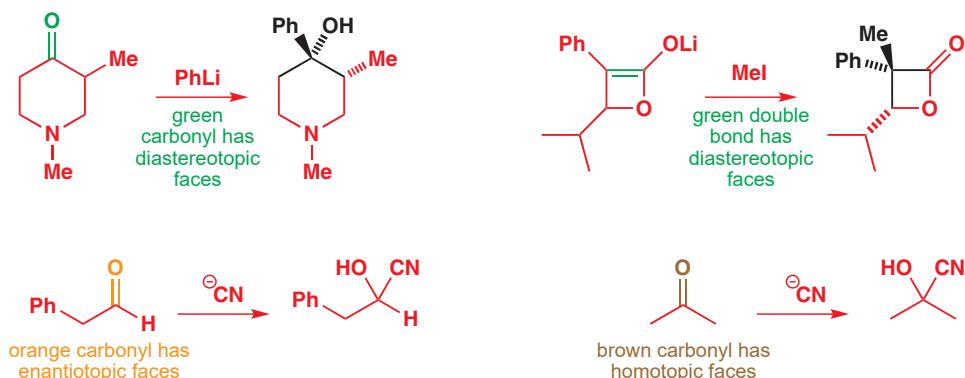


► Enantiotopic and diastereotopic protons and groups are discussed in Chapter 31, p. 820.

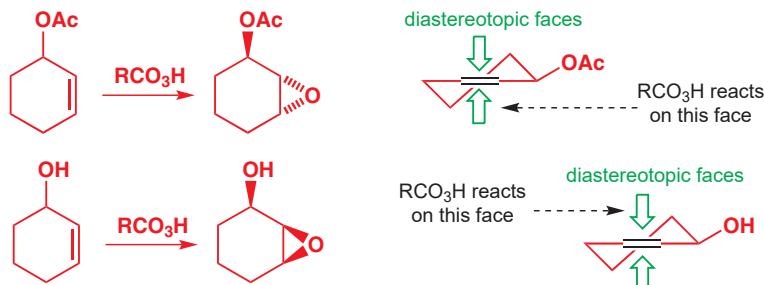
Glycine is the only common  $\alpha$  amino acid without a chiral centre, but replacing one of the two protons on the central carbon with, say, deuterium creates one: the  $\text{CH}_2$  carbon is prochiral. Similarly, converting a malonate derivate into its monoester makes a chiral centre where there was none: the central C is prochiral. Now, does this ring any bells? It should remind you very much of the definitions in Chapter 31 of *enantiotopic* and *diastereotopic* in connection with NMR spectra. Replacing one of two enantiotopic groups with another group leads to one of two enantiomers; replacing one of two diastereotopic groups with another group leads to

one of two diastereoisomers. Diastereotopic groups are chemically different; enantiotopic groups are chemically identical.

Exactly the same things are true for the faces of a prochiral carbonyl group or double bond. If reaction on one of two faces of the prochiral group generates one of two enantiomers, the faces are enantiotopic; if the reaction generates one of two diastereoisomers, the faces are diastereotopic. We will now apply this thinking to the first few reactions in this chapter: they are shown again below. The two examples in the top row have prochiral C=C or C=O bonds with diastereotopic faces: choosing which face of the double bond or carbonyl group to react on amounts to choosing which diastereoisomer to form. In the third example, the faces of the prochiral carbonyl group are enantiotopic: choosing which face to attack amounts to choosing which enantiomer to form. In the fourth example, the two faces of C=O are **homotopic**: an identical product is formed whichever face is attacked.



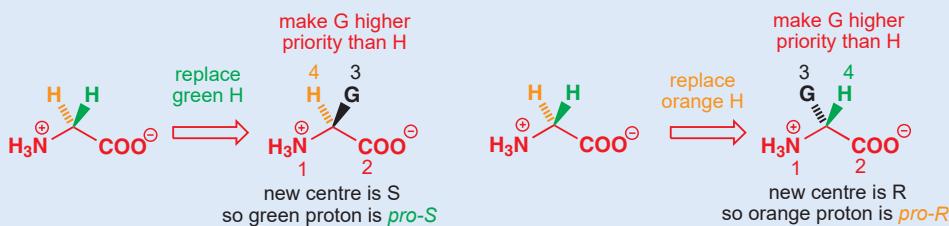
Knowing this throws some new light on the last chapter. Almost without exception, every stereoselective reaction there involved a double bond (usually C=C, sometimes C=O) with diastereotopic faces. The diastereotopic faces were distinguished by steric hindrance, or by a nearby hydrogen-bonding group, and so were able to react differently with an incoming reagent.



### Using an R/S-type system to name prochiral faces and groups

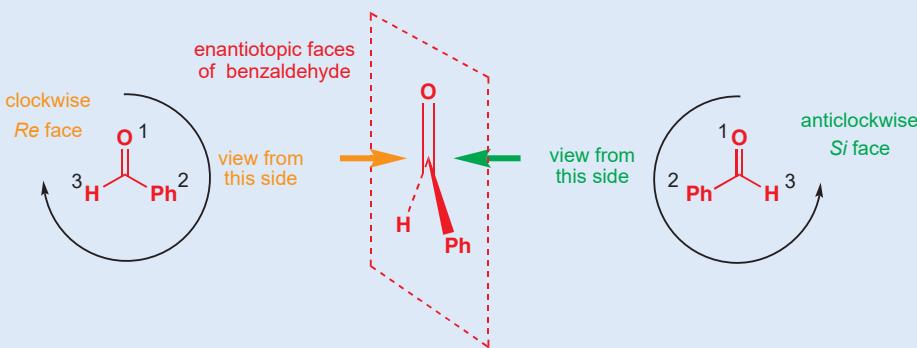
Just as stereogenic centres can be described as *R* or *S*, it is possible to assign labels to the enantiotopic groups at prochiral tetrahedral carbon atoms or the enantiotopic faces of prochiral trigonal carbon atoms. The basis of the system is the usual *R,S* system for stereogenic centres, but *pro-R* and *pro-S* are used for groups and *Re* and *Si* for faces.

*Pro-R* and *pro-S* can be assigned to a pair of enantiotopic groups simply by using the usual rules to assign *R* or *S* to the centre created if the group in question is artificially elevated to higher priority than its enantiotopic twin. We'll use *G* to replace *H* as we did in Chapter 31: just assume that *G* has priority immediately higher than *H*. The method is illustrated for glycine.



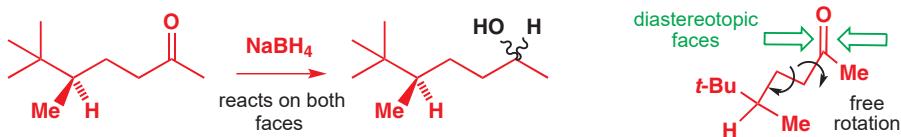
Faces of a prochiral trigonal carbon atom are assigned *Re* and *Si* by viewing the carbon from that side and counting down the groups in priority 1–3. Counting round to the right (clockwise) means the face is *Re*; counting round to the left (anticlockwise) means it's *Si*. Remember our advice from Chapter 14: think of turning a steering wheel in the direction of the numbers: does the car go to the right or the left?

Like *R* and *S*, these stereochemical terms are merely labels: they are of no consequence chemically.



In Chapter 32 we showed that homotopic and enantiotopic protons are identical by NMR. Similarly homotopic faces or groups are always chemically identical. Enantiotopic faces are also chemically identical provided that all the reagents in the reaction in question are achiral or racemic. In Chapter 41 we will consider what happens to enantiotopic faces when *enantiomerically pure* reagents are used.

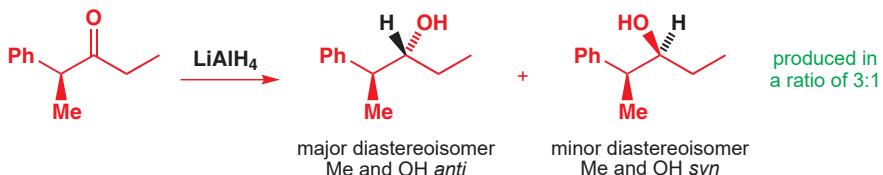
Just like diastereotopic signals in an NMR spectrum, diastereotopic faces are always different in principle, but sometimes not so in practice. The very first reaction of Chapter 32 is a case in point: this C=O group has two diastereotopic faces, which, due to free rotation about single bonds, average out to about the same reactivity, so we cannot expect any reasonable level of diastereoselectivity.



We put Chapter 32 first because in rings conformation is well defined, and this 'averaging' effect is held at bay. We are about to let it out again, but we will show you how it can be tamed to surprisingly good effect.

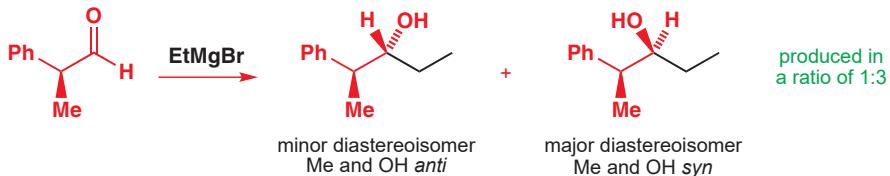
## Additions to carbonyl groups can be diastereoselective even without rings

What happens if we bring the stereogenic centre closer to the carbonyl group than it was in the last example? You might expect it to have a greater influence over the carbonyl group's reactions. And it does. Here is an example.



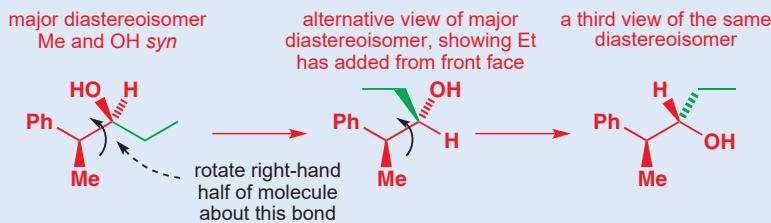
We have termed the major diastereoisomer *anti* because the two substituents (Me and OH) are on opposite sides of the chain as drawn. There is no formal definition of *anti* and *syn*: they should be used only in conjunction with a structural drawing.

There is three times as much of one of the two diastereoisomeric products as there is of the other, and the major (*anti*) diastereoisomer is the one in which the nucleophile has added to the front face of the carbonyl group as drawn here. We can make these same two diastereoisomers by addition of an organometallic to an aldehyde. For example, this Grignard reagent gives three times as much of the *syn* diastereoisomer as the *anti* diastereoisomer. The major product has changed, but the product still arises from attack on the front face of the carbonyl as shown.



### Drawing diastereoisomers of acyclic molecules

The three structures below all show the same diastereoisomer (the major product from the last reaction), but in three different conformations (we are just rotating about a bond to get from one to another).



Which is the best? A good guideline, which we suggested in Chapter 14, is to place the longest carbon chain zig-zagging across the page in the plane of the paper, and allow all the smaller substituents to extend above or below that chain. The first structure here is drawn like that. But this is only a guideline, and the second structure here is a bit more informative regarding the reaction because, when it is drawn like this, you can clearly see from which direction the ethyl group has attacked the carbonyl. Our advice would be that you first of all draw the product of any reaction in more or less the same conformation as the starting material to ensure you make no mistakes, and then rotate about a single bond to place the longest chain in the plane of the paper.

If you still have problems manipulating structures mentally—for example, if you find it hard to work out whether the substituents that aren't in the plane should be in front of or behind the page—build some models.

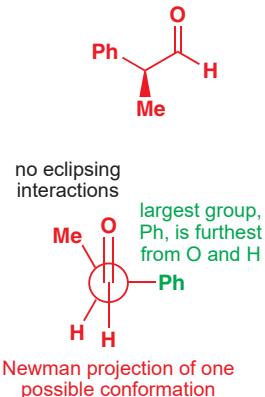
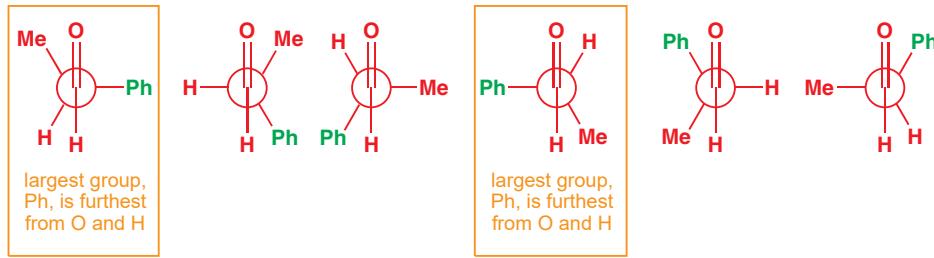
These two reactions are not nearly as diastereoselective as most of the reactions of cyclic compounds you met in the last chapter. But we do now need to explain why they are diastereoselective at all, given the free rotation possible in an acyclic molecule. The key, as much with acyclic as with cyclic molecules, is **conformation**.

→ We shall draw heavily on the first part of Chapter 16: if you haven't read it recently, now might be a good time to refresh your memory.

### The conformation of a chiral aldehyde

What will be the conformation of the aldehyde in the margin? Using the principles we outlined in Chapter 16, we can expect it to be staggered, with no eclipsing interactions, and also with large substituents as far apart from one another as possible. A Newman projection of one of the possible conformers might look like the one shown in the margin. There are no eclipsing interactions, and the large phenyl group is held satisfactorily far away from the O and the H atoms of the aldehyde.

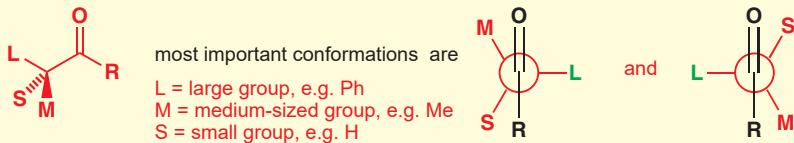
By rotating about the central bond of the aldehyde (the one represented by a circle in the Newman projection) we can suggest a series of possible conformations. Provided we move in 60° steps, none of them will have any eclipsing interactions. The full set of six conformers is shown here. Look at them for a moment and notice how they differ.



Only two of them, boxed in orange, place the large Ph group perpendicular to the carbonyl group. These yellow-boxed conformations are therefore the lowest-energy conformers and, for the purpose of the discussion that follows, they are the only ones whose reactions we need to consider.

● Lowest-energy conformations of a carbonyl compound

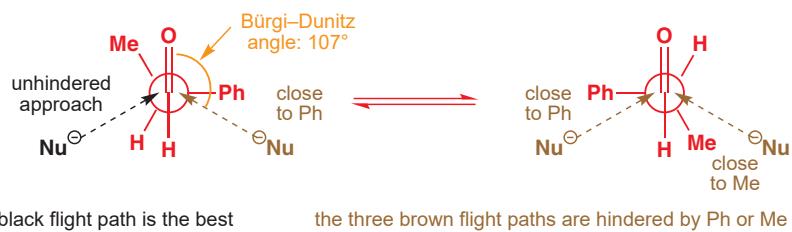
The most important conformations of a carbonyl compound with a stereogenic centre adjacent to the carbonyl group are those that place the largest group perpendicular to the carbonyl group.



**The major product arises from the most reactive conformer**

Now that we have decided which are the important conformations, how do we know which gives the product? We need to decide which is the *most reactive*. All we need to do is to remember that any nucleophile attacking the carbonyl group will do so from the Bürgi–Dunitz angle—about 107° from the C=O bond. The attack can be from either side of C=O, and the following diagrams show the possible trajectories superimposed on the two conformations we have selected, which are in equilibrium with one another.

► We introduced the idea that attack on a C=O group followed this trajectory in Chapter 6 (p. 127).

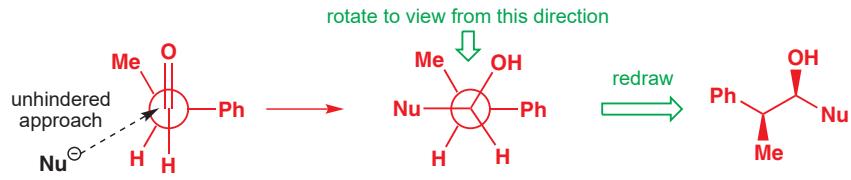


This is an example of the **Curtin–Hammett principle**, which says that it is the relative energies of the transition states that control selectivity, not the relative energies of the starting materials. It's really more of a reminder not to make a mistake than a principle.

### Cram's rule

You may hear 'Cram's rule' used to explain the outcome of reactions involving attack on chiral carbonyl compounds. Cram was the first to realize that these reactions could be predicted, but we now know why these compounds react in a predictable way. We will not describe Cram's rule because, although it often does predict the right product, in this case it does so for the wrong reason. Explanations and clear logical thinking are more important than rules, and you must be able to account for and predict the reactions of chiral aldehydes and ketones using the Felkin–Anh model.

Not all four possible 'flight paths' for the nucleophile are equally favourable. For the three shown in brown, the nucleophile passes within 30° or so of another substituent. But, for the one shown in black, there is no substituent nearby except H to hinder attack: the conformation on the left is the most reactive one, and it reacts to give the diastereoisomer shown below.



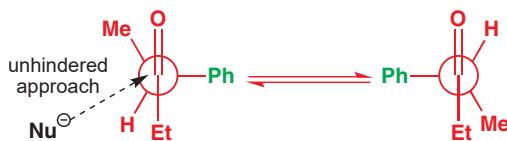
● In order to avoid making mistakes, we suggest you:

- first draw the product in a conformation similar to that of the starting material
- then redraw to put the longest chain in the plane of the paper.

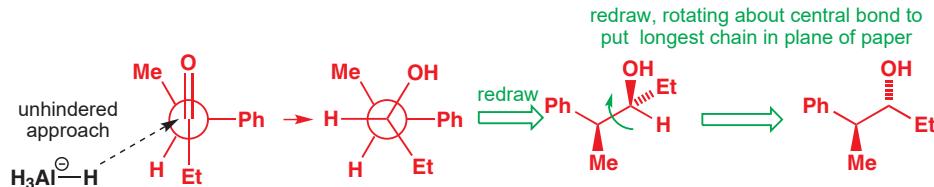
Here, this just means drawing the view from the top of the Newman projection—there is no need to rotate any bonds in this case.

With Nu=Et we have the right product and, more importantly, we can be pretty sure it is for the right reason: this model of the way a nucleophile attacks a carbonyl compound, called the **Felkin–Anh model**, is supported by theoretical calculations and numerous experimental results. Notice that we don't have to decide which is the lower energy of the two conformations: this is not necessary because the attack in black will occur even if the conformer on the left is the minor one in the mixture.

The same reasoning accounts for the diastereoselectivity of the reduction on p. 858: first we need to draw the two important conformers of the ketone; the ones that have the large group (Ph) perpendicular to the C=O group.



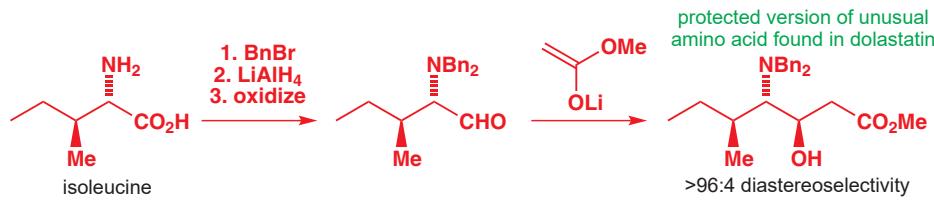
Now choose the angle of attack that is the least hindered and draw a Newman projection of the product. Finally, redraw the Newman projection as a normal structure, preferably with the longest chain in the plane of the paper.



Interactive Felkin–Anh model for ketone reduction

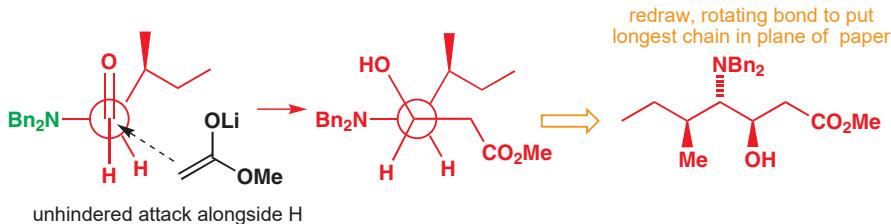
### The effect of electronegative atoms

One of the most powerful anticancer agents known is dolastatin, isolated from the sea-hare *Dolabella*. Dolastatin contains an unusual amino acid, with three stereogenic centres, and chemists in Germany managed to exploit Felkin–Anh control very effectively to make it from the much more widespread amino acid isoleucine. This is the sequence of reactions.



When you see a selectivity given as 'greater than' something it means that the other diastereoisomer was undetectable and here 96:4 was the limit of detection by the method used—possibly NMR.

The key step is the aldol reaction of the enolate of methyl acetate with the protected amino aldehyde. To rationalize the stereoselectivity, we first need to draw the two most important conformations of this aldehyde with the large group perpendicular to C=O. The trouble is, which do we choose as 'large': the NBn<sub>2</sub> group or the branched alkyl group? Since we know which diastereoisomer is produced we can work backwards to find that it must be the NBn<sub>2</sub> group that sits perpendicular to C=O in the reactive transition state, and not alkyl. We can draw the best conformation without worrying about alternatives.



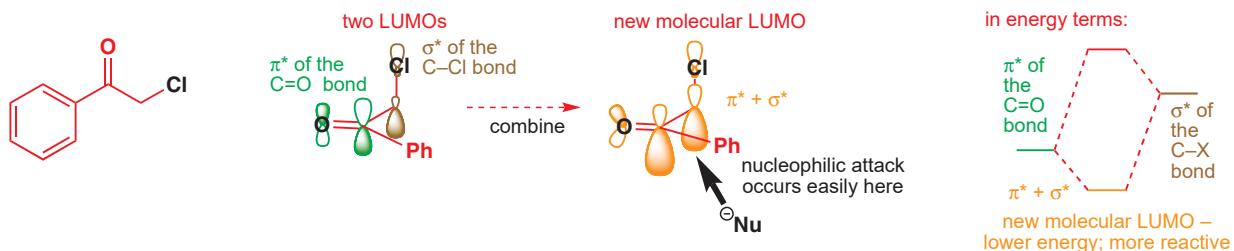
Try for yourself putting alkyl perpendicular to C=O: you will get the wrong diastereoisomer.

Now look at the diastereoselectivity of the reaction: it is much greater than the 3:1 we saw before—more like 20:1. This really does suggest that there is a further factor at work here, and that further factor is the electronegative N atom.

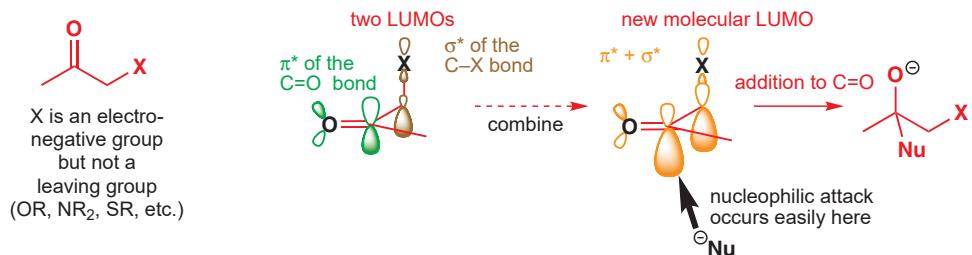
Carbonyl groups increase the reactivity of adjacent leaving groups towards nucleophilic substitution by several orders of magnitude. This was an effect that we noted in Chapter 15, where we showed that the ketone below reacts by the S<sub>N</sub>2 mechanism 5000 times as fast as methyl chloride itself. We explained this effect by saying that the  $\pi^*$  of the C=O and the  $\sigma^*$  of C–Cl overlap to form a new, lower-energy (and therefore more reactive) LUMO. What we did not

→ This is discussed on p. 341 of Chapter 15.

note then, because it was not relevant, is that this overlap can only occur when the C–Cl bond is perpendicular to the C=O bond, because only then are the  $\pi^*$  and  $\sigma^*$  orbitals aligned correctly.



The same thing happens even with electronegative atoms X that are not leaving groups in the  $S_N2$  reaction (for example, X=OR, NR<sub>2</sub>, SR, etc.). The  $\pi^*$  and  $\sigma^*$  orbitals add together to form a new, lower-energy molecular orbital, more susceptible to nucleophilic attack. But, if X is not a leaving group, attack on this orbital will result not in nucleophilic substitution but in addition to the carbonyl group. Again, this effect will operate only when the C–X and C=O bonds are perpendicular so that the orbitals align correctly.



What does this mean for stereoselectivity? Conformations of the chiral carbonyl compound that place an electronegative atom perpendicular to the C=O bond will be more reactive—size doesn't matter. So, in the dolastatin amino acid example, the conformations with NBn<sub>2</sub> perpendicular to C=O are the only conformations we need to consider.

#### Using the Felkin–Anh model

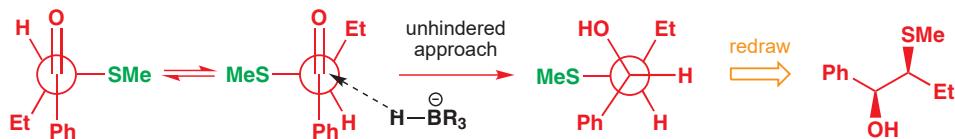
To predict or explain the stereoselectivity of reactions of a carbonyl group with an adjacent stereogenic centre, use the Felkin–Anh model. If you look at the next example, just below this box, you can follow exactly the series of steps we suggest you take:

- Draw Newman projections of the conformations of the starting material that place a large group or an electronegative group perpendicular to C=O.
- Allow the nucleophile to attack along the least hindered trajectory, taking into account the Bürgi–Dunitz angle.
- Draw a Newman projection of the product that arises from attack in this way.
- Carefully flatten the Newman projection on to the page to produce a normal structure, preferably with the longest chain of C atoms in the plane of the page. Check that you have done this last step correctly: it is very easy to make mistakes here. Use a model if necessary, or do the 'flattening out' in two stages—first view the Newman projection from above or below and draw that; then rotate some of the molecule about a bond if necessary to get the long chain into the plane of the page.

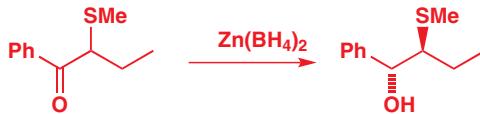
#### Chelation can reverse stereoselectivity



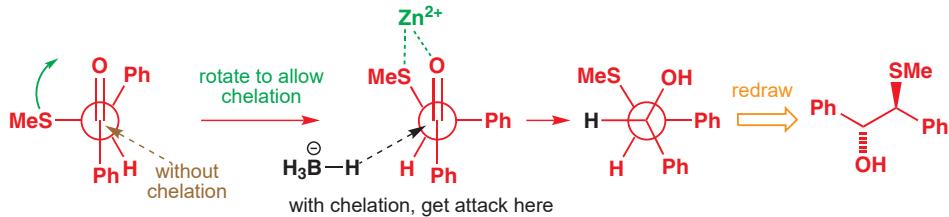
You should now be in a position to explain the outcome of this reaction without much difficulty. Sulfur is the electronegative atom, so the conformations we need to consider are the two following. Unhindered attack on the second gives the diastereoisomer shown.



But, from what we have told you so far, the next reaction would present a problem: changing the metal from lithium to zinc has reversed the stereoselectivity. Using the simple Felkin–Anh model no longer works: it gives the wrong answer.



The reason is that zinc can chelate sulfur and the carbonyl group. Chelation is the coordination of two heteroatoms carrying lone pairs to the same metal atom, and here it changes the conformation of the starting material. No longer does the most reactive or most populated conformation place the electronegative S atom perpendicular to C=O; instead it prefers S to lie as close to the carbonyl oxygen as possible so that Zn can bridge between S and O, like this:



A chelate (from the Greek for 'claw') is a coordination compound with a metal atom bonded to an organic molecule at two or more atoms.

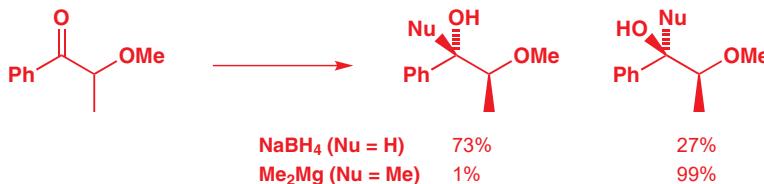
Interactive model for chelation-controlled ketone reduction

When chelation is possible, this is the conformation to consider—the one with the carbonyl O and the other chelating atom almost eclipsing one another. It is the most populated because it is stabilized by the chelation, and it is also the most reactive, because the Lewis-acidic metal atom increases the reactivity of the carbonyl group. Attack is still along the less hindered pathway, but this now leads to the other face of the carbonyl group, and the stereochemical outcome is reversed.

Two things are needed for chelation to occur:

- a heteroatom with lone pairs available for coordination to a metal
- a metal ion that prefers to coordinate to more than one heteroatom at once—these are mainly more highly charged ions, as shown in the table.

Here is another example of a reversal in selectivity that can be explained using a non-chelated Felkin–Anh model with Na<sup>+</sup> and a chelated model with Mg<sup>2+</sup>.



Metals commonly involved in chelation	Metals not usually involved in chelation
Li <sup>+</sup> often	Na <sup>+</sup>
Mg <sup>2+</sup>	K <sup>+</sup>
Zn <sup>2+</sup>	
Cu <sup>2+</sup>	
Ti <sup>4+</sup>	
Ce <sup>3+</sup>	
Mn <sup>2+</sup>	

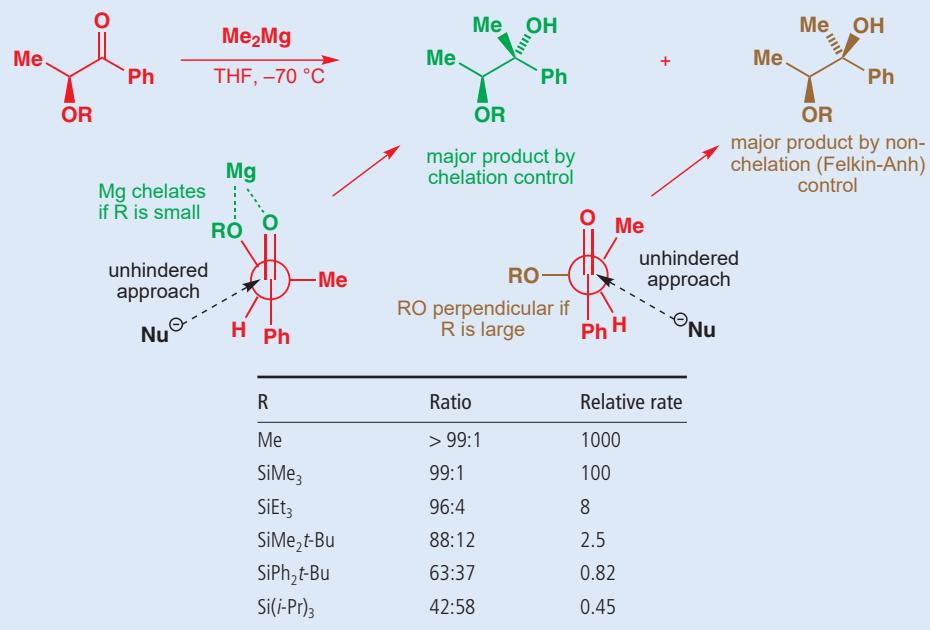
Not only does chelation control reverse the stereoselectivity, it gives a much higher degree of stereoselectivity. Stereoselectivities in chelation-controlled additions to C=O groups are typically >95:5. But this fits in nicely with the ideas we presented at the end of the last chapter: stereoselectivity is likely to be high if a cyclic transition state is involved. Chelation involves

Interactive model for chelation-controlled organo-Mg addition

just such a transition state, so it should be no surprise that it lets us achieve much higher levels of control than the acyclic Felkin–Anh model does.

### Chelation, rate, and stereoselectivity

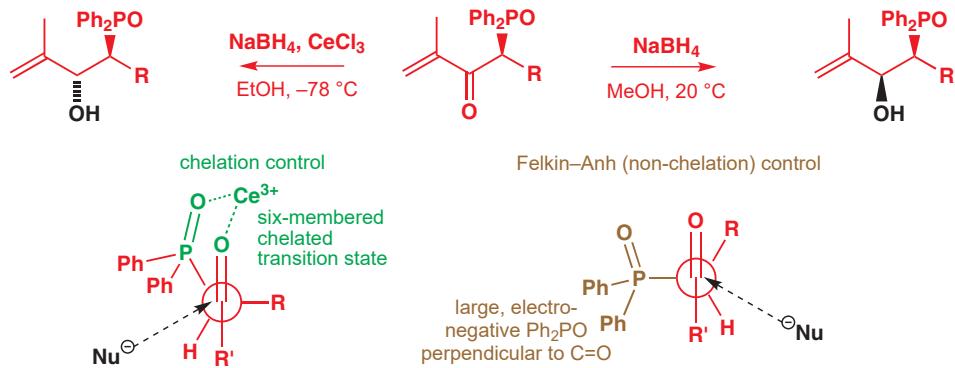
The correlation of rate of addition with diastereoselectivity was demonstrated in a series of experiments that involved reacting  $\text{Me}_2\text{Mg}$  with protected  $\alpha$ -hydroxy-ketones. As the protecting group was changed from a methyl ether to a trimethylsilyl ether and then through a series of increasingly bulky silyl ethers, both the rate of the reaction and the diastereoselectivity decreased. With small protecting groups the reaction takes place through the chelated transition state—the selectivity shows this—and the rate is faster because of the activating effect of the Lewis-acidic magnesium ion. But with larger protecting groups chelation of  $\text{Mg}^{2+}$  between the two oxygen atoms is frustrated: the rate drops off and the selectivity becomes more what would be expected from the Felkin–Anh model.



#### • Chelation:

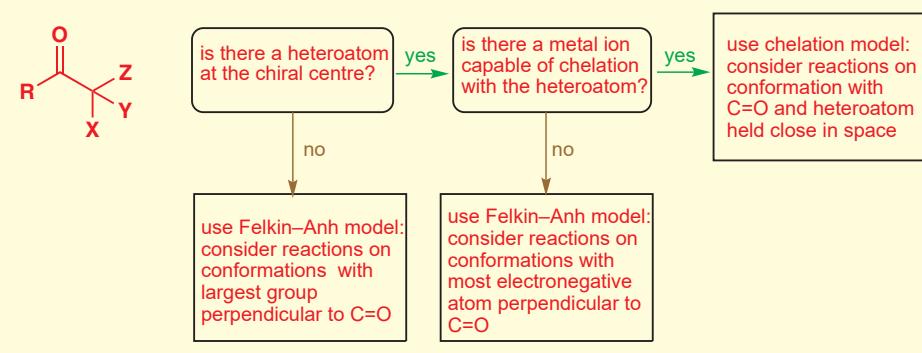
- may change the direction of diastereoselectivity
- leads to high levels of diastereoselectivity
- increases the rate of the addition reaction.

Chelation is possible through six- as well as five-membered rings and the reduction of the ketone below is a nice example of the reversal of diastereoselectivity observed when chelating  $\text{Ce}^{3+}$  ions are added to a normal sodium borohydride reduction. The products were important for making single geometrical isomers of alkenes in a modification of the Wittig reaction. Notice too that the rate changes: with  $\text{Ce}^{3+}$  the reaction can be done at  $-78^\circ\text{C}$ .



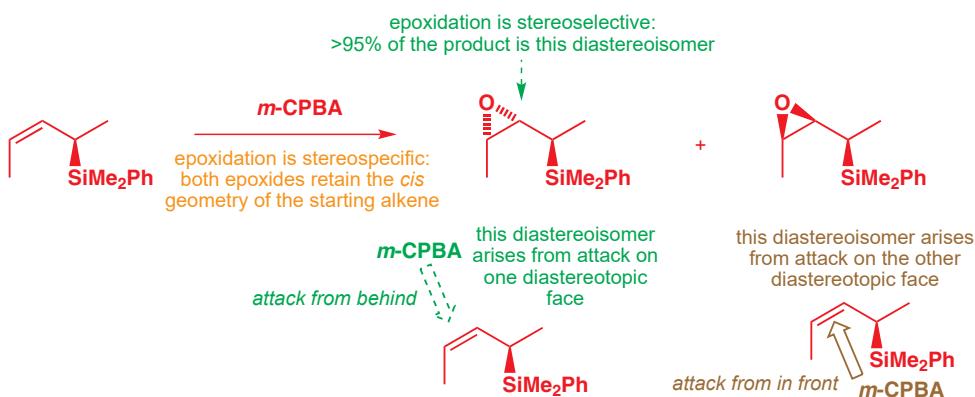
● Attack on  $\alpha$ -chiral carbonyl compounds: summary

The flow chart summarizes what you should consider when you need to predict or explain the stereochemical outcome of nucleophilic attack on a chiral carbonyl compound.



## Stereoselective reactions of acyclic alkenes

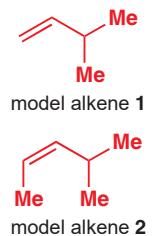
Earlier in the chapter we discussed how to make single diastereoisomers by stereospecific additions to double bonds of fixed geometry. But if the alkene also contains a chiral centre there will be a stereoselective aspect to its reactions too: its faces will be diastereotopic, and there will be two possible outcomes even if the reaction is fully stereospecific. Here is an example where the reaction is an epoxidation.



### The Houk model

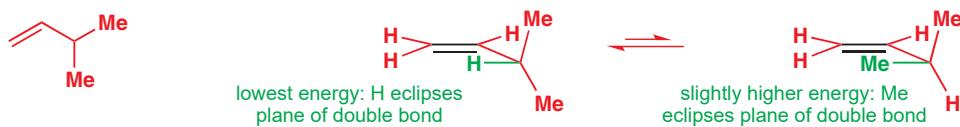
In order to explain reactions of chiral alkenes like this, we need to assess which conformations are important and consider how they will react, just as we have done for chiral carbonyl compounds. Much of the work on alkene conformations was done by K. N. Houk using theoretical computer models, and we will summarize the most important conclusions of these studies. The theoretical studies looked at two model alkenes, shown in the margin.

The calculations found that the low-energy conformations in each case were those in which a substituent eclipses the double bond. For the simple model alkene 1, the lowest-energy conformation is the one that has the proton in the plane of the alkene. Another low-energy conformation—only 3.1 kJ mol<sup>-1</sup> higher—has one of the methyl groups eclipsing the double bond, so that when we start looking at reactions of this type of alkene, we shall have to consider both conformations.

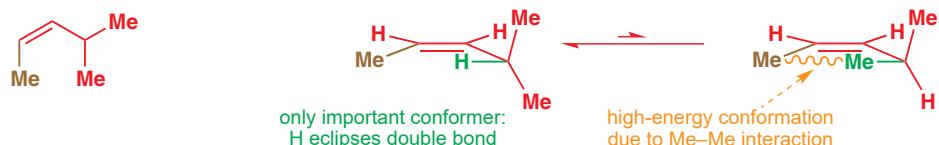


K. N. Houk works at the University of California in Los Angeles. He has provided explanations for a number of stereochemical results by using powerful computational methods.

model alkene **1** has two low-energy conformations



model alkene **2** has only one low-energy conformation



This effect—the control of conformation by a *cis* substituent—is known as **allylic strain** or  $A^{1,3}$  strain because the groups involved are on carbons 1 and 3 of an allylic system.

For the model alkene 2, with a *cis* substituent, the conformation is more predictable and the only low-energy conformer is the one with the hydrogen eclipsing the double bond. There is no room for a methyl group to eclipse the double bond because if it did it would get too close to the *cis* substituent at the other end of the double bond.

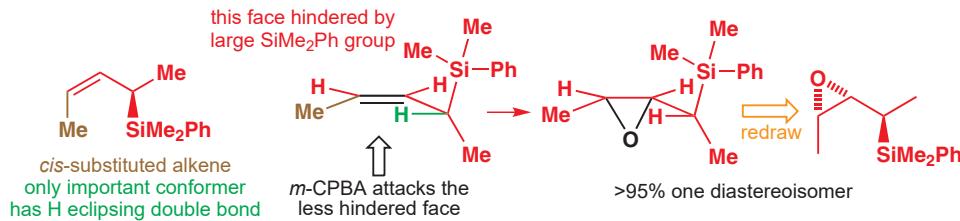
The message from the calculations is this:

- The lowest-energy conformation of a chiral alkene will have H eclipsing the double bond.
- If there is a *cis* substituent on the alkene, this will be the only important conformation; if there is no *cis* substituent, other conformations may be important too.

Now we can apply the theoretical model to some real examples.

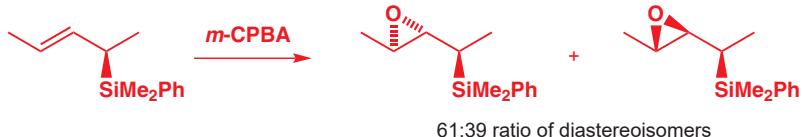
### Stereoselective epoxidation

We started this section with a diastereoselective epoxidation of an alkene. The alkene was this one, and it has a substituent *cis* to the stereogenic centre. We can therefore expect it to have one important conformation, with H eclipsing the double bond. When a reagent—*m*-CPBA here—attacks this conformation, it will approach the less hindered face, and the outcome is shown.

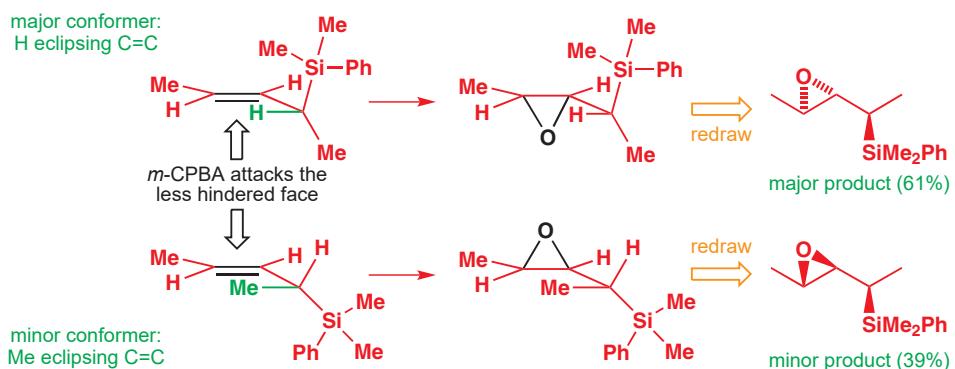


Interactive model for epoxidation controlled by allylic strain

Without the *cis* substituent, selectivity is much lower.

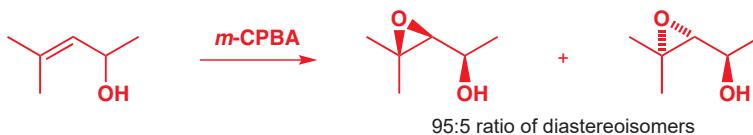


*m*-CPBA still attacks the less hindered face of the alkene, but with no *cis* substituent there are two low-energy conformations: one with H eclipsing the double bond, and one with Me eclipsing. Each gives a different stereochemical result, explaining the low stereoselectivity of the reaction.

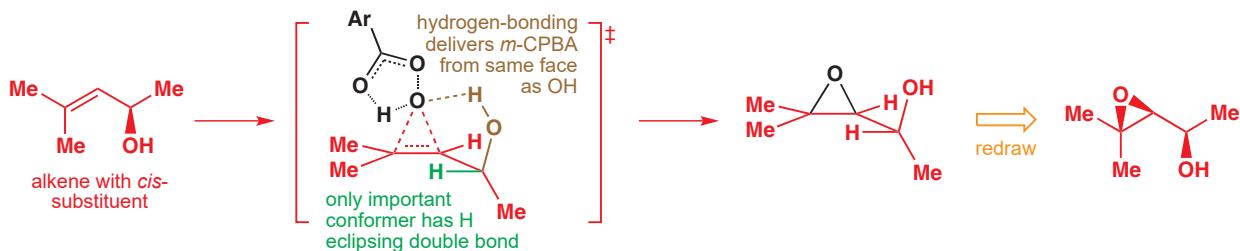


Again, draw the product in the same conformation as the starting material then flatten into the plane of the page.

You saw at the end of the last chapter that the reactions of *m*-CPBA can be directed by hydroxyl groups, and the same thing happens in the reactions of acyclic alkenes. This allylic alcohol epoxidizes to give a 95:5 ratio of diastereoisomers.



Drawing the reactive conformation explains the result. The thing that counts is the *cis* methyl group: the fact that there is a *trans* one too is irrelevant as it is just too far away from the stereogenic centre to have an effect on the conformation. The reaction uses a racemic mixture, but to explain the diastereoselectivity we just have to pick one enantiomer and show what happens to that.

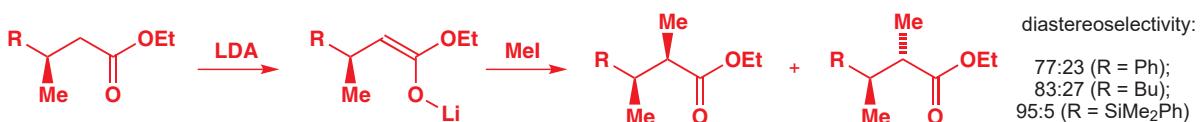


#### To explain the stereoselectivity of reactions of chiral alkenes:

- Draw the conformation with H eclipsing the double bond.
- Allow the reagent to attack the less hindered of the two faces or, if coordination is possible, to be delivered to the face *syn* to the coordinating group.
- Draw the product in the same conformation as the starting material.
- Redraw the product as a normal structure with the longest chain in the plane of the paper.

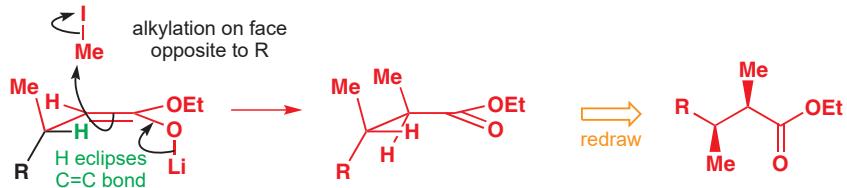
#### Stereoselective enolate alkylation

Chiral enolates can be made from compounds with a stereogenic centre  $\beta$  to a carbonyl group. Once the carbonyl is deprotonated to form the enolate, the stereogenic centre is next to the double bond and in a position to control the stereoselectivity of its reactions. The scheme below shows stereoselectivity in the reactions of some chiral enolates with methyl iodide.



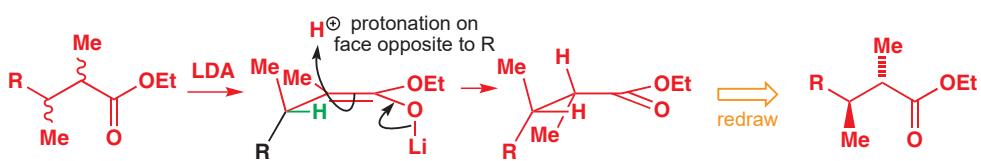
The enolate is a *cis*-substituted alkene because either O or OEt must be *cis* to the stereogenic centre, so that to explain the stereoselectivity we need consider only the conformation with H eclipsing the double bond. Notice how the diastereoselectivity increases as the group R gets bigger because there is then more contrast between the size of Me and R. In each case, the electrophile adds to the less hindered face, opposite R.

Interactive model for enolate alkylation controlled by allylic strain



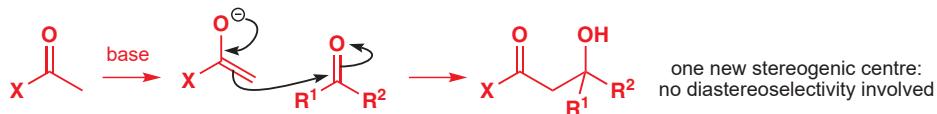
The other diastereoisomer can be made just by having the methyl group in place first and then protonating the enolate. The selectivities are lower (because a proton is small), but this does illustrate the way in which reversing the order of introduction of two groups can reverse the stereochemical outcome of the reaction.

■ The relative stereochemistry of the starting material is lost in the enolization step so either diastereoisomer or a mixture can be used.

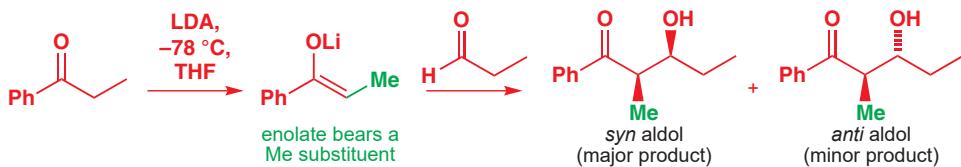


## Aldol reactions can be stereoselective

In Chapter 26 you met the **aldol reaction**: reaction of an enolate with an aldehyde or a ketone. Many of the examples you saw approximated to this general pattern.



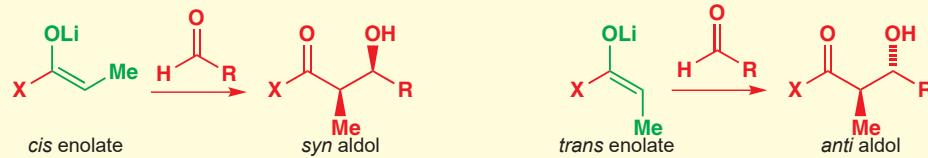
Only one new stereogenic centre is created, so there is no question of diastereoselectivity. But with substituted enolates, two new stereogenic centres are created and we need to be able to predict which diastereoisomer will be formed. Here is an example from p. 626. We did not consider stereochemistry at that stage, but we can now reveal that the *syn* diastereoisomer is the major product of the reaction.



The important point about substituted enolates is that they can exist as two geometrical isomers, *cis* or *trans*. Which enolate is formed is an important factor controlling the diastereoselectivity because it turns out that, in many examples of the aldol reaction, *cis* enolates give *syn* aldols preferentially and *trans* enolates give *anti* aldols preferentially.

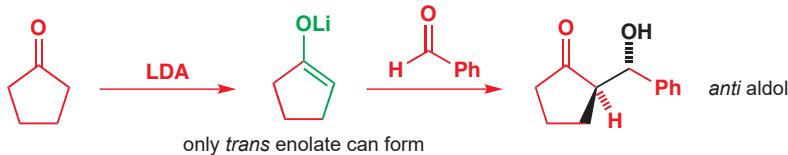
### ● Diastereoselectivity in aldol reactions

Generally (but certainly not always!) in aldol reactions:



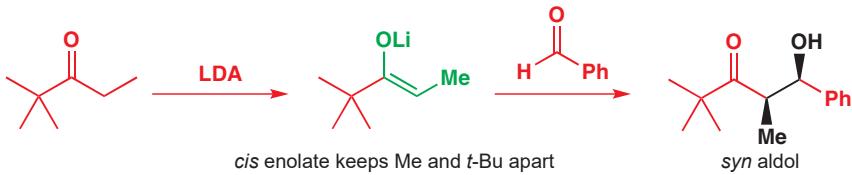
This is a very general rule and there are many exceptions—the enolates of some metals [Sn(II), Zr, Ti] give *syn* aldols regardless of enolate geometry. Some related reactions are discussed in Chapter 41.

Let's start by showing some examples and demonstrating how we know this to be the case. Some enolates can exist only as *trans* enolates because they are derived from cyclic ketones. This enolate, for example, reacts with aldehydes to give only the *anti* aldol product.



Interactive mechanism for *anti* stereoselective aldol reaction

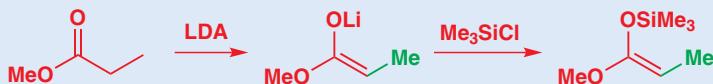
If we choose the group 'X', next to the carbonyl group, to be large, then we can be sure of getting just the *cis* enolate. So, for example, the lithium enolate of this *t*-butyl ketone forms just as one geometrical isomer, and reacts with aldehydes to give only the *syn* aldol product.



Interactive mechanism for *syn* stereoselective aldol reaction

### *cis* and *trans*, *E* and *Z*, *syn* and *anti*

Before going further, there are two points we must clarify. The first is a problem of nomenclature, and concerns the enolates of esters. Here are two closely related ester enolate equivalents, drawn with the same double bond geometry. Is it *E* or *Z*?

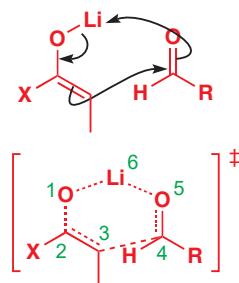


The answer is both! For the Li enolate, the usual rule makes OLi of lower priority than OMe (because Li has a smaller atomic number than C), so it's *E*, while the silyl enol ether (or 'silyl ketene acetal') has OSi of higher priority than OMe (Si has a larger atomic number than C), so it's *Z*. This is merely a nomenclature problem, but it would be irritating to have to reverse all our arguments for lithium and boron enolates (as opposed to, say, tin or silicon ones). So, for the sake of consistency, it is much better to avoid the use of *E* and *Z* with enolates and instead use *cis* and *trans*, which then always refer to the relationship between the substituent and the anionic oxygen (bearing the metal).

The other point concerns *syn* and *anti*. We said earlier that there is no precise definition of these terms: they are a useful way of distinguishing two diastereoisomers provided the structure of at least one of them is presented in diagrammatic form. For aldol products the convention is that *syn* or *anti* refers to the enolate substituent (the green Me in the last example) and the new hydroxyl group, provided the main chain is in the plane of the paper, the way we have encouraged you to draw molecules.

### The aldol reaction has a chair-like transition state

These are the experimental facts: how can we explain them? Aldol reactions are another class of stereoselective process with a cyclic transition state. During the reaction, the lithium is transferred from the enolate oxygen to the oxygen of the carbonyl electrophile. This is represented in the margin both in curly arrow terms and as a transition state structure. A six-membered ring is involved, and we can expect this ring to adopt more or less a chair



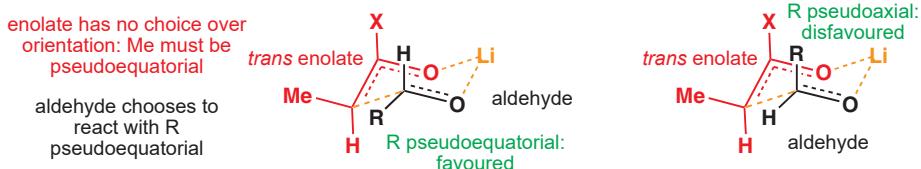
conformation. The easiest way to draw this is first to draw the chair, and then convert atoms to O or Li as necessary. Here it is.

The six-membered ring transition state for the aldol reaction was proposed by Zimmerman and Traxler and is sometimes called the **Zimmerman–Traxler transition state**.

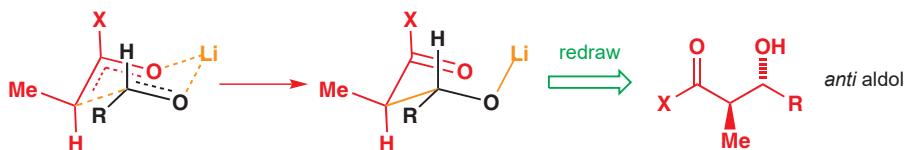
■ Our advice on p. 860, which we follow again here, was to draw the product first of all in the conformation of the starting material and only then to flatten it out to a 'normal' structure.

Interactive mechanism: *trans* enolate gives *anti* stereoselective aldol reaction

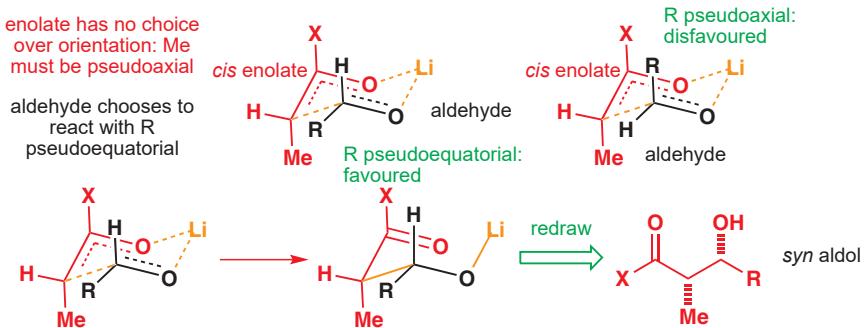
Interactive mechanism: *cis* enolate gives *syn* stereoselective aldol reaction



In drawing this chair, we have one choice: do we allow the aldehyde to place R equatorial or axial? Both are possible but, as you should now expect, there are fewer steric interactions if R is equatorial. Note that the enolate doesn't have the luxury of choice. If it is to have three atoms in the six-membered ring, as it must, it can do nothing but place the methyl group pseudoequatorial. The aldol formed from the favoured transition state structure, with R pseudoequatorial, is shown below—first in the conformation of the transition state, and then flattened out on to the page, and it is *anti*.

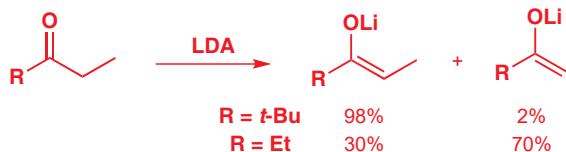


We can do the same for the *cis* enolate. The enolate has no choice but to put its methyl substituent pseudoaxial, but the aldehyde can choose either pseudoequatorial or pseudoaxial. Again, pseudoequatorial is better and the reaction gives the product shown—the *syn* aldol.



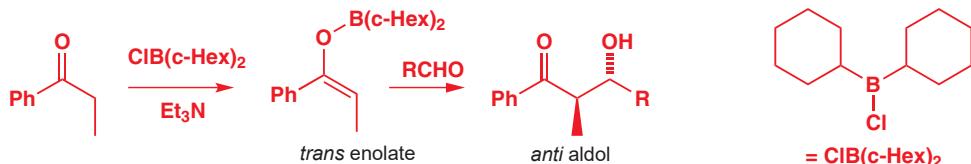
### Stereoselective enolization is needed for stereoselective aldols

The cyclic transition state explains how enolate geometry controls the stereochemical outcome of the aldol reaction. But what controls the geometry of the enolate? For lithium enolates of ketones the most important factor is the size of the group that is not enolized. Large groups force the enolate to adopt the *cis* geometry; small groups allow the *trans* enolate to form. Because we can't separate the lithium enolates, we just have to accept that the reactions of ketones with small R will be less diastereoselective.



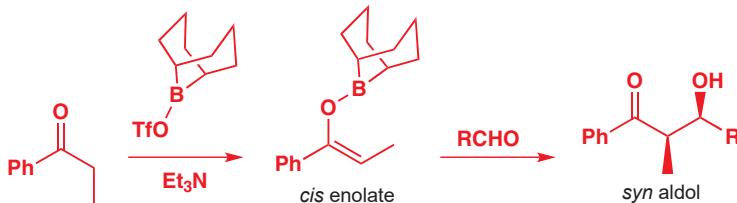
With *boron* enolates, we don't have to rely on the structure of the substrate—we choose the groups on boron—and we can get either *cis* or *trans* depending on which groups these are. Boron enolates are made by treating the ketone with an amine base (often Et3N or i-PrNEt2) and R2B-X, where X- is a good leaving group such as chloride or triflate (CF3SO3-). With bulky

groups on boron, such as two cyclohexyl groups, a *trans* enolate forms from most ketones. The boron enolate reacts reliably with aldehydes to give *anti* aldol products through the same six-membered transition state that you saw for lithium enolates.



With smaller B substituents, the *cis* enolate forms selectively. Here, the boron is part of a bicyclic structure known as 9-BBN (9-borabicyclononane). The bicyclic part may look large but, as far as the rest of the molecule is concerned, it's 'tied back' behind the boron, and the methyl group can easily lie *cis* to oxygen. The *cis* enolate then gives *syn* aldol products. Di-*n*-butylboron triflate ( $\text{Bu}_2\text{BOTf}$ ) also gives *cis* enolates.

→ 9-BBN was mentioned in Chapter 19.



#### ● Summary: How to make *syn* and *anti* aldols

To make *syn* aldols of ketones:

- use boron enolate with 9-BBN-OTf or  $\text{Bu}_2\text{BOTf}$
- from a ketone  $\text{RCOEt}$  with bulky R, use lithium enolate

To make *anti* aldols of ketones:

- use boron enolate with  $(\text{c-Hex})_2\text{BCl}$
- from a cyclic ketone, use lithium enolate

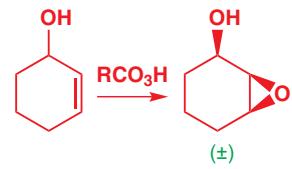
## Single enantiomers from diastereoselective reactions

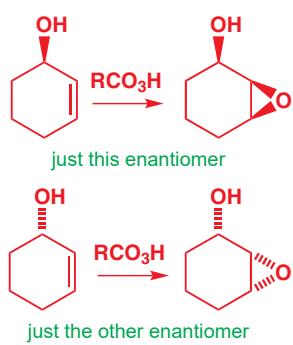
The aldol reactions in the last section made single diastereoisomers from two achiral compounds. No enantiomerically pure reagents were used, so the reaction had no choice but to give the product diastereoisomer as a racemic mixture of its two enantiomers.

In all the other diastereoselective reactions in this chapter, the starting material has been chiral, with the formation of new chiral centres controlled by the configuration of the starting material. Whatever the diastereoselectivity of the reaction, if the starting material is racemic, so will be the product; if the starting material is enantiomerically pure, so will be the product. The epoxidation of the allylic alcohol in the margin illustrates this point.

The reaction starts with racemic material (no stereochemistry is shown at the chiral centre) and makes a racemic product. Of course we have only drawn one enantiomer—the only way to draw one diastereoisomer is to choose one enantiomer and draw that—but the indication ‘±’ underneath tells you to expect an equal amount of the other enantiomer as well. Even without this indication, you should be able to work out, in any given case, whether a compound is racemic or not, providing you know where it comes from. Here the starting material is racemic and the reagent is achiral so the product must be racemic.

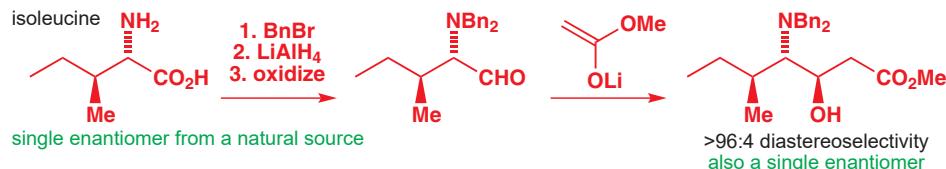
The example of this reaction earlier in the chapter (p. 856) was this type of reaction. The starting alcohol was racemic and the product was just one racemic diastereoisomer—the all *cis* compound. But if the starting material *had* been enantiomerically pure, so would the product. One enantiomer gives one enantiomer of the product: the other enantiomer of the alcohol





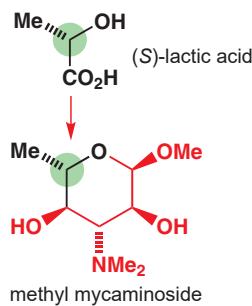
gives the other. Both products are the same diastereoisomer (all *cis*) but they are mirror images of each other. If you start with enantiomerically pure compounds, the products will be enantiomerically pure as well.

We gave an example of this during the discussion of the Felkin–Anh model. The starting material was the natural amino acid isoleucine and was the enantiomer shown. The product of the aldol reaction was therefore also a single enantiomer. The original chiral centre in both these examples is not affected by the reaction and remains unchanged.



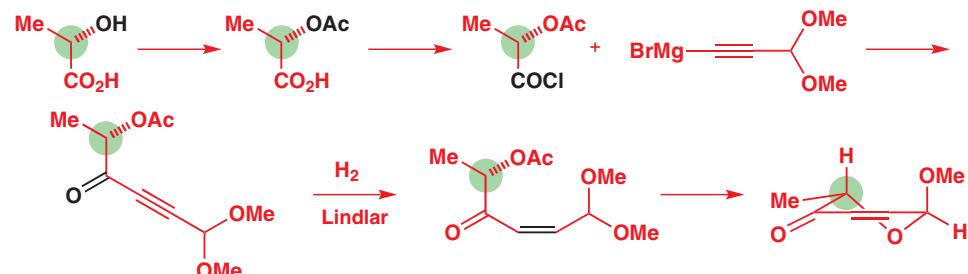
It is much more useful to make enantiomerically pure as well as diastereoisomerically pure compounds, particularly in the synthesis of a drug. The strategy used here is to make the starting material from an enantiomerically pure compound available from nature: in this case an amino acid. These available enantiomerically pure compounds are known collectively as the **chiral pool**. You can read more about this in Chapter 41 on asymmetric synthesis.

If you are making an enantiomerically pure compound with more than one stereogenic centre, only one needs be borrowed from the chiral pool, provided diastereoselective reactions can be used to introduce the others with control over relative stereochemistry. Because the first chiral centre has defined absolute configuration, any diastereoselective reaction that controls the relative stereochemistry of a new chiral centre also defines its absolute configuration.

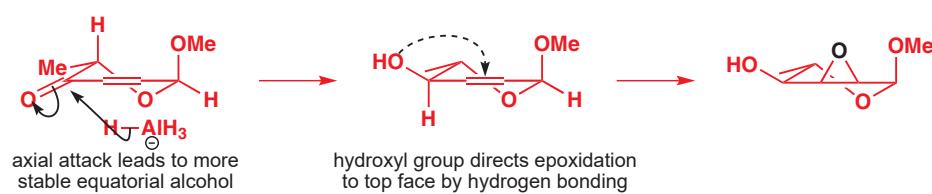


We'll use as an illustration a synthesis of a rare sugar, methyl mycaminoside, containing five chiral centres. Only one chiral centre comes directly from the chiral pool—the rest are introduced diastereoselectively. The naturally derived, enantiomerically pure compound used as the starting material is (S)-lactic acid. The starting chiral centre, preserved right through the sequence, is ringed in green.

The ring was built up using familiar chemistry from acetylated (S)-lactic acid, and a cyclization step introduced the second chiral centre in the final step of the scheme below. The methyl group goes pseudoequatorial on the newly formed ring, while the anomeric effect, which was explained on p. 801 of Chapter 31, induces the methoxy group to prefer the pseudoaxial position.

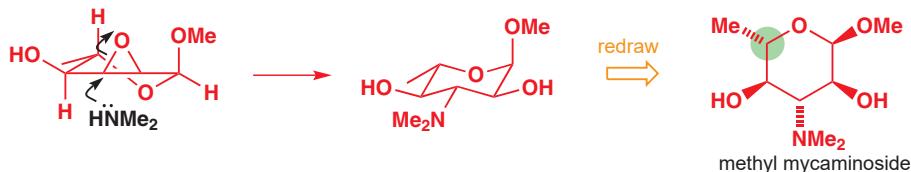


The third stereogenic centre was controlled by reduction of the ketone from the axial direction to give the equatorial alcohol, which then directed introduction of the fourth and fifth stereogenic centres by epoxidation.



► The conformational factors governing reduction of cyclohexanones are discussed in Chapter 16. The directing effects of OH groups in epoxidation are discussed in Chapters 32 and earlier in this chapter.

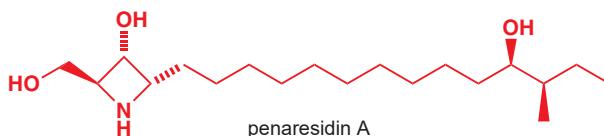
Finally, the simple nucleophilic amine  $\text{Me}_2\text{NH}$  attacks the epoxide with inversion of configuration to give methyl mycaminoside. The conformational drawing shows that all substituents are equatorial except the  $\text{MeO}$  group, which prefers to be axial because of the anomeric effect. Starting from an enantiomerically pure compound containing one chiral centre, four new chiral centres are introduced in sequence by diastereoselective reactions of various kinds. The final product is necessarily a single enantiomer.



■ Normally, axial attack occurs on cyclohexane epoxides, as explained in Chapter 32, but the rule is not rigid, as you can see here. Equatorial attack occurs because the transition state already has much of the stability of the equatorially substituted product. You should continue to assume that related epoxides will typically undergo axial attack.

### The structure and synthesis of penaresidin

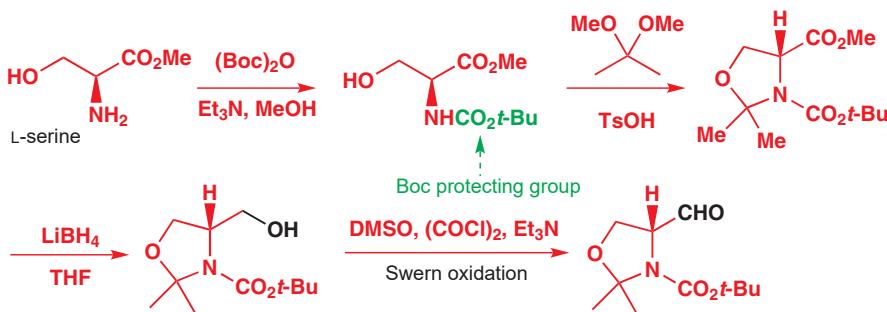
Our last example is a natural product called penaresidin A. It was isolated from a Japanese sponge in 1991, and is now known to have the structure shown below. When it was first discovered, it proved difficult to find out the stereochemistry and, in particular, the relative stereochemistry between the two remotely related groups of chiral centres was not initially known.



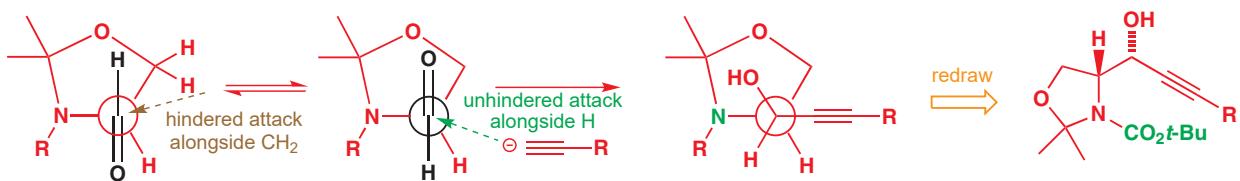
What is sure is the relative stereochemistry around the four-membered azetidine ring: the NMR methods described in Chapter 31 give that. What is also certain is that natural penaresidin A is enantiomerically pure. What Mori and his co-workers set out to do was to make, using unambiguous stereoselective methods, the possible diastereoisomers of penaresidin A to discover which was the same as the natural product.

The challenge of constructing the three chiral centres at the left-hand end of the molecule can be solved by taking just one of them from a natural source—in this case the amino acid L-serine. The amino group of serine was protected as the Boc derivative, and the hydroxyl and amino groups condensed with the dimethoxyacetal of acetone to form a five-membered ring. Now the free ester could be reduced with  $\text{LiBH}_4$  and oxidized to the aldehyde by the Swern method (Chapter 27).

► The Boc protecting group was introduced on p. 557; the Swern oxidation is on p. 667.

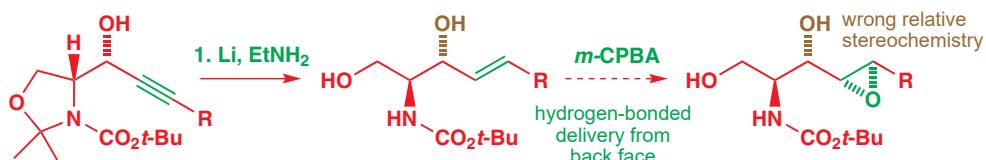


How will this aldehyde react with nucleophiles such as lithiated alkynes? Consider a Felkin–Anh transition state: again, we know that the substituted nitrogen atom, being electronegative and bulky, will lie perpendicular to the carbonyl group in the most reactive conformation. Looking at the two alternatives shown below, it's easy to see that the one on the right allows unhindered attack, and in the synthesis an alkynyl anion was used to make the product shown.



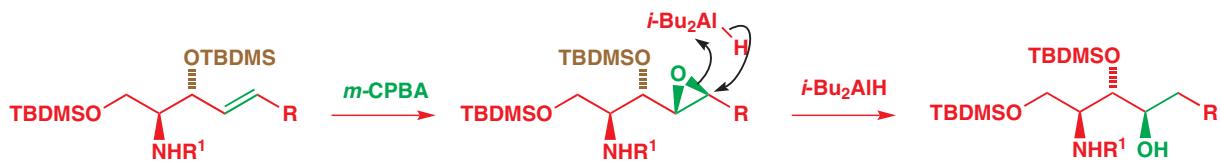
► Reduction of alkynes to *E* double bonds is covered in Chapter 27, p. 681.

The alkyne was then reduced to an *E* alkene by a dissolving metal reduction, a step which also hydrolysed the five-membered heterocycle. The next step, an epoxidation, is needed to install the third of the chiral centres at the left-hand end of penarisiidine. However, hydrogen-bond directed epoxidation of this allylic alcohol would be expected to give the *syn* product shown, which has the wrong relative stereochemistry between the brown OH group and the epoxide.

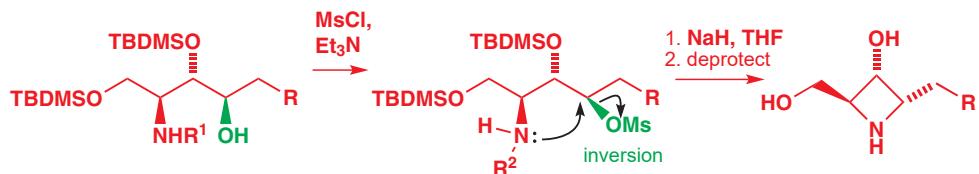


■ The selectivity of the epoxidation of the *E* double bond was still only moderate (about 60:40). From the discussion on p. 866 you should be able to deduce why.

The solution is to use a large blocking group to prevent this brown OH group hydrogen bonding to the *m*-CPBA. The *t*-butyldimethylsilyl group (TBDMS) is the best, and when both OH groups are protected, some of the right diastereoisomer is formed by attack of *m*-CPBA on the top face of the alkene. Reduction of the epoxide with DIBAL (*i*-Bu<sub>2</sub>AlH) now gives the correct diastereoisomer.



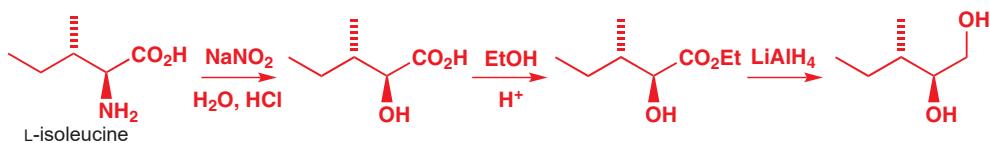
To close the ring, the green hydroxyl group was converted to a good leaving group, mesylate ( $\text{MeSO}_3^-$ ), ready for an attack by the nitrogen with inversion on treatment with base. Make sure you can see how inversion at this centre gives the stereochemistry shown! The chemists knew at this stage they were on the right track with regard to relative stereochemistry because the NMR spectrum of structures containing any long alkyl chain R were very similar to that of the natural compound.



### Confirming the stereochemistry by synthesis

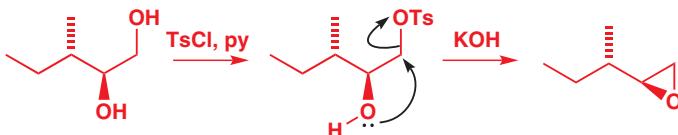
The other two chiral centres at the right-hand end of the chain are so far removed from the ring (by 10  $\text{CH}_2$  groups) that there is no simple way to determine their stereochemistry relative to the three at the left-hand end by NMR. The solution to problems of assignment like this is often to make the various isomers by unambiguous synthesis and compare the NMR spectra of the natural and synthetic compounds. This is what Mori did in this case.

The chiral pool can again be called into play by using another amino acid, L-isoleucine, as starting material. First the amino group must be converted to a leaving group by diazotization with nitrous acid (sodium nitrite in dilute HCl) and substituted by water to give a hydroxy acid. The acid is esterified and reduced to a diol.

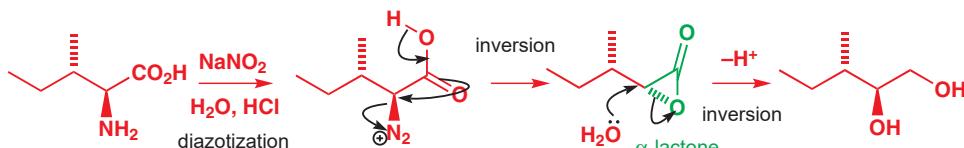


→ We used  $\text{NaNO}_2$  in acid to convert amino groups into diazonium salts containing the excellent leaving group  $\text{N}_2$  in Chapter 22, p. 520.

Conversion of the diol's primary hydroxyl group to a leaving group (here a tosylate) allows the epoxide to be formed with retention of the two stereogenic centres of the starting material. Cyclization in base gives an epoxide. Overall, the enantiomerically pure starting material is converted stereospecifically into a single enantiomer of a single diastereoisomer of the epoxide.

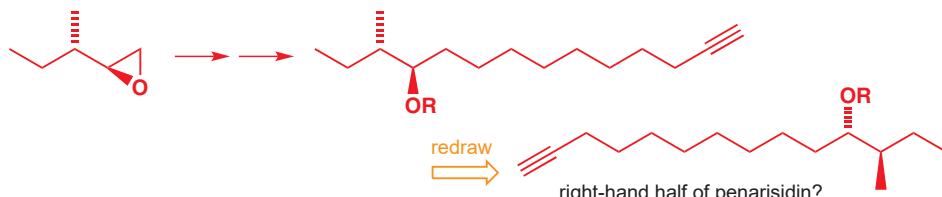


Before we go on, look back at the first reaction of this sequence—the conversion of L-leucine to the hydroxy acid. The stereochemistry may surprise you: look carefully and you will see that the amino group has been displaced with *retention* of stereochemistry. Retentive substitutions usually indicate double inversions, and here the carboxylic acid gets involved in the displacement to give (with inversion) a very unstable compound called an  $\alpha$ -lactone whose strained ring is opened by water, also with inversion.

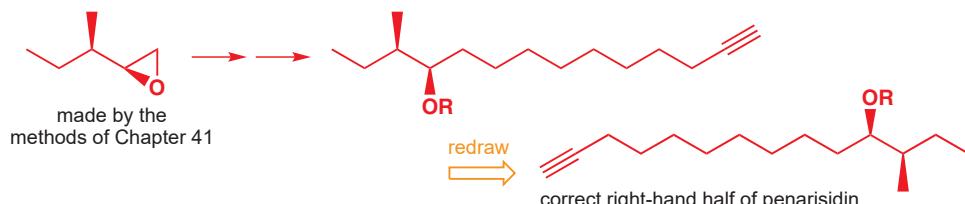


→ We will address similar examples of 'neighbouring group participation' in Chapter 36. There is more on  $\alpha$ -lactones on p. 934. The mechanism for the diazotization step is in Chapter 22, p. 521.

The epoxide may now be opened with a nucleophile to give the right-hand half of the target molecule. The alkyne shown below, which has an *anti* relationship between the hydroxyl and methyl groups, was made and linked to the left-hand half of penarisdin A by using it to attack the aldehyde the method described above. However, the final product was not the same as natural penarisdin A!



Clearly, some aspect of relative stereochemistry was wrong. So the synthesis was repeated, this time using the *syn* diastereoisomer of the substituted alkyne obtained using one of the methods we will describe in Chapter 41. With this isomer the final compound had spectroscopic data identical with the natural product, and the question of its stereochemistry was solved. It is not uncommon for synthesis to be the only reliable way of proving the detailed structure of a compound.



## Looking forward

Once you have got hold of a molecule as a single enantiomer, however simple that molecule may be, you can always use reliably diastereoselective reactions of the type described in this chapter and the one before to decorate it with further chiral centres. This is a very important point that underlies the field of asymmetric synthesis, which we will cover in Chapter 41. There you will see developments of the ideas we have just been describing, where chiral centres derived from nature are used to introduce new stereochemistry even though they themselves need not appear in the final product. But before we move on to such reactions, we need to cover a handful of important new reaction mechanisms, many of which provide further ways of introducing new stereochemical features into molecules. The first of these new classes of reactions is *cycloadditions*.

## Further reading

For explanations of pericyclic reactions and other reactions, using the full molecular orbital treatment, consult: Ian Fleming, *Molecular Orbitals and Organic Chemical Reactions, Student Edition*, Wiley, Chichester 2009. There is also a more comprehensive edition intended for practicing chemists, called the *Library Edition*.

For a comprehensive treatment of diastereoselectivity and the chiral pool approach to asymmetric synthesis as well as control of double bond geometry see P. Wyatt and S. Warren, *Organic*

*Synthesis: Strategy and Control*, Wiley, Chichester, 2007 and the accompanying *Workbook*, also Wiley, 2008.

Leading references for the synthesis of penaresidin are K. Mori and group, *J. Chem. Soc., Perkin Trans. 1*, 1997, 97; S. Knapp and Y. Dong, *Tetrahedron Lett.*, 1997, **38**, 3813 and H. Yoda and group, *Tetrahedron Lett.*, 2003, **44**, 977. The synthesis of methyl mycaminoside is from Koga, K., Yamada, S.-I., Yoh, M., Mizoguchi, T. *Carbohydr. Res.* 1974, **36**, C9–C11.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 周环反应 1: 环加成

34

## 联系

### 基础

- Structure of molecules ch4
- Reaction mechanisms ch5
- Conjugation and delocalization ch7
- Reactions of alkenes ch19 & ch22
- Aromatic heterocycles ch29 & ch30

### 目标

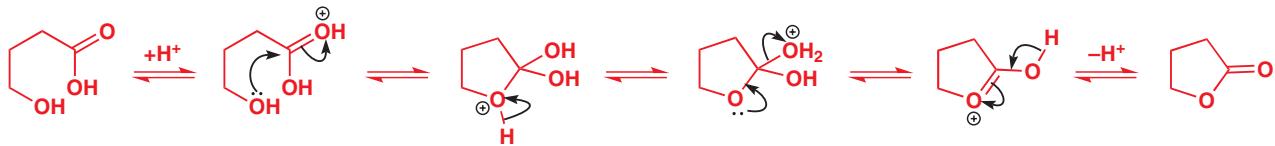
- In cycloadditions electrons move in a ring
- In cycloadditions more than one bond is formed simultaneously
- There are no intermediates in cycloadditions
- Cycloadditions are a type of pericyclic reaction
- The rules that govern cycloadditions: how to predict what will and will not work
- Photochemical reactions: reactions that need light
- Making six-membered rings by the Diels–Alder reaction
- Making four-membered rings by [2 + 2] cycloaddition
- Making five-membered rings by 1,3-dipolar cycloaddition
- Using cycloaddition to functionalize double bonds stereospecifically
- Using ozone to break C=C double bonds

### 展望

- Electrocyclic reactions and sigmatropic rearrangements ch35
- Radical reactions ch37
- Reactions of carbenes ch38
- Asymmetric synthesis ch41

## A new sort of reaction

Most organic reactions are ionic. Electrons move from an electron-rich atom towards an electron-poor atom: anions or cations are intermediates. Formation of a cyclic ester (a lactone) is an example. The reaction involves five steps and four intermediates. The reaction is acid-catalysed and each intermediate is a cation. Electrons flow in one direction in each step—towards the positive charge. This is an ionic reaction.



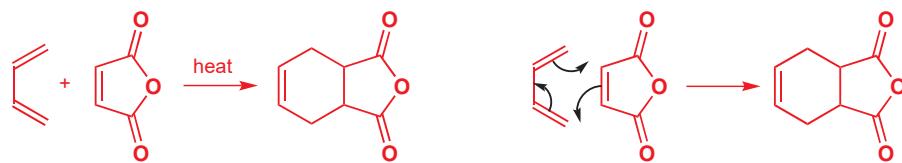
This chapter is about a totally different reaction type. Electrons move round a circle and there are no positive or negative charges on any intermediates—indeed, there are no inter-

■ In Chapter 24 you met a brief introduction to a third category—radical reactions—in which one electron instead of two is on the move. This will be developed in more detail in Chapter 37.

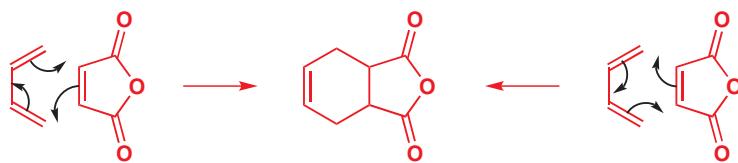
Otto Diels (1876–1954) and his research student Kurt Alder (1902–58) worked at the University of Kiel and discovered this reaction in 1928. They won the Nobel Prize in 1950. Diels also discovered carbon suboxide,  $\text{C}_2\text{O}_3$  (see p. 420).

■ Cycloadditions are the first of three classes of pericyclic reactions, and the whole of this chapter will be devoted to cycloadditions. The other two—sigmatropic and electrocyclic reactions—are discussed in Chapter 35.

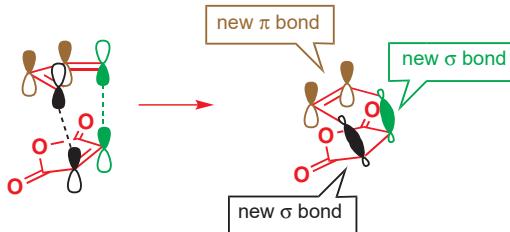
mediates at all. This type of reaction is called **pericyclic**. The most famous example is the **Diels–Alder reaction**. This reaction goes in a single step simply on heating. We can draw the mechanism with the electrons going round a six-membered ring.



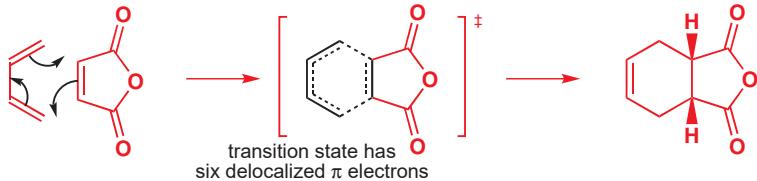
Each arrow leads directly to the next, and the last arrow connects to the first. We have drawn the electrons rotating clockwise, but it would make no difference at all if we drew the electrons rotating anticlockwise.



Both mechanisms are equally correct. The electrons do not really rotate at all. In reality two  $\pi$  bonds disappear and two  $\sigma$  bonds take their place by the electrons moving smoothly out of the  $\pi$  orbitals into the  $\sigma$  orbitals. Such a reaction is called a **cycloaddition**. We must spend some time working out how this could happen. First, just consider the orbitals that overlap to form the new bonds. Providing the reagents approach in the right way, nothing could be simpler.



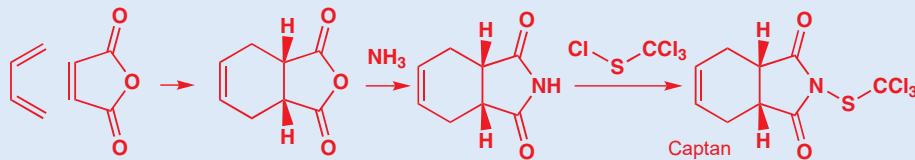
The black p orbitals are perfectly aligned to make a new  $\sigma$  bond, as are the two green orbitals, while the two brown orbitals are exactly right for the new  $\pi$  bond at the back of the ring. As this is a one-step reaction there are no intermediates but there is one transition state looking something like this:



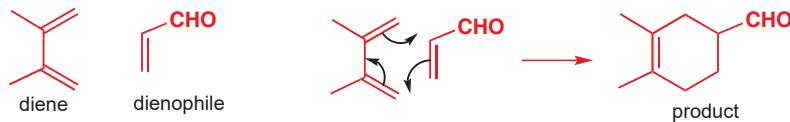
One reason that the Diels–Alder reaction goes so well is that the transition state has six delocalized  $\pi$  electrons and thus is aromatic in character, having some of the special stabilization of benzene. You could look at it as a benzene ring having all its  $\pi$  bonds but missing two  $\sigma$  bonds. This simple picture is fine as far as it goes, but it is incomplete. We shall return to a more detailed orbital analysis when we have described the reaction in more detail.

**Captan**

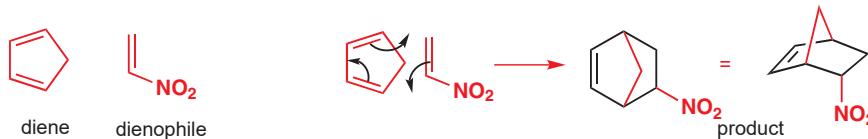
One important industrial application of the Diels–Alder reaction we have been discussing is in the synthesis of the agricultural fungicide Captan.

**General description of the Diels–Alder reaction**

Diels–Alder reactions occur between a **conjugated diene** and an alkene, usually called the **dienophile**. Here are some examples: first an open-chain diene with a simple unsaturated aldehyde as the dienophile.

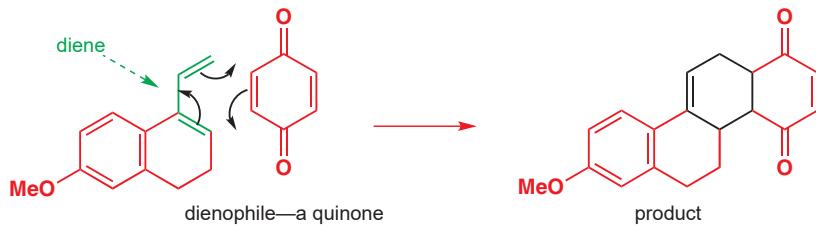


The mechanism is the same and a new six-membered ring is formed having one double bond. Now a reaction between a cyclic diene and a nitroalkene.



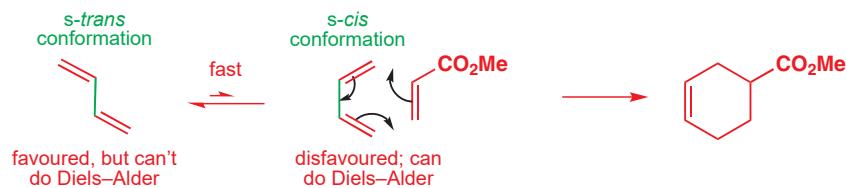
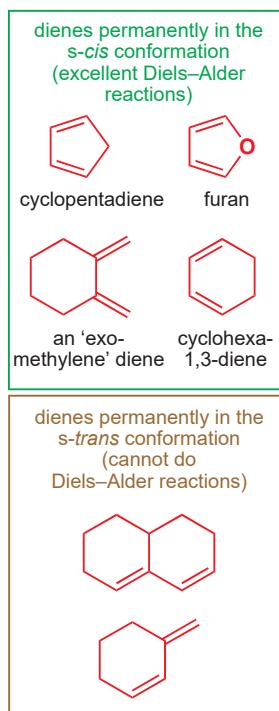
► This fused ring system, and how to draw it, was described in more detail in Chapter 32.

The mechanism leads clearly to the first drawing of the product but this is a cage structure and the second drawing is better. The new six-membered ring is outlined in black in both diagrams. A more elaborate example shows that quite complex molecules can be quickly assembled with this wonderful reaction.

**The diene**

The diene component in the Diels–Alder reaction can be open-chain or cyclic and it can have many different kinds of substituents. There is only one limitation: it must be able to take up the conformation shown in the mechanism. Butadiene normally prefers the *s-trans* conformation with the two double bonds as far away from each other as possible for steric reasons. The barrier to rotation about the central  $\sigma$  bond is small (about 30 kJ mol<sup>-1</sup> at room temperature) and rotation to the less favourable but reactive *s-cis* conformation is rapid.

► The ‘s’ in the terms ‘*s-cis*’ and ‘*s-trans*’ refers to a  $\sigma$  bond and indicates that these are conformations about a single bond and not configurations about a double bond.



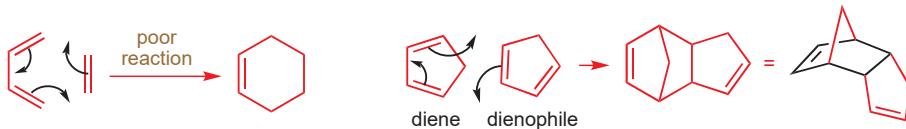
Cyclic dienes that are permanently in the *s-cis* conformation are exceptionally good at Diels–Alder reactions—cyclopentadiene is a classic example—but cyclic dienes that are permanently in the *s-trans* conformation and cannot adopt the *s-cis* conformation will not do the Diels–Alder reaction at all. The two ends of these dienes cannot get close enough to react with an alkene and, in any case, the product would have an impossible *trans* double bond in the new six-membered ring. (In the Diels–Alder reaction, the old  $\sigma$  bond in the centre of the diene becomes a  $\pi$  bond in the product and the conformation of that  $\sigma$  bond becomes the configuration of the new  $\pi$  bond in the product.)

### ● The diene

The diene must have the *s-cis* conformation.

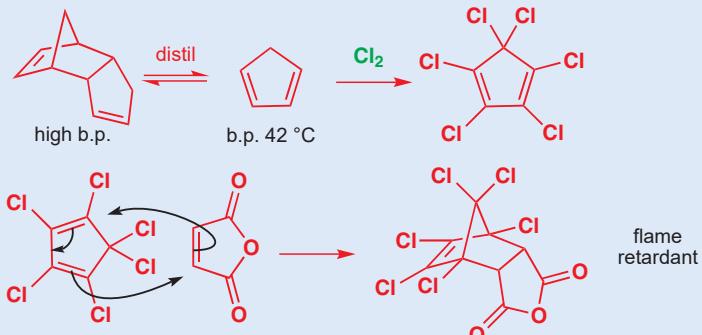
### The dienophile

The dienophiles you have seen in action so far all have one thing in common. They have an electron-withdrawing group conjugated to the alkene. This is a common, although not exclusive, feature of Diels–Alder dienophiles. There must be some extra conjugation—at least a phenyl group or a chlorine atom—or the cycloaddition does not occur. You will often see the reaction between butadiene and a simple alkene (even ethylene) given in books as the basic Diels–Alder reaction. This occurs in only poor yield. Attempts to combine even such a reactive diene as cyclopentadiene with a simple alkene lead instead to the dimerization of the diene. One molecule acts as the diene and the other as the dienophile to give the cage structure shown.



### Cyclopentadiene

Cyclopentadiene is formed in considerable amounts during the refining of petroleum. It exists as its dimer at room temperature but can be dissociated into the monomer on heating—the effect of the increased importance of entropy at higher temperatures (Chapter 12). It can be chlorinated to give hexachlorocyclopentadiene, and the Diels–Alder product of this diene with maleic anhydride is a flame retardant.

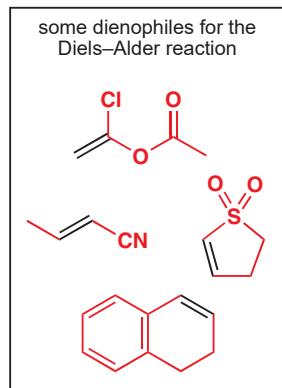
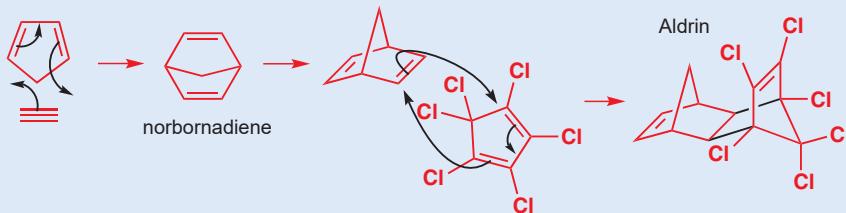


Simple alkenes that do undergo the Diels–Alder reaction include conjugated carbonyl compounds, nitro compounds, nitriles, sulfones, aryl alkenes, vinyl ethers and esters, haloalk-

enes, and dienes. In addition to those you have seen so far, a few examples are shown in the margin. In the last example it is the isolated double bond in the right-hand ring that accepts the diene. Conjugation with the left-hand ring activates this alkene. But what exactly do we mean by ‘activate’ in this sense? We shall return to that question in a minute.

### Dieldrin and Aldrin

In the 1950s two very effective pesticides were launched and their names were ‘Dieldrin’ and ‘Aldrin’. As you may guess they were made by the Diels–Alder reaction. Aldrin is derived from two consecutive Diels–Alder reactions. In the first, cyclopentadiene reacts with acetylene to give a simple symmetrical cage molecule ‘norbornadiene’ (bicyclo[2.2.1]hepta-2,5-diene). Norbornadiene is not conjugated and cannot take part in a Diels–Alder reaction as a diene. However, it is quite strained because of the cage and it reacts as a *dienophile* with perchlorocyclopentadiene to give Aldrin.



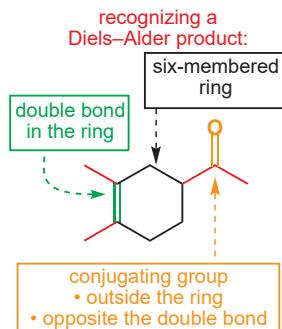
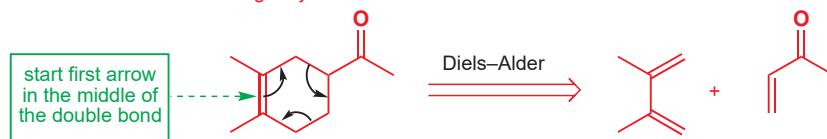
This is quite a complex product but we hope you can see how it is made up by looking at the two new bonds marked in black. Dieldrin is the epoxide of Aldrin. The use of these compounds, like that of many organochlorine compounds, was eventually banned when it was found that chlorine residues were accumulating in the fat of animals high up in the food chain, such as birds of prey and humans.

### The product

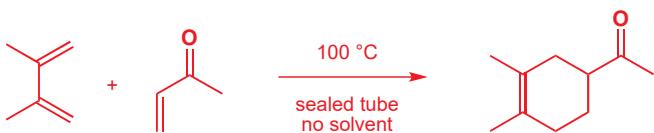
Recognizing a Diels–Alder product is straightforward. Look for the six-membered ring, the double bond inside the ring, and the conjugating group outside the ring and on the opposite side of the ring from the alkene. These three features mean that the compound is a possible Diels–Alder product.

The simplest way to find the starting materials is to carry out a disconnection that is closer to a real reaction than most. Just draw the reverse Diels–Alder reaction. To do this, draw three arrows going round the cyclohexene ring, starting the first arrow in the middle of the double bond. It doesn’t, of course, matter which way round you go.

the disconnection is the imaginary reverse Diels–Alder reaction



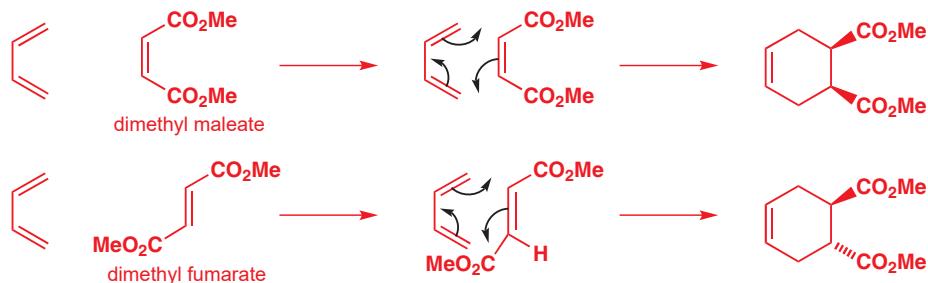
The reaction couldn’t be simpler—just heat the components together without solvent or catalyst. Temperatures of around 100–150°C are often needed and this may mean using a sealed tube if the reagents are volatile, as here.



■ Disconnections and retrosynthetic arrows of the type shown here are ways of thinking about how to make molecules. They appear throughout Chapter 28.

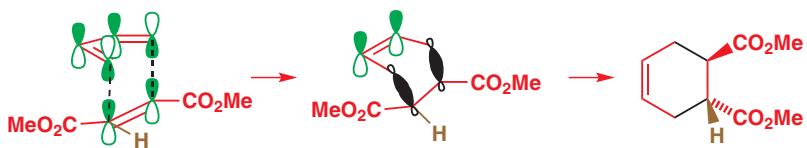
### Stereochemistry

The Diels–Alder reaction is stereospecific. If there is stereochemistry in the dienophile, then it is faithfully reproduced in the product. Thus *cis* and *trans* dienophiles give different diastereoisomers of the product. Esters of maleic and fumaric acids provide a simple example.



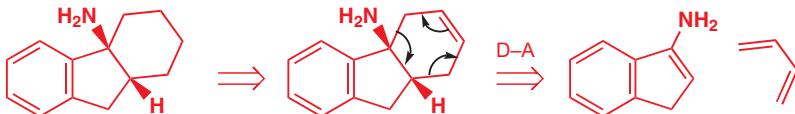
Interactive explanation of the effect of dienophile stereochemistry

In both cases the ester groups simply stay where they are. They are *cis* in the dienophile in the first reaction and remain *cis* in the product. They are *trans* in the dienophile in the second reaction and remain *trans* in the product. The second example may look less convincing—may we remind you that the diene actually comes down on top of the dienophile like this:

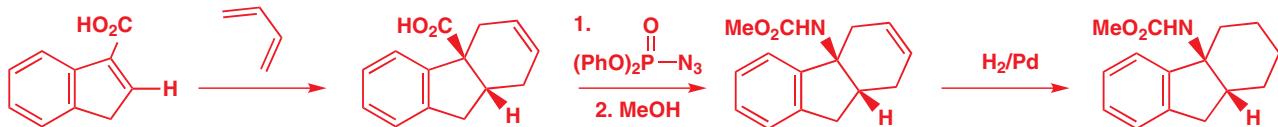


One of the  $\text{CO}_2\text{Me}$  groups is tucked under the diene in the transition state and then, when the product molecule is flattened out in the last drawing, that  $\text{CO}_2\text{Me}$  group appears underneath the ring. The brown hydrogen atom remains *cis* to the other  $\text{CO}_2\text{Me}$  group.

The search by the Parke-Davis company for drugs to treat strokes provided an interesting application of dienophile stereochemistry. The kinds of compound they wanted were tricyclic amines. They don't look like Diels–Alder products at all. But if we insert a double bond in the right place in the six-membered ring, Diels–Alder (D–A) disconnection becomes possible.



Butadiene is a good diene, but the enamine required is not a good dienophile. An electron-withdrawing group such as a carbonyl or nitro group is preferable: either would do the job. In the event a carboxylic acid that could be converted into the amine by a rearrangement with  $(\text{PhO})_2\text{PON}_3$  was used.



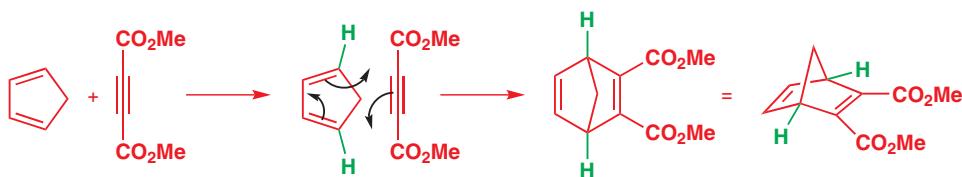
■ The rearrangement with  $(\text{PhO})_2\text{PON}_3$  is a Curtius rearrangement: it is described in Chapter 38.

■ You can add the Diels–Alder reaction to your mental list of reactions to consider for making a single diastereoisomer from a single geometrical isomer of an alkene: see Chapter 33.

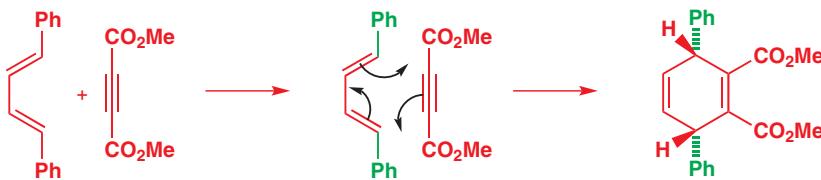
The stereochemistry at the ring junction must be *cis* because the cyclic dienophile can have only a *cis* double bond. Hydrogenation removes the double bond in the product and shows just how useful the Diels–Alder reaction is for making saturated rings, particularly when there is some stereochemistry to be controlled.

### Stereochemistry of the diene

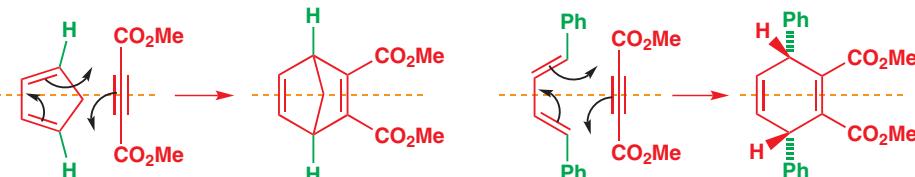
This is slightly more complicated as the diene can be *cis,cis*, or *cis,trans* (there are two of these if the diene is unsymmetrical), or *trans,trans*. We shall look at each case with the same dienophile, an acetylene dicarboxylate, as there is then no stereochemistry in the triple bond! Starting with *cis,cis*-dienes is easy if we make the diene cyclic.



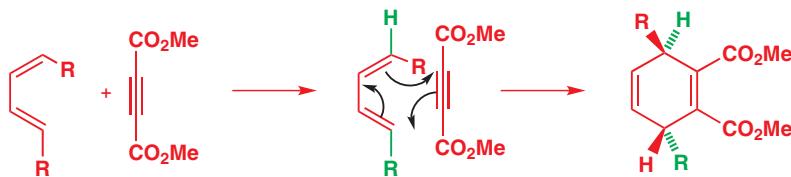
The diene has two sets of substituents—inside and outside. The inside one is the bridging  $\text{CH}_2$  group and it has to end up on one side of the molecule (above in the last diagram) while the two green hydrogens are outside and remain so. In the final diagram they are below the new six-membered ring. With a *trans,trans*-diene we simply exchange the two sets of substituents, in this example putting Ph where H was and putting H where the bridging  $\text{CH}_2$  group was. This is the reaction:



The green Ph groups end up where the hydrogens were in the first example—beneath the new six-membered ring—and the hydrogens end up above. It may seem puzzling at first that a *trans,trans*-diene gives a product with the two phenyls *cis*. Another way to look at these two reactions is to consider their symmetry. Both have a plane of symmetry throughout and the products must have this symmetry too because the reaction is concerted and no significant movement of substituents can occur. The orange dotted line shows the plane of symmetry, which is at right angles to the paper.



The remaining case—the *cis,trans*-diene—is rarer than the first two, but is met sometimes. This unsymmetrical diene means the two substituents clearly end up on opposite sides of the new six-membered ring.

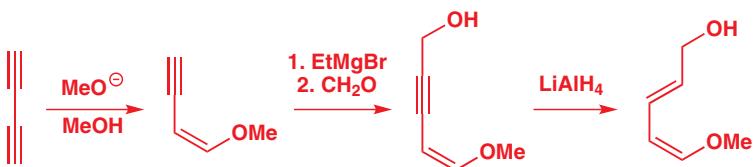


The red R group may seem to get in the way of the reaction but, of course, the dienophile is not approaching in the plane of the diene but from underneath. It is difficult to find a convincing example of this stereochemistry as there are so few known, partly because of the difficulty of making *E,Z* dienes. One good approach uses two reactions you met in Chapter 29 for the control of double-bond geometry. The *cis* double bond is put in first by the addition of methanol to butadiyne and the *trans* double bond then comes from  $\text{LiAlH}_4$  reduction of the intermediate acetylenic alcohol.

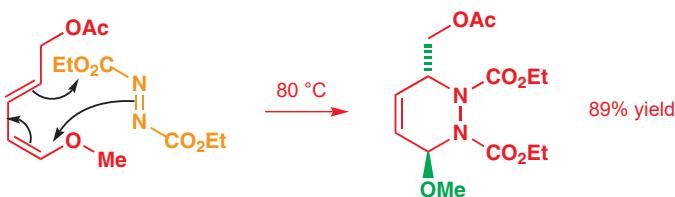
Interactive explanation of the effect of diene stereochemistry

► The mechanism for these reactions is given on pp. 682 and 684.

► DEAD is a key component of the Mitsunobu reaction: see p. 349.



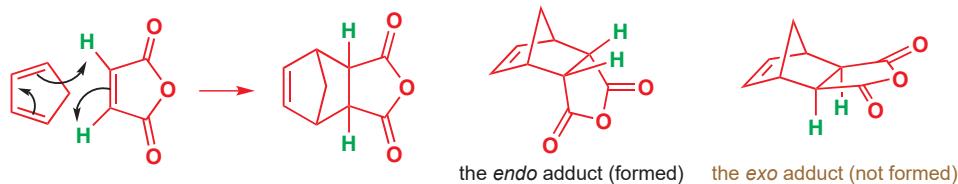
The acetate of this alcohol is used in a Diels–Alder reaction with the interesting dienophile DEAD (diethyl azodicarboxylate—in orange). The product is formed in excellent yield and has the *trans* stereochemistry that was predicted. The amide nitrogen atoms are planar, so there is no question of stereochemistry there. DEAD itself can equilibrate rapidly between *E* and *Z* isomers, but the *E* predominates.



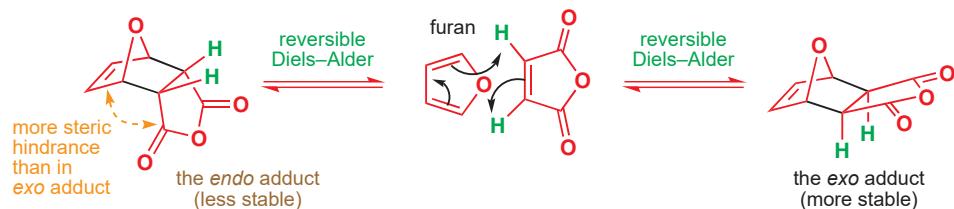
Now to the most interesting cases of all, when both the diene and the dienophile have stereochemistry.

### The *endo* rule for the Diels–Alder reaction

It is probably easier to see this when both the diene and the dienophile are cyclic. All the double bonds are *cis* and the stereochemistry is clearer. In the most famous Diels–Alder reaction of all time, that between cyclopentadiene and maleic anhydride, there are two possible products that obey all the rules we have so far described. They are the only possible diastereoisomers of the product—although it has four stereogenic centres, any other diastereoisomers would be impossibly strained.



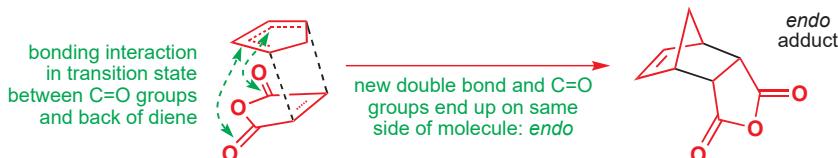
The two green hydrogen atoms must be *cis* in the product, but now there are two such compounds, known as the *exo* and *endo* products. When the reaction is carried out, the product is, in fact, the *endo* compound. Only one diastereoisomer is formed, and it is the less stable one. How do we know this? Well, for cases in which the Diels–Alder reaction is reversible and therefore under thermodynamic control, the *exo* product is formed instead. The best known example results from the replacement of cyclopentadiene with furan in reaction with the same dienophile.



Why is the *exo* product the more stable? Look again at these two structures. On the left-hand side of the molecules, there are two bridges across the ends of the new bonds (highlighted in black): a one-C-atom bridge and a two-C-atom bridge. There is less steric hindrance if the smaller (that is, the one-atom) bridge eclipses the anhydride ring.

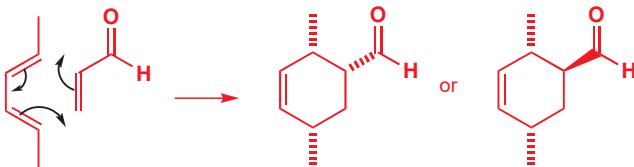
The *endo* product is less stable than the *exo* product and yet it is preferred in irreversible Diels–Alder reactions—it must be the kinetic product of the reaction. It forms faster because

a bonding interaction between the electron-deficient carbonyl groups of the dienophile and the developing  $\pi$  bond at the back of the diene lowers the energy of the transition state, leading to the *endo* product.



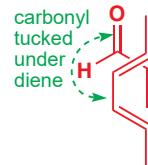
Interactive explanation of *endo* selectivity

The same result is found with acyclic dienes and dienophiles. Normally one diastereoisomer is preferred—the one with the carbonyl groups of the dienophile closest to the developing  $\pi$  bond at the back of the diene. Here is an example.

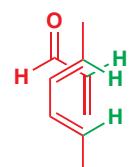


From our previous discussion (it's a *trans,trans* diene) we expect the two methyl groups to be *cis* to each other and the only question remaining is the stereochemistry of the aldehyde group—up or down? The aldehyde will be *endo*—but which compound is that? The easiest way to find the answer is to draw the reagents coming together in three dimensions. Here is one way to do this.

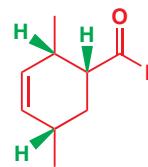
1. Draw the mechanism of the reaction and diagrams of the product to show what you are trying to decide. Put in the known stereochemistry if you wish. This we have just done (see above).
2. Draw both molecules in the plane of the paper with the diene on top and the carbonyl group of the dienophile tucked under the diene so it can be close to the developing  $\pi$ -bond.



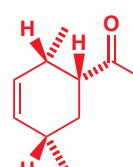
3. Now draw in all the hydrogen atoms on the carbon atoms that are going to become stereogenic centres, that is, those shown in green here.



4. Draw a diagram of the product. Unfold the molecule to show the six-membered ring. All the substituents to the right in the previous diagram are on one side of the new molecule. That is, all the green hydrogen atoms are *cis* to each other.



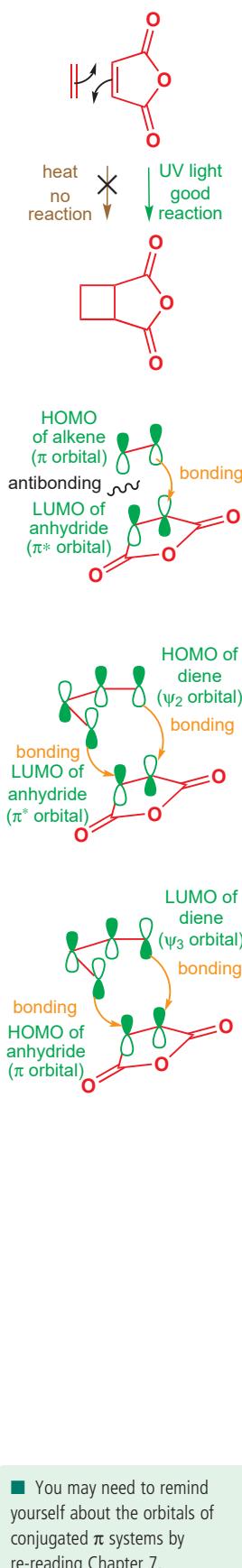
5. Draw a final diagram of the product with the stereochemistry of the other substituents shown too in the usual way. This is the *endo* product of the Diels–Alder reaction.



### Time for some explanations

We have accumulated rather a lot of unexplained results.

- Why does the Diels–Alder reaction work so well?
- Why must we have a conjugating group on the dienophile?
- Why is the stereochemistry of each component retained so faithfully?
- Why is the *endo* product preferred kinetically?



There is more. The simpler picture we met earlier in this chapter also fails to explain why the Diels–Alder reaction occurs simply on heating while attempted additions of simple alkenes (rather than dienes) to maleic anhydride fail on heating but succeed under irradiation with UV light.

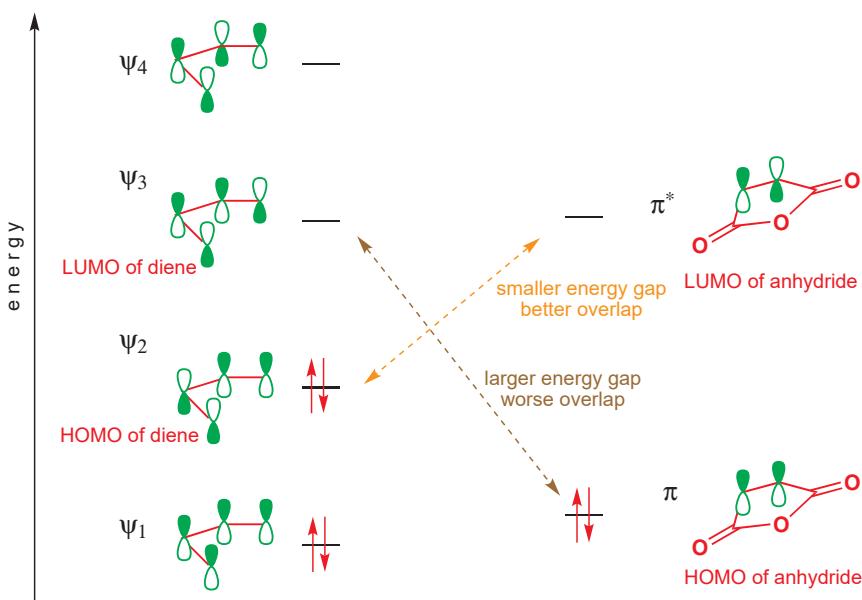
We shall now explain all this in one section using frontier molecular orbitals. Of all the kinds of organic reactions, pericyclic ones are the most tightly controlled by orbitals, and the development of the ideas we are about to expound is one of the greatest triumphs of modern theoretical chemistry. It is a beautiful and satisfying set of ideas based on very simple principles.

## The frontier orbital description of cycloadditions

When an ionic cyclization reaction occurs, such as the lactonization at the head of this chapter, one important new bond is formed. It is enough to combine one full orbital with one empty orbital to make the new bond. But in a cycloaddition two new bonds are formed at the same time. We have to arrange for two filled p orbitals and two empty p orbitals to be available at the right place and with the right symmetry. See what happens if we draw the orbitals for the reaction above. We could try the HOMO ( $\pi$ ) of the alkene and the LUMO ( $\pi^*$ ) of the double bond in the anhydride (as in the margin). This combination is bonding at one end, but antibonding at the other so that no cycloaddition reaction occurs. It obviously doesn't help to use the other HOMO/LUMO pair, that is the HOMO of the aldehyde and the LUMO of the alkene, as they will have the same mismatched symmetry.

Now see what happens when we replace the alkene with a diene. We shall again use the LUMO of the electron-poor anhydride. Now the symmetry is right because there is a node in the middle of the HOMO of the diene (the HOMO is  $\psi_2$  of the diene) just as there is in the LUMO of the dienophile.

If we had tried the opposite arrangement, the LUMO of the diene ( $\psi_3$ ) and the HOMO of the dienophile, the symmetry would again be right. The LUMO of the diene has two nodes and gives the same symmetry as the HOMO of the dienophile, which has no nodes. So either combination is excellent. In fact most Diels–Alder reactions use electron-deficient dienophiles and electron-rich dienes so we prefer the first arrangement. The electron-deficient dienophile has a low-energy LUMO and the electron-rich diene has a high-energy HOMO so this combination gives a better overlap in the transition state. The energy levels will look like this, and the interaction shown in orange is better than the interaction shown in brown because the orbitals are closer in energy.



You may need to remind yourself about the orbitals of conjugated  $\pi$  systems by re-reading Chapter 7.

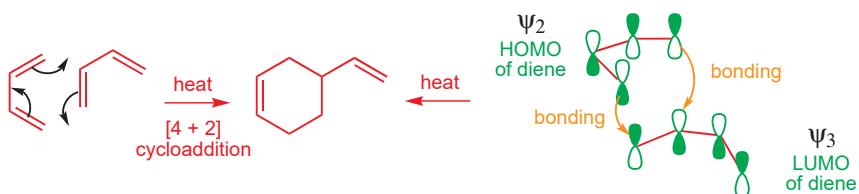
This is why we usually use dienophiles with conjugating groups for good Diels–Alder reactions. Dienes react rapidly with electrophiles because their HOMOs are relatively high in energy, but simple alkenes are not suitable electrophiles because they have relatively high energy LUMOs. The most effective modification we can make is to lower the energy of the alkene's LUMO by conjugating the double bond with an electron-withdrawing group such as carbonyl or nitro. These are the most common type of Diels–Alder reactions—between electron-rich dienes and electron-deficient dienophiles.

### Dimerizations of dienes by cycloaddition reactions

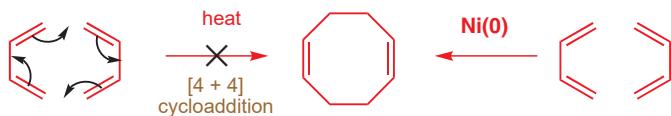
Because dienes have relatively high-energy HOMOs and low-energy LUMOs they should be able to take part in cycloadditions with themselves. And indeed, dienes do dimerize, by a Diels–Alder reaction. One molecule of the diene plays the role of the dienophile. The symmetry is correct for the interaction shown, and we call such reactions (like all the Diels–Alder reactions in this chapter) '[4 + 2] cycloadditions'—the numbers referring to the number of atoms of each component taking part in the reaction.

A rarer type is the **reverse electron demand Diels–Alder reaction** in which the dienophile has electron-donating groups and the diene has a conjugated electron-withdrawing group. These reactions use the HOMO of the dienophile and the LUMO of the diene. This combination still has the right orbital symmetry.

The same features of dienes allow them to react with both electrophiles and nucleophiles: see p. 148.



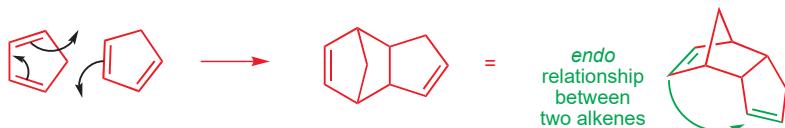
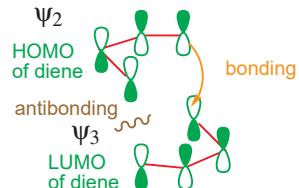
What dienes cannot do is form an eight-membered ring in one step in a [4 + 4] cycloaddition (although this is possible photochemically or with transition metal catalysis, as we shall see later).



You should have expected this failure because the ends of the required orbitals must again have the wrong symmetry, just as they had when we tried the alkene dimerization.

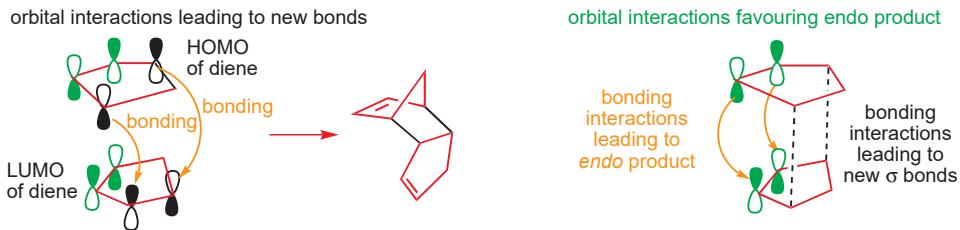
### The orbital explanation for *endo* preference in Diels–Alder reactions

We are going to use a diene dimerization to add more detail to our explanation of the formation of *endo* products. To make matters even easier we shall look at the dimerization of a cyclic diene—we might almost say *the* cyclic diene—cyclopentadiene. We introduced the preference for *endo* products on p. 885 by saying there was a favourable electronic interaction between the conjugating group on the dienophile and the back of the diene.



If we now draw the frontier orbitals in the two components as they come together for the reaction, we can see first of all that the symmetry is correct for bond formation (orbitals shown in black). But we can also see what is happening at the back of the diene (orbitals in green). The symmetry of the orbitals is correct for a bonding interaction at the back of the diene too. This interaction does not lead to the formation of any new bonds but it leaves its imprint in the stereochemistry of the product. The *endo* product is favoured because of this bonding interaction across the space between the orbitals.

 Interactive orbital explanation for *endo* preference in Diels–Alder reactions

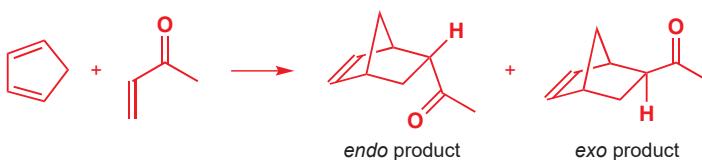


### The solvent in the Diels–Alder reaction

We discussed some effects of varying the solvent in Chapter 12, and we shall now introduce a remarkable and useful special solvent effect in the Diels–Alder reaction. The reaction does not *need* a solvent and often the two reagents are just mixed together and heated. Solvents can be used but, because there are no ionic intermediates, it seems obvious that *which* solvent is unimportant—any solvent that simply dissolves both reagents will do. This is, in general, true and hydrocarbon solvents are often the best.

However, in the 1980s an extraordinary discovery was made. Water, a most unlikely solvent for most organic reactions, has a large accelerating effect on the Diels–Alder reaction. Even some water added to an organic solvent accelerates the reaction. And that is not all. The *endo* selectivity of these reactions is often superior to those in no solvent or in a hydrocarbon solvent. Here is a simple example.

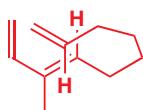
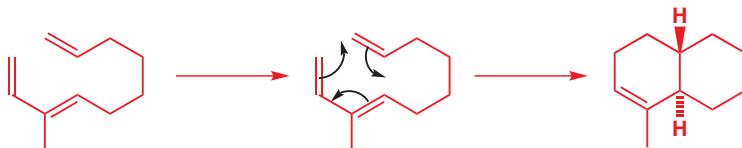
Solvent	Relative rate	<i>endo:</i> <i>exo</i> ratio
hydrocarbon (isooctane)	1	80:20
water	700	96:4



The suggestion is that the reagents, which are not soluble in water, are clumped together in oily drops by the water and forced into close proximity. Water is not exactly a solvent—it is almost an anti-solvent! Reactions like this are sometimes called reactions ‘on water’ rather than reactions ‘in water’.

### Intramolecular Diels–Alder reactions

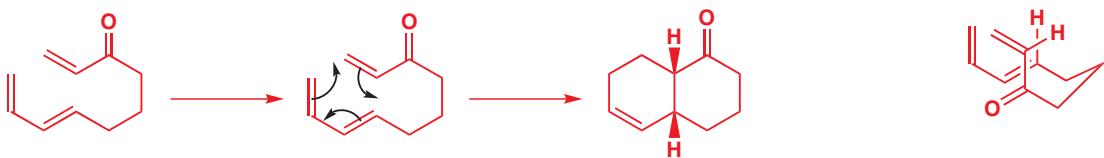
When the diene and the dienophile are already part of the same molecule it is not so important for them to be held together by bonding interactions across space and the *exo* product is often preferred. Indeed, many intramolecular Diels–Alder reactions are governed more by normal steric considerations than by the *endo* rule.



If you think about the way a Diels–Alder reaction goes, the forming ring must *always* adopt a boat-like conformation. This is clear if you make a model.

This reaction happens only because it is intramolecular. There is no conjugating group attached to the dienophile and so there are no orbitals to overlap with the back of the diene. The molecule simply folds up in the sterically most favourable way (as shown in the margin, with the linking chain adopting a chair-like conformation) and this leads to the *trans* ring junction. You can see this easily in the arrangement of the hydrogen atoms.

In the next example there is a carbonyl group conjugated with the dienophile. Now the less stable *cis* ring junction is formed because the molecule can fold so that the carbonyl group can enjoy a bonding overlap with the back of the diene. This time the linking chain has to adopt a boat-like conformation.

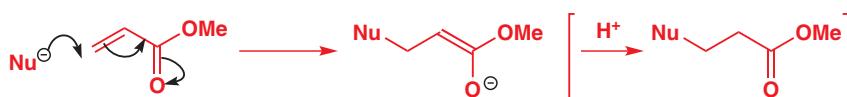


● **Intramolecular Diels–Alder**

Intramolecular Diels–Alder reactions may give the *endo* product or they may not! Be prepared for either *exo* or *endo* products or a mixture.

## Regioselectivity in Diels–Alder reactions

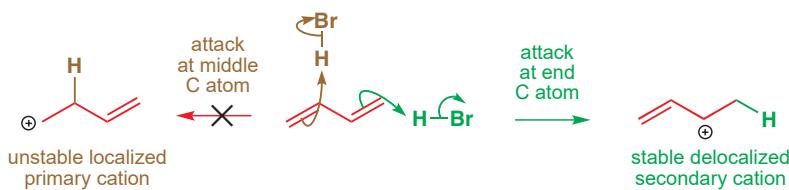
The compounds that we are now calling dienophiles were the stars of Chapters 22 and 25, where we called them **Michael acceptors** as they were the electrophilic partners in conjugate addition reactions. Nucleophiles always add to the  $\beta$  carbon atoms of these alkenes because the product is then a stable enolate. Ordinary alkenes do not react with nucleophiles.



In frontier orbital terms this is because conjugation with a carbonyl group lowers the energy of the LUMO (the  $\pi^*$  orbital of the alkene) and at the same time distorts it so that the coefficient on the  $\beta$  carbon atom is larger than that on the  $\alpha$  carbon atom. Nucleophiles approach the conjugated alkene along the axis of the large p orbital of the  $\beta$  carbon atom.

These same features can ensure regioselective Diels–Alder reactions. The same orbital of the dienophile is involved and, if the HOMO of the diene is also unsymmetrical, the regioselectivity of the reaction will be controlled by the two largest coefficients bonding together.

So what about distortion of the HOMO in the diene? If a diene reacts with an electrophile, the largest coefficient in the HOMO will direct the reaction. Consider the attack of HBr on a diene. We should expect attack at the ends of the diene because that gives the most stable possible cation—an allyl cation as an intermediate.



► This is discussed in Chapter 22.

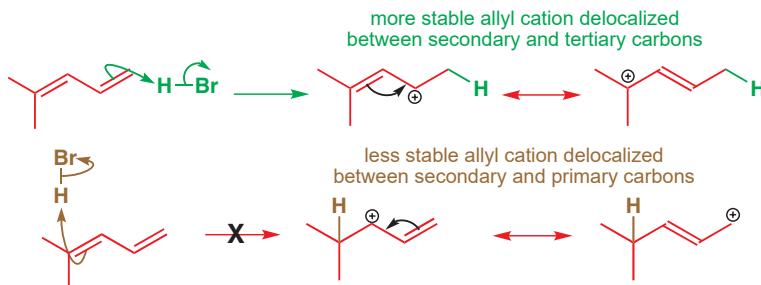


- high energy
- coefficients of same size



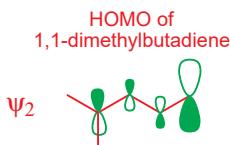
- lower energy
- unequal coefficients

In orbital terms attack occurs at the ends of the diene because the coefficients in the HOMO are larger there. We need simply to look at the HOMO ( $\psi_2$ ) of butadiene, shown in the margin, to see this. So it is not surprising that the dienes react in the Diels–Alder reaction through their end carbons. But supposing the two ends are different—which reacts now? We can again turn to the reaction with HBr as a guide. Addition of HBr to an unsymmetrical diene will give the more stable of the two possible allyl cations as the intermediate.



HOMO of butadiene

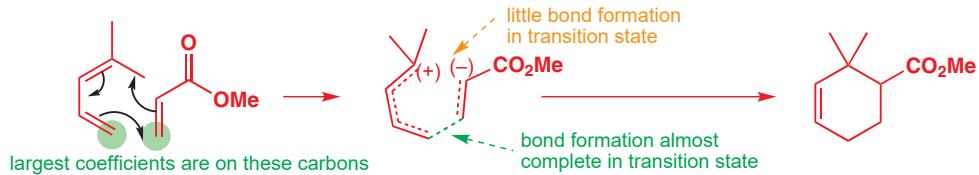




It is not 'cheating' to use the regioselectivity of chemical reactions to tell us about the coefficients in orbitals. Chemistry is about using experimental evidence to find out about the theoretical background and not about theory telling us what *ought* to happen. In fact, computational chemists have calculated the HOMO energies and coefficients of unsymmetrical dienes and have reached the same conclusions.

Interactive explanation of regioselectivity in Diels–Alder reactions

In orbital terms, this must mean that the HOMO of the diene is distorted so that the end that reacts has the larger coefficient. When the unsymmetrical diene and the unsymmetrical dienophile combine in a Diels–Alder reaction, the reaction itself becomes unsymmetrical. It remains concerted but, in the transition state, bond formation between the largest coefficients in each partner is more advanced and this determines the regioselectivity of the reaction.



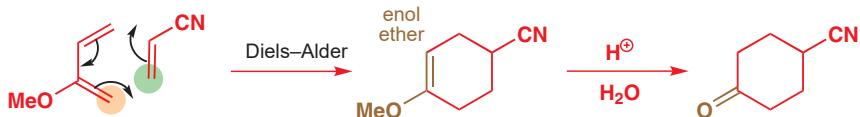
The simplest way to decide which product will be formed is to draw an 'ionic' stepwise mechanism for the reaction to establish which end of the diene will react with which end of the dienophile. Of course this stepwise mechanism is not completely correct but it does lead to the correct orientation of the reagents and you can draw the right mechanism afterwards. As an example, try a diene with a substituent in the middle. This is the reaction:



First decide where the diene will act as a nucleophile and where the dienophile will act as an electrophile. This indicates where the largest coefficients of the HOMO and LUMO must lie. The two circles represent those largest coefficients.



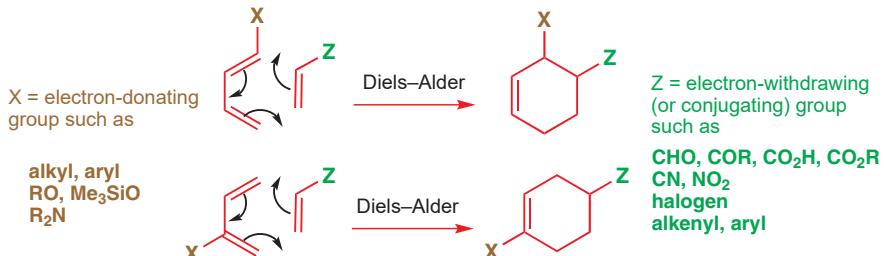
Now draw the reagents in the correct orientation for these two ends to combine and draw a concerted Diels–Alder reaction.



This is an important example because an enol ether functional group is present in the product, which can be hydrolysed to a ketone in aqueous acid (Chapter 20).

### Summary of regioselectivity in Diels–Alder reactions

The important substitution patterns are a diene with an electron-donating group (X) at one end or in the middle and a dienophile with an electron-withdrawing group (Z) at one end. These are the products formed.



- A useful mnemonic

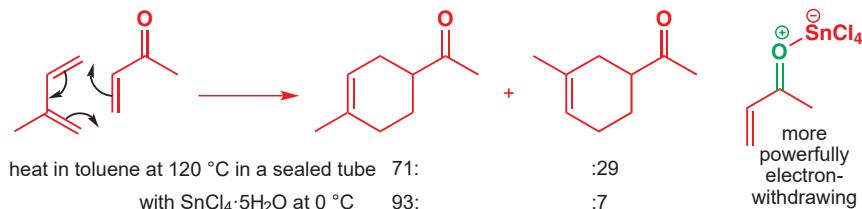
If you prefer a rule to remember, try this one.

- The Diels–Alder reaction is a cycloaddition with an aromatic transition state that is *ortho* and *para* directing.

You can see that this mnemonic works if you look at the two products above: the first has the two substituents X and Z on neighbouring carbon atoms, just like *ortho* substituents on a benzene ring, while the second has 1,4-related X and Z just like *para* substituents. The connection with aromaticity (the ‘aromatic transition state’) simply means that the transition state is cyclic and has six electrons. We have not yet explored the consequences of this, but we will do shortly.

## Lewis acid catalysis in Diels–Alder reactions

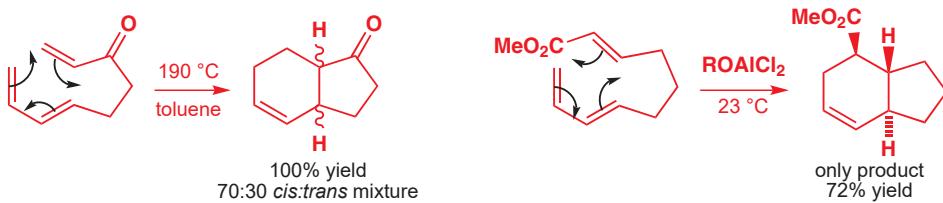
Where the reagents are unsymmetrical, a Lewis acid that can bind to the electron-withdrawing group of the dienophile often catalyses the reaction by lowering the LUMO of the dienophile still further. It has another important advantage: it increases the difference between the coefficients in the LUMO (a Lewis-acid complexed carbonyl group is a more powerful electron-withdrawing group) and may therefore increase regioselectivity.



This Diels–Alder reaction is useful because it produces a substitution pattern (*para*) common in natural terpenes (see Chapter 42). But the regioselectivity introduced by one methyl group on the diene is not very great—this reaction gives a 71:29 mixture when the two compounds are heated together at 120°C in a sealed tube. In the presence of the Lewis acid ( $\text{SnCl}_4$ ) the reaction can be carried out at lower temperatures (below 25°C) without a sealed tube and the regioselectivity improves to 93:7.

## Regioselectivity in intramolecular Diels–Alder reactions

Just as the stereoselectivity may be compromised in intramolecular reactions, so may the regioselectivity. It may be simply impossible for the reagents to get together in the ‘right’ orientation. The examples below have a very short chain—just three carbon atoms—joining diene to dienophile and so the same regioselectivity is found regardless of the position of the conjugating carbonyl group.



The first example has the ‘right’ orientation (*ortho*) but the second has the ‘wrong’ orientation (*meta*). The short tether entails no prospect of any other orientation and, as the reaction is intramolecular, it goes anyway. Notice the lower temperature required for the Lewis acid ( $\text{ROAlCl}_2$ ) catalysed reaction.

## The Woodward–Hoffmann description of the Diels–Alder reaction

Kenichi Fukui and Roald Hoffmann won the Nobel prize in 1981 (Woodward died in 1979 and so couldn't share this prize: he had already won a Nobel prize in 1965 for his work on synthesis) for the application of orbital symmetry to pericyclic reactions. There is an alternative description to the frontier orbital method we have used and you need to know a little about it. They started by considering a more fundamental correlation between the symmetry of all the orbitals in the starting materials and all the orbitals in the products. This is rather too complex for us to cover here, and we shall concentrate only on a summary of the conclusions—the **Woodward–Hoffmann rules**. The most important of these states:

### ● Woodward–Hoffmann rules

In a thermal pericyclic reaction the total number of  $(4q + 2)_s$  and  $(4r)_a$  components must be odd.

This needs some explanation. A component is a bond or orbital taking part in a pericyclic reaction as a single unit. A double bond is a  $\pi_2$  component. The number 2 is the most important part of this designation and simply refers to the number of electrons. The prefix  $\pi$  tells us the type of electrons. A component may have any number of electrons (a diene is a  $\pi_4$  component) but may not have mixtures of  $\pi$  and  $\sigma$  electrons. Now look back at the rule. Those designations  $(4q + 2)$  and  $(4r)$  simply refer to the number of electrons in the component where  $q$  and  $r$  are integers. An alkene is a  $\pi_2$  component and so it is of the  $(4q + 2)$  kind while a diene is a  $\pi_4$  component and so is of the  $(4r)$  kind. You have already seen the importance of  $4n + 2$  numbers in aromaticity; here the significance is closely related.

Now what about the suffixes 's' and 'a'? The suffix 's' stands for suprafacial and 'a' for antarafacial. A **suprafacial** component forms new bonds on the same face at both ends while an **antarafacial** component forms new bonds on opposite faces at both ends. If you find it easier to understand, you can think of the Woodward–Hoffmann rules like this:

### ● Woodward–Hoffmann rules: alternative version

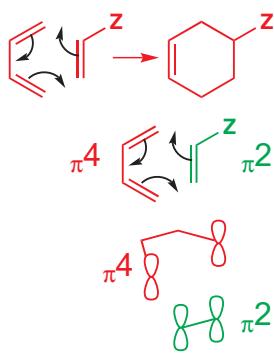
In an allowed thermal pericyclic reaction this sum:

$$\begin{aligned} &\text{number of suprafacial components with 2, 6, or 10 electrons} \\ &+ \text{number of antarafacial components with 0, 4, or 8 electrons} \\ &= \text{an odd number} \end{aligned}$$

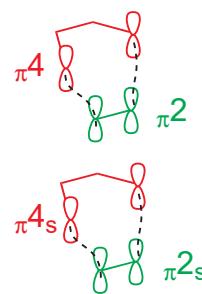
It's the number of relevant **components** that must be odd, not (obviously) the number of electrons, and you must ignore any components which aren't mentioned in the sum (for example you can have as many suprafacial components with four electrons as you like—they just don't count).

See how this works for the Diels–Alder reaction. Here is the routine.

1. Draw the mechanism for the reaction (we shall choose a general one).
2. Choose the components. All the bonds taking part in the mechanism must be included and no others.
3. Make a three-dimensional drawing of the way the components come together for the reaction, putting in orbitals at the ends of the components (only!). The orbitals are just unshaded p orbitals, and do not make up HOMOs or LUMOs nor any particular molecular orbital. Don't attempt to mix frontier orbital and Woodward–Hoffmann descriptions of pericyclic reactions.



4. Join up the components where new bonds are to be formed. Coloured dotted lines are often used.

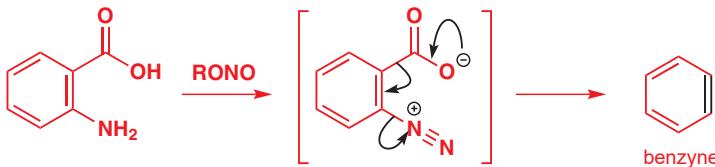


5. Label each component 's' or 'a' depending on whether new bonds are formed on the same or on opposite sides. In all of the cycloadditions you have seen so far (and indeed the vast majority of those you will ever see), both components react suprafacially.
6. Count the number of  $(4q + 2)_s$  and  $(4r)_a$  components. If the total count is odd, the reaction is allowed. In this case, **there is one  $(4q + 2)_s$  component (the alkene) and no  $(4r)_a$  components. Total = 1 so it is an allowed reaction.** Components of the other symmetry, that is  $(4q + 2)_a$  and  $(4r)_s$  components, do not count. You can have as many of these as you want.

You may well feel that there is very little to be gained from the Woodward–Hoffmann treatment of the Diels–Alder reaction. It does not explain the *endo* selectivity nor the regioselectivity. However, the Woodward–Hoffmann treatment of other pericyclic reactions (particularly electrocyclic reactions, in the next chapter) is very helpful.

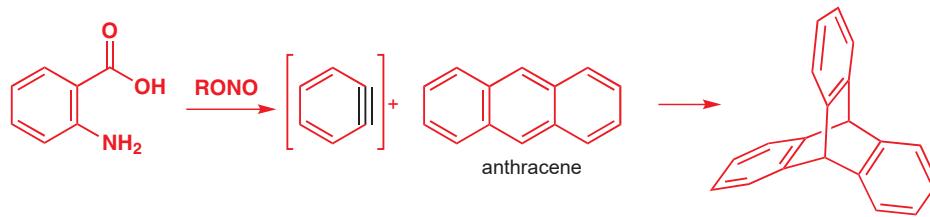
## Trapping reactive intermediates by cycloadditions

In Chapter 22 you met the remarkable intermediate benzyne. Convincing evidence for the existence of this implausible structure is provided by the fact that it can be trapped in a Diels–Alder reaction. One way of generating benzyne for this purpose is the diazotization of anthranilic acid (2-aminobenzoic acid).

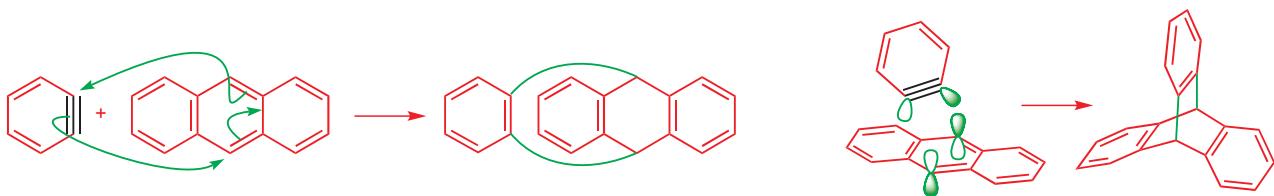


It also explains why the  $[4 + 4]$  cycloaddition on p. 887 and the  $[2 + 2]$  cycloaddition on p. 886 fail: draw out the reactions and you find there are no  $(4q + 2)_s$  and  $(4r)_a$  components—and you must have an *odd* number for a successful reaction.

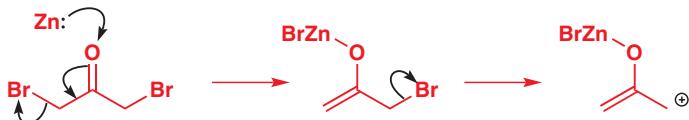
Benzyne may not look like a good dienophile but it is an unstable electrophilic molecule so it must have a low-energy LUMO ( $\pi^*$  of the triple bond). If benzyne is generated in the presence of a diene, efficient Diels–Alder reactions take place. Anthracene gives a specially interesting product with a symmetrical cage structure.



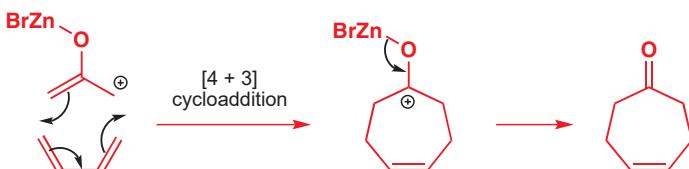
It is difficult to draw this mechanism convincingly. The two flat molecules approach each other in orthogonal planes, so that the (orbitals) of the localized  $\pi$  bond of benzyne interact with the p orbitals on the central ring of anthracene.



Another intermediate for which a cycloaddition product provides convincing evidence is the oxyallyl cation. This compound can be made from  $\alpha,\alpha'$ -dibromoketones on treatment with zinc metal. The first step is the formation of a zinc enolate (compare the Reformatsky reaction), which can be drawn in terms of the attack of zinc on oxygen or bromine. Now the other bromine can leave as an anion. It could not do so before because it was next to an electron-withdrawing carbonyl group. Now it is next to an electron-rich enolate so the cation is stabilized by conjugation.

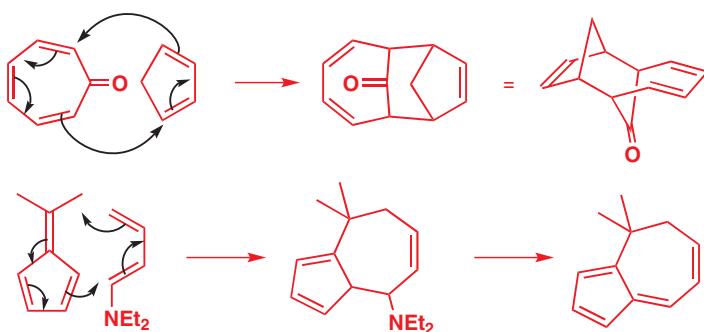


The allyl cation has three atoms but only two electrons so it can take part in cycloadditions with dienes—the total number of electrons is six, just as in the Diels–Alder reaction. This is a [4 + 3] all-suprafacial cycloaddition.



## Other thermal cycloadditions

A simple consequence of the Woodward–Hoffmann rules is that cycloadditions involving a total  $(4n + 2)$  electrons, if they are all suprafacial, are always allowed: they must always involve an odd number of  $(4q + 2)_s$  components. Such reactions are often referred to as having ‘aromatic transition states’ because of the obvious link with the aromatic requirement for  $(4n + 2)$  electrons. Six is the most common  $(4n + 2)$  number, but there are also a few cycloadditions involving ten electrons. These are mostly diene + triene, that is,  $\pi^4_s + \pi^6_s$  cycloadditions. Here are a couple of examples.

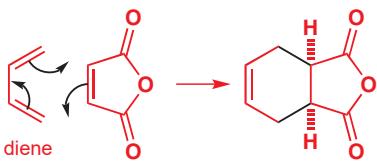


In the first case, there is an *endo* relationship between the carbonyl group and the back of the diene—this product is formed in 100% yield. In the second case  $\text{Et}_2\text{NH}$  is lost from the first product under the reaction conditions to give the hydrocarbon shown. This type of reaction is more of an oddity: by far the most important type of cycloaddition is the Diels–Alder reaction.

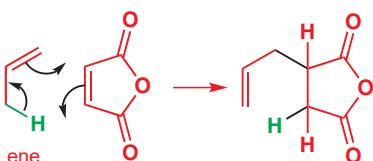
## The Alder 'ene' reaction

The Diels–Alder reaction was originally called the ‘diene reaction’ so, when half of the famous team (Kurt Alder) discovered an analogous reaction that requires only one alkene, it was called the **Alder ene reaction** and the name has stuck. Compare here the Diels–Alder and the Alder ene reactions.

the Diels–Alder reaction



the Alder ene reaction



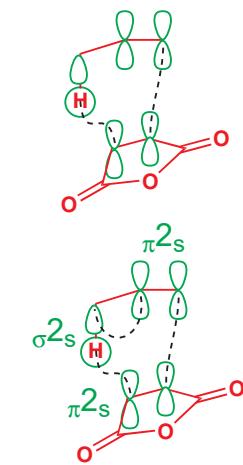
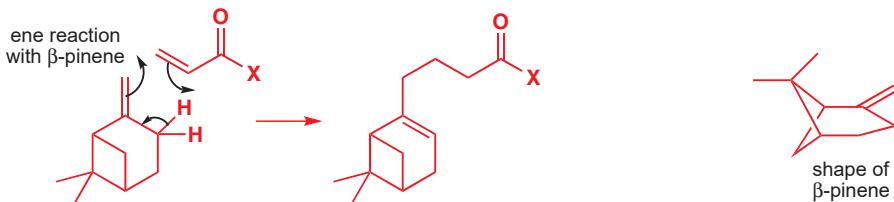
The simplest way to look at the ene reaction is to picture it as a Diels–Alder reaction in which one of the double bonds in the diene has been replaced by a C–H bond (green). The reaction does not form a new ring, the product has only one new C–C bond (shown in black on the product), and a hydrogen atom is transferred across space. Otherwise, the two reactions are remarkably similar.

The ene reaction is rather different in orbital terms. For the Woodward–Hoffmann description of the reaction we must use the two electrons of the C–H bond to replace the two electrons of the double bond in the Diels–Alder reaction, but we must make sure that all the orbitals are parallel, as shown.

The C–H bond is parallel with the p orbitals of the ene so that the orbitals that overlap to form the new  $\pi$  bond are already parallel. The two molecules approach one another in parallel planes so that the orbitals that overlap to form the new  $\sigma$  bonds are already pointing towards each other. Because the electrons are of two types,  $\pi$  and  $\sigma$ , we must divide the ene into two components, one  $\pi_2$  and one  $\sigma_2$ . We can then have an all-suprafacial reaction with three components.

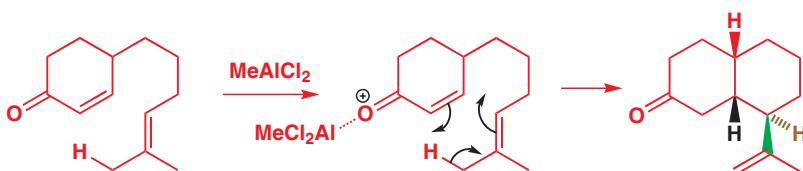
All three components are of the  $(4q + 2)_s$  type so all count and the total is three—an odd number—so the reaction is allowed. We have skipped the step-by-step approach we used for the Diels–Alder reaction because the two are so similar, but you should convince yourself that you can apply it here.

Now for some real examples. Most ene reactions with simple alkenes are with maleic anhydride. Other dienophiles—or enophiles as we should call them in this context—do not work very well. However, with one particular alkene, the natural pine tree terpene  $\beta$ -pinene, a reaction does occur with enophiles such as acrylates.



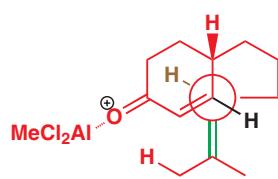
We discuss in more detail in Chapter 35 how to assign s or a with  $\sigma$  bonds. Here the  $\sigma$  bond reacts suprafacially because the 1s orbital of H has no nodes.

The major interaction between these two molecules is between the nucleophilic end of the exocyclic alkene and the electrophilic end of the acrylate. These atoms have the largest coefficients in the HOMO and LUMO, respectively, and, in the transition state, bond formation between these two will be more advanced than anywhere else. For most ordinary alkenes and enophiles, Lewis acid catalysis to make the enophile more electrophilic, or an intramolecular reaction (or both!), is necessary for an efficient ene reaction.

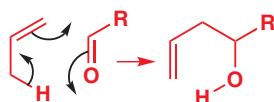


We looked at using tethers to constrain the formation of a single diastereoisomer in Chapter 32, p. 847.

The ‘ene’ component is delivered to the bottom face of the enone, as its tether is too short for it to reach the top face, and a *cis* ring junction is formed. The stereochemistry of the third centre is most easily seen by a Newman projection (Chapter 16) of the reaction. In the diagram in the margin we are looking straight down the new C–C bond and the colour coding should help you to see how the stereochemistry follows.

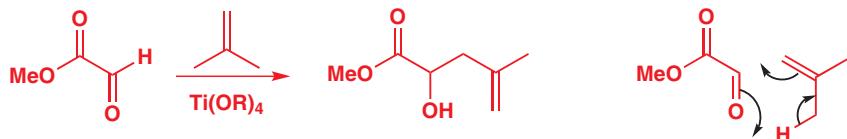


the carbonyl ene reaction



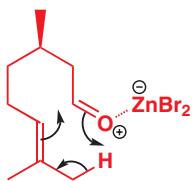
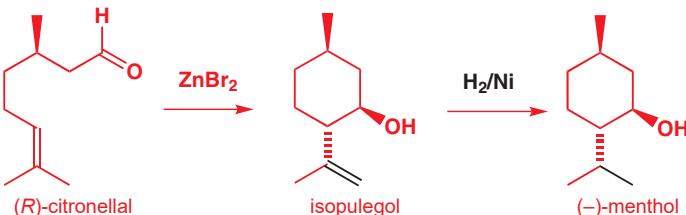
Since the twin roles of the enophile are to be attacked at one end by a C=C double bond and at the other by a proton, a carbonyl group is actually a very good enophile. These reactions are usually called ‘carbonyl ene’ reactions.

The important interaction is between the HOMO of the ene system and the LUMO of the carbonyl group—and a Lewis-acid catalyst can lower the energy of the LUMO still further. If there is a choice, the more electrophilic carbonyl group (the one with the lower LUMO) reacts.



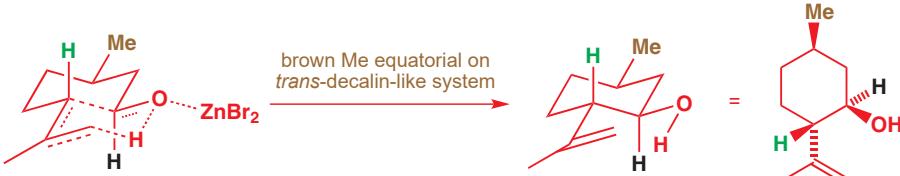
It may not be obvious that an ene reaction has occurred because of the symmetry of the alkene. The double bond in the product is not, in fact, in the same place as it was in the starting material, as the mechanism shows.

One carbonyl ene reaction is of commercial importance as it is part of a process for the production of menthol used to give a peppermint smell and taste to many products. This is an intramolecular ene reaction on another terpene derivative.



It is not obvious what has happened in the first step, but the movement of the alkene and the closure of the ring with the formation of one (not two) new C–C bonds should give you the clue that this is a Lewis-acid-catalysed carbonyl ene reaction.

The stereochemistry comes from an all-chair arrangement in the conformation of the transition state. The methyl group will adopt an equatorial position in this conformation, fixing the way the other bonds are formed. Again, colour coding should make it clearer what has happened.



Interactive mechanism for the intramolecular carbonyl ene reaction

### Allowed reactions

Because a reaction is ‘allowed’ doesn’t mean that it will happen. It just means it is theoretically possible. In the same way you might be ‘allowed’ to jump off a three metre wall, but you wouldn’t do it.

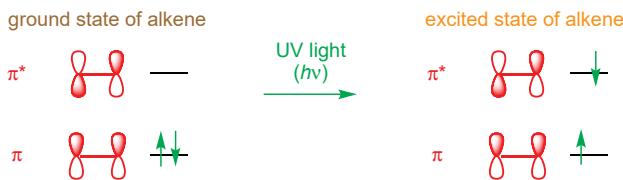
### Menthol manufacture

It may seem odd to you to have a chemical process to produce menthol, which would be available naturally from mint plants. This process is now responsible for much of the world’s menthol production so it must make some sort of sense! The truth is that menthol *cultivation* is wasteful in good land that could produce food crops such as rice while the starting material for menthol *manufacture* is the same  $\beta$ -pinene we have just met. This is available in large quantities from pine trees grown on poor land for paper and furniture. The earlier stages of the process are discussed in Chapter 41.

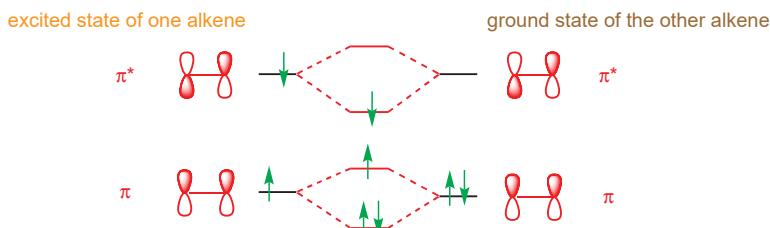
### Photochemical [2 + 2] cycloadditions

We shall now leave six-electron cycloadditions such as the Diels–Alder and ene reactions and move on to some four-electron cycloadditions. Clearly, four is not a  $(4n + 2)$  number, but when we described the Woodward–Hoffman rules on p. 892 we used the term ‘thermally’. All

suprafacial cycloadditions with  $4n$  electrons *are* allowed if the reaction is not thermal (that is, driven by heat energy) but **photochemical** (that is, driven by light energy). Under photochemical conditions, the rules switch such that all the cycloadditions that are not allowed thermally are allowed photochemically. This works because the problem of the incompatible symmetry in trying to add two alkenes together is avoided by converting one of them into the excited state photochemically. First, one electron is excited by the light energy from the  $\pi$  to the  $\pi^*$  orbital.



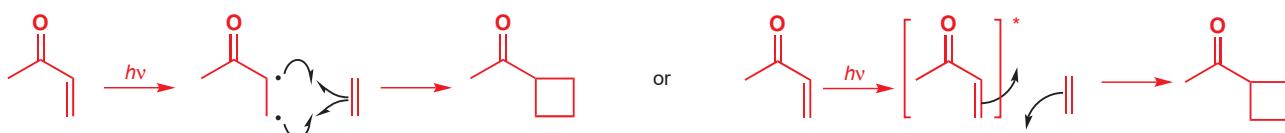
Now, combining the excited state of one alkene with the ground state of another solves the symmetry problem. Mixing the two  $\pi$  orbitals leads to two molecular orbitals, and two electrons go down in energy while only one goes up. Mixing the two  $\pi^*$  orbitals is as good—one electron goes down in energy and none goes up. The result is that three electrons go down in energy and only one goes up. Bonding can occur.



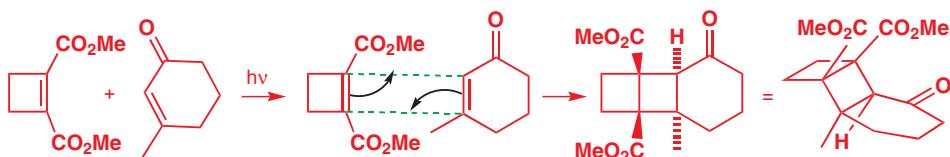
► In Chapter 7 we discussed why conjugated systems absorb UV light more readily than do unconjugated ones.

Alkenes can be dimerized photochemically in this way, but reaction between two different alkenes is more interesting. If one alkene is bonded to a conjugating group, it alone will absorb UV light and be excited while the other will remain in the ground state. It is difficult to draw a mechanism for these reactions as we have no simple way to represent the excited alkene. Some people draw it as a diradical (since each electron is in a different orbital); others prefer to write a concerted reaction on an excited alkene marked with an asterisk.

A photochemical [2 + 2] cycloaddition: two ways of writing the mechanism



The reaction is stereospecific within each component but there is no *endo* rule—there is a conjugating group but no ‘back of the diene’. The least hindered transition state usually results. The dotted lines on the central diagram simply show the bonds being formed. The two old rings keep out of each other’s way during the reaction and the conformation of the product looks reasonably unhindered.

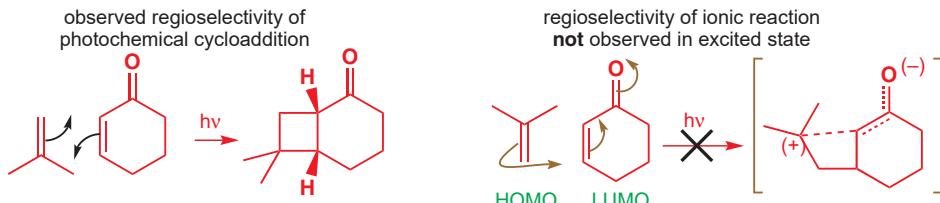


You may be wondering why the reaction works at all, given the strain in a four-membered ring: why doesn’t the product just go back to the two starting materials? This reverse reaction is governed by the Woodward–Hoffmann rules, just like the forward one, and to go back again the four-membered ring products would have to absorb light. But since they have now lost

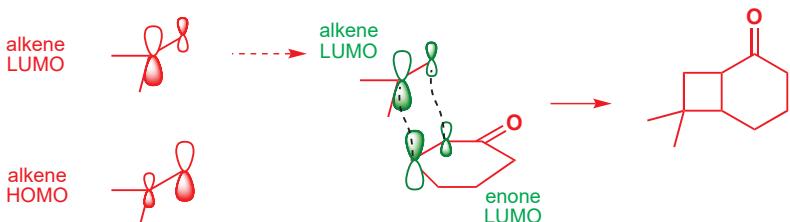
their  $\pi$  bonds they have no low-lying empty orbitals into which light can promote electrons (see Chapter 7). The reverse photochemical reaction is simply not possible because there is no mechanism for the compounds to absorb light.

### Regioselectivity in photochemical [2 + 2] cycloadditions

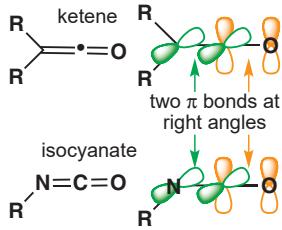
The observed regioselectivity is shown below. If we had combined the HOMO of the alkene with the LUMO of the enone, as we should in a thermal reaction, we would expect the opposite orientation so as to use the larger coefficients of the frontier orbitals and to maximize charge stabilization in the transition state.



But we are not doing a thermal reaction. If you look back at the orbital diagram on p. 897, you will see that it is the HOMO/HOMO and LUMO/LUMO interactions that now matter in the reactions of the excited state. The sizes of the coefficients in the LUMO of the alkene are the other way round to those in the HOMO. There is one electron in this pair of orbitals—in the LUMO of the enone in fact, as the enone has been excited by the light—so overlap between the two LUMOs (shown in the frame) is bonding and leads to the observed product. The easiest way to work it out quickly is to draw the product you do *not* expect from a normal HOMO/LUMO or curly arrow controlled reaction.

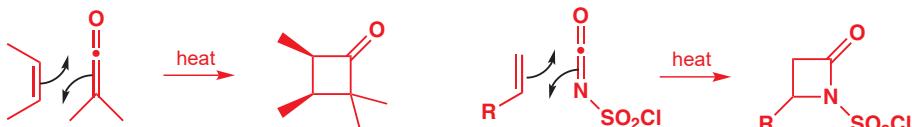
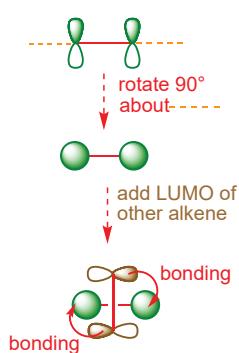


### Thermal [2 + 2] cycloadditions



Despite what we have told you about allowed cycloadditions, there *are* some thermal [2 + 2] cycloadditions giving four-membered rings. These feature a simple alkene reacting with an electrophilic alkene of a peculiar type. It must have two double bonds to the *same* carbon atom. The most important examples are ketenes and isocyanates. The structures have two  $\pi$  bonds at right angles.

Here are typical reactions of dimethyl ketene to give a cyclobutanone and chlorosulfonyl isocyanate to give a  $\beta$ -lactam.



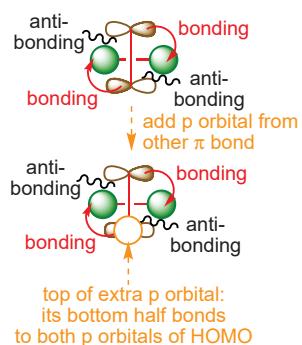
To understand why these reactions work, we need to consider a new and potentially fruitful way for two alkenes to approach each other. As you saw on p. 886, thermal cycloadditions between two alkenes do not work because the HOMO/LUMO combination is antibonding at one end.

If one alkene turns at 90° to the other, there is a way in which the HOMO of one might bond at both ends to the LUMO of the other. First we turn the HOMO of one alkene so that we are

looking down on the p orbitals. Then we add the LUMO of the other alkene on top of this HOMO and at 90° to it so that there is the possibility of bonding overlap at both ends.

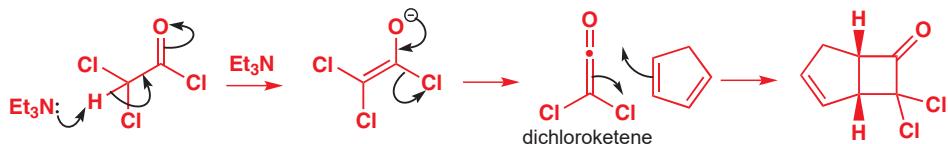
This arrangement looks quite promising until we notice that there is antibonding at the other two corners! Overall there is no net bonding. We can tilt the balance in favour of bonding by adding a p orbital to one end of the LUMO and at a right angle to it so that both orbitals of the HOMO can bond to this extra p orbital. There are now four bonding interactions but only two antibonding. The balance is in favour of a reaction. This is also quite difficult to draw!

Ketenes have a central sp carbon atom with an extra  $\pi$  bond (the C=O) at right angles to the first alkene—perfect for thermal [2 + 2] cycloadditions. They are also electrophilic and so have suitable low-energy LUMOs.

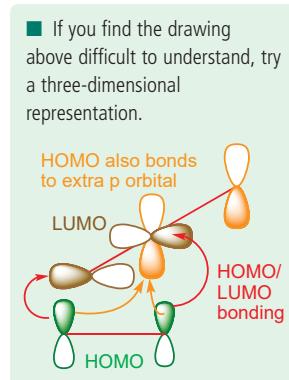


### Ketene [2 + 2] cycloadditions

Ketene itself is usually made by high-temperature pyrolysis of acetone but some ketenes are easily made in solution. The very acidic proton on dichloroacetyl chloride can be removed even with a tertiary amine and loss of chloride ion then gives dichloroketene in an E<sub>1cB</sub> elimination reaction. If the elimination is carried out in the presence of cyclopentadiene a very efficient regio- and stereospecific [2 + 2] cycloaddition occurs.

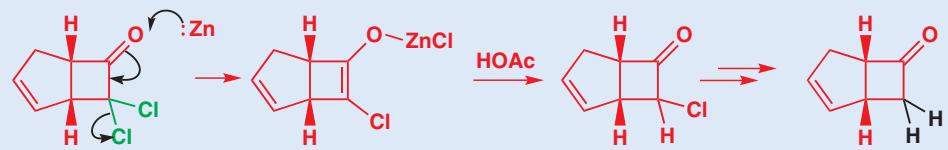


The most nucleophilic atom on the diene adds to the most electrophilic atom on the ketene and the *cis* geometry at the ring junction comes from the *cis* double bond of cyclopentadiene. It is impressive that even this excellent diene undergoes no Diels–Alder reaction with ketene as dienophile. The [2 + 2] cycloaddition must be much faster.



### Using the products

Dichloroketene is convenient to use, but the two chlorine atoms are not usually needed in the product. Fortunately, these can be removed by zinc metal in acetic acid solution. Zinc forms a zinc enolate, which is converted into the ketone by the acid. Repetition removes both chlorine atoms. You saw the reductive formation of a zinc enolate earlier in the chapter (p. 894) and in the Reformatsky reaction (Chapter 26, p. 631).



But what do we do if we *want* the product of a ketene [4 + 2] cycloaddition? We must use a compound that is not a ketene but that can be transformed into a ketone afterwards—a **masked ketene** or a **ketene equivalent**. The two most important types are nitroalkenes and compounds such as the ‘cyanohydrin ester’ in the second example.



### Finding the starting materials for a cyclobutanone synthesis

The disconnection of a four-membered ring is very simple—you just split in half and draw the two alkenes. There may be two ways to do this.

The conversion of nitro compounds to ketones by  $TiCl_3$  is an alternative to the Nef reaction that you met in Chapter 26 (p. 631), and you should be able to write a mechanism for the reaction involving  $NaOH$  yourself.



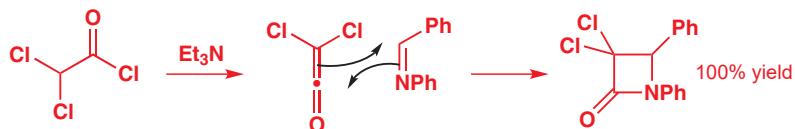
Both sets of starting materials look all right—the regiochemistry is correct for the first and doesn't matter for the second. However, we prefer the second because we can control the stereochemistry by using *cis*-butene as the alkene and we can make the reaction work better by using dichloroketene instead of ketene itself, reducing out the chlorine atoms with zinc.

### Synthesis of $\beta$ -lactams by [2 + 2] cycloadditions

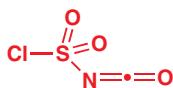
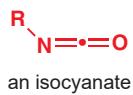
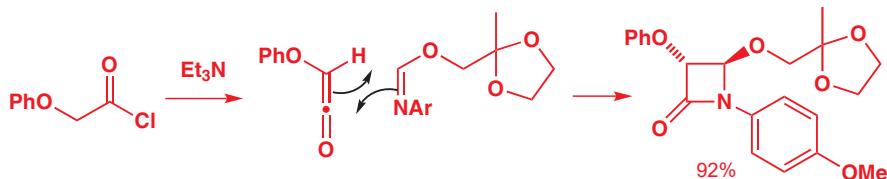
Now the disconnections are really different—one requires addition of a ketene to an imine and the other the addition of an isocyanate to an alkene. Isocyanates are like ketenes, but have a nitrogen atom instead of the end carbon atom. Otherwise the orbitals are the same.



And the good news is that both work, providing we have the right substituents on nitrogen. The dichloroacetyl chloride trick works well with imines and, as you ought to expect, the more nucleophilic nitrogen atom attacks the carbonyl group of the ketene so that the regioselectivity is right to make  $\beta$ -lactams.



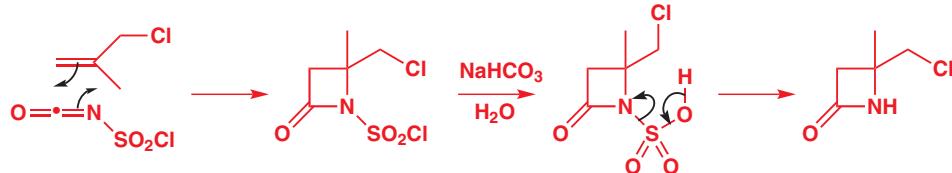
If both components have one substituent, these will end up *trans* on the four-membered ring just to keep out of each other's way. This example has more functionality and the product is used to make  $\beta$ -lactams with antibiotic activity.



chlorosulfonyl isocyanate

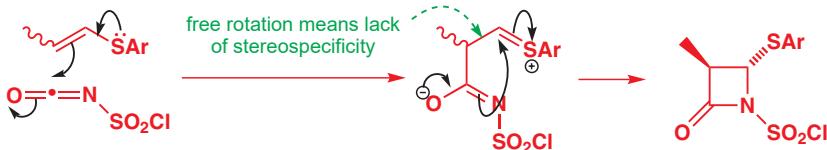
You will notice that in both of these examples there is an aryl substituent on the nitrogen atom of the imine. This is simply because *N*-aryl imines are more stable than their NH analogues (Chapter 11, p. 231).

When we wish to make  $\beta$ -lactams by the alternative addition of an isocyanate to an alkene, a substituent on nitrogen is again required, but for quite a different reason. Because alkenes are only moderately nucleophilic, we need a strongly electron-withdrawing group on the isocyanate that can be removed after the cycloaddition, and the most popular by far is the chlorosulfonyl group. The main reason for its popularity is the commercial availability of chlorosulfonyl isocyanate. It reacts even with simple alkenes.



The alkene's HOMO interacts with the isocyanate's LUMO, and the most electrophilic atom is the carbonyl carbon so this is where the terminal carbon atom of the alkene attacks. The chlorosulfonyl group can be removed simply by hydrolysis under mild conditions via the sulfonic acid.

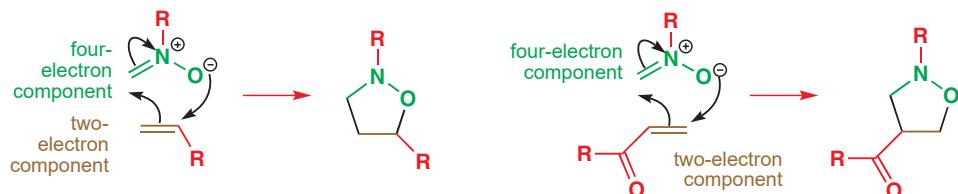
With a more electron-rich alkene—an enol ether, for example, or the following example with its sulfur analogue, a vinyl sulfide—the reaction ceases to be a concerted process and occurs stepwise. We know this must be the case in the next example because, even though the starting material is an *E/Z* mixture, the product has only *trans* stereochemistry: it is stereoselective rather than stereospecific, indicating the presence of an intermediate in which free rotation can take place.



■ The lack of stereospecificity in some non-concerted reactions is discussed in Chapter 38 in relation to carbenes.

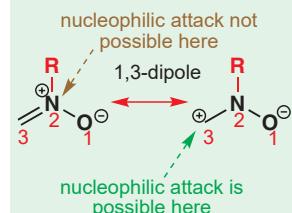
## Making five-membered rings: 1,3-dipolar cycloadditions

We have seen how to make four-membered rings by [2 + 2] cycloadditions, how to make six-membered rings by [4 + 2] cycloadditions, and an example of making a seven-membered ring by a [4 + 3] cycloaddition. But what about five-membered rings? What we need is a three-atom, four-electron equivalent of a 'diene' and we can do a Diels–Alder reaction. Such molecules exist: they are called 1,3-dipoles and they are good reagents for [3 + 2] cycloadditions. The molecule containing N and O atoms labelled 'four-electron component' is an example. It has a nucleophilic end ( $O^-$ ) and an electrophilic end—the end of the double bond next to the central  $N^+$ . These are 1,3-related, so it is indeed a 1,3-dipole.

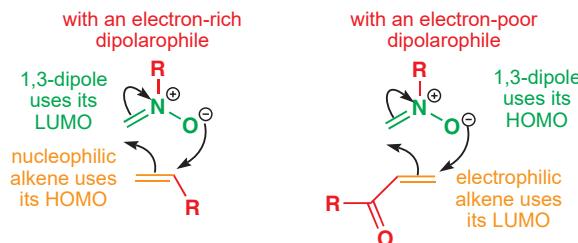


► You saw 1,3-dipolar cycloaddition being used to make heterocycles in Chapter 30 (pp. 772–775).

■ The charges make the nitrone look like a 1,2-dipole, but nucleophilic attack on  $N^+$  is impossible.

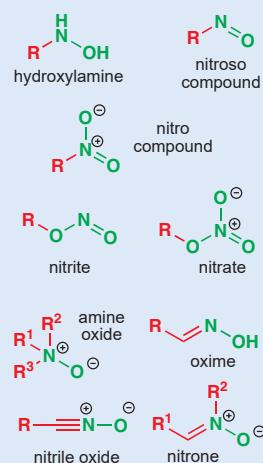


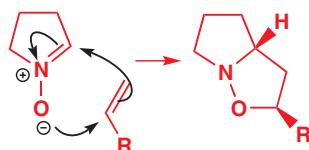
This functional group is known as a nitrone. You could think of it as the  $N$ -oxide of an imine. The nitrone gets its four electrons in this way: there are two  $\pi$  electrons in the  $N=C$  double bond and the other two come from one of the lone pairs on the oxygen atom. The two-electron component in each of these reactions is an alkene which, in a Diels–Alder reaction, would be called a dienophile. Here it is called a **dipolarophile**. Simple alkenes (which are bad dienophiles) are good dipolarophiles and so are electron-deficient alkenes. The difference between dienes and 1,3-dipoles is that dienes are nucleophilic and prefer to use their HOMO in cycloadditions with electron-deficient dienophiles while 1,3-dipoles, as their name implies, are both electrophilic and nucleophilic. They can use either their HOMO or their LUMO depending on whether the dipolarophile is electron-deficient or electron-rich.



## N–O functionality

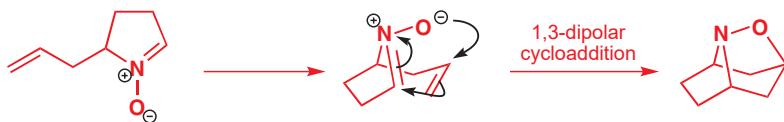
There are many functional groups containing N–O bonds. Here are a few:





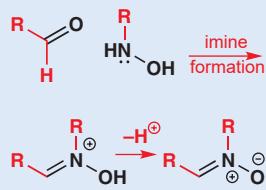
One important nitrone is a cyclic compound that has the structure in the margin and adds to dipolarophiles (essentially any alkene) in a [3 + 2] cycloaddition to give two five-membered rings fused together. The stereochemistry comes from the best approach with the least steric hindrance, as shown. There is no *endo* rule in these cycloadditions as there is no conjugating group to interact across space at the back of the dipole or dipolarophile. The product shown here is the more stable *exo* product.

If the alkene is already joined on to the nitrone by a covalent bond, the dipolar cycloaddition is an intramolecular reaction, and one particular outcome may be dictated by the impossibility of the alternatives. In the simple case below, the product has a beautifully symmetrical cage structure. The mechanism shows the only way in which the molecule can fold up to allow a 1,3-dipolar cycloaddition to occur.



### Making nitrones

The most important route to nitrones starts from hydroxylamines. Open-chain nitrones are usually made simply by imine formation between a hydroxylamine and an aldehyde.



The importance of the Diels–Alder reaction is that it makes six-membered rings with control over stereochemistry. The importance of 1,3-dipolar cycloadditions is not so much in the heterocyclic products but in what can be done with them. Almost always, the first formed heterocyclic ring is broken down in some way by carefully controlled reactions. The nitrone adducts we have just seen contain a weak N–O single bond that can be selectively cleaved by reduction. Reagents such as LiAlH<sub>4</sub> or zinc metal in various solvents (acetic acid is popular) or hydrogenation over catalysts such as nickel reduce the N–O bond to give NH and OH functionality without changing the structure or stereochemistry of the rest of the molecule. From the examples above, we get these products:

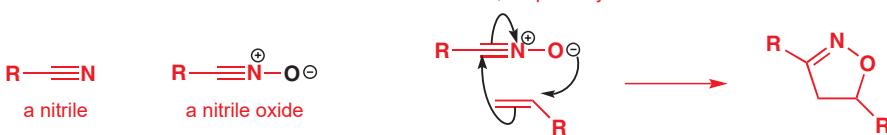


In each cycloaddition, one permanent C–C and one C–O bond (shown in brown) were made. These were retained while the N–O bond present in the original dipole was discarded. The final product is an amino-alcohol with a 1,3-relationship between the OH and NH groups.

### Linear 1,3-dipoles

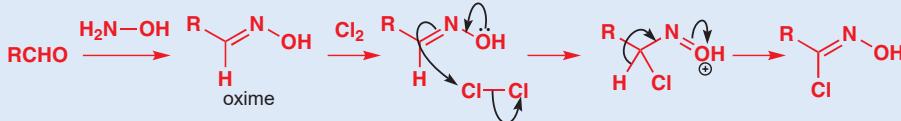
In the Diels–Alder reaction, the dienes had to have an *s-cis* conformation about the central single bond so that they were already in the shape of the product. Many useful 1,3-dipoles are actually linear and although their 1,3-dipolar cycloadditions look very awkward they still work well. We shall start with the nitrile oxides, which have a triple bond where the nitrone had a double bond.

Interactive mechanism for nitrile oxide cycloaddition



### Making nitrile oxides

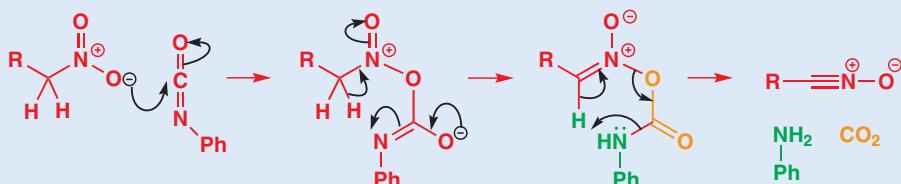
There are two important routes to these compounds, both of which feature interesting chemistry. Oximes, easily made from aldehydes with hydroxylamine ( $\text{NH}_2\text{OH}$ ), are rather enol-like and can be chlorinated on carbon.



Treatment of the chloro-oxime with base ( $\text{Et}_3\text{N}$  is strong enough) leads directly to the nitrile oxide with the loss of  $\text{HCl}$ . This is an elimination of a curious kind as we cannot draw a connected chain of arrows for it. We must use two steps—removal of the OH proton and then loss of chloride. It is a  $\gamma$  elimination rather than the more common  $\beta$  elimination.



The other method starts from nitroalkanes and is a dehydration. Inspect the two molecules and you will see that the nitro compound contains one molecule of  $\text{H}_2\text{O}$  more than the nitrile oxide. But how to remove the molecule of water? The reagent usually chosen is phenyl isocyanate ( $\text{Ph}-\text{N}=\text{C}=\text{O}$ ), which removes the molecule of water atom-by-atom to give aniline ( $\text{PhNH}_2$ ) and  $\text{CO}_2$ . This is probably the mechanism, although the last step might not be concerted, as we have shown.

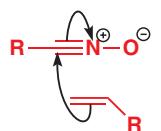


Interactive mechanism for nitrile oxide formation

As you might expect, this [3 + 2] cycloaddition is a reaction involving the HOMO of the alkene and the LUMO of the nitrile oxide so that the leading interaction that determines the structure of the product is the one in the margin. If there is stereochemistry in the alkene, it is faithfully reproduced in the heterocyclic adduct as is usual for a concerted cycloaddition.



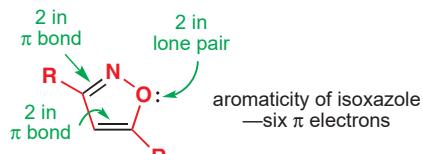
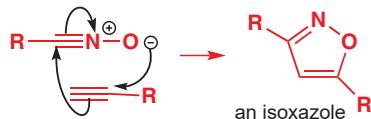
LUMO of nitrile oxide



HOMO of alkene

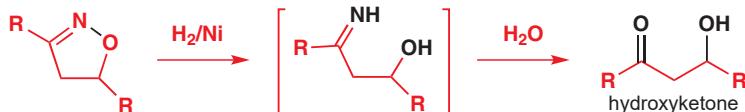
Both partners in nitrile oxide cycloadditions can have triple bonds—the product is then a stable aromatic heterocycle called an isoxazole.

#### cycloaddition of nitrile oxide and alkyne



Interactive mechanism for isoxazole formation

Reduction of the  $\text{N}-\text{O}$  bond and the  $\text{C}=\text{N}$  double bond of the nitrile oxide cycloadducts produces useful amino alcohols with a 1,3-relationship between the two functional groups. As the  $\text{N}-\text{O}$  bond is the weaker of the two, it is alternatively possible to reduce just that and leave the  $\text{C}=\text{N}$  bond alone. This gives an imine, which usually hydrolyses during work-up.

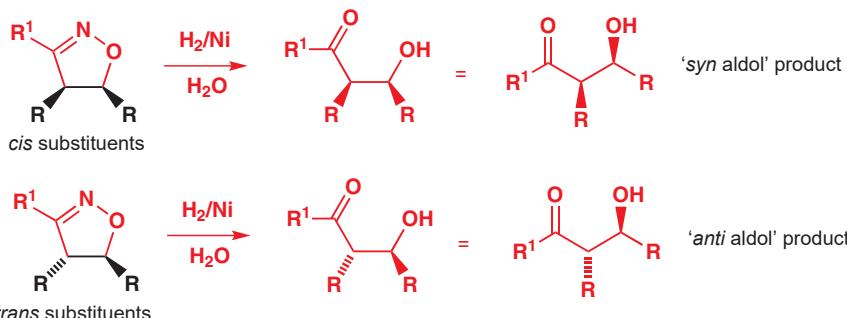
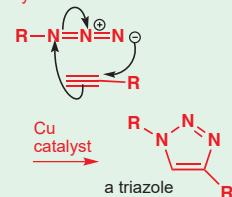


Any stereochemistry in the adduct is preserved right through this reduction and hydrolysis sequence: you might like to compare the products with the products of the stereoselective aldol reactions you saw in Chapter 33.

### ■ Other heterocycles by 1,3-dipolar cycloaddition

The synthesis of aromatic heterocycles by 1,3-dipolar cycloadditions was also treated in some detail in Chapter 30. There we discussed the important related reaction of azides with alkynes to make triazoles (p. 774).

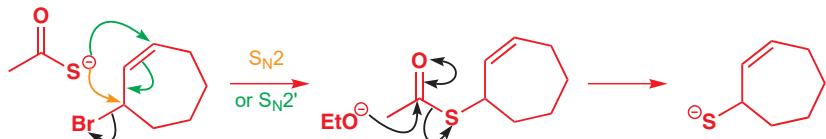
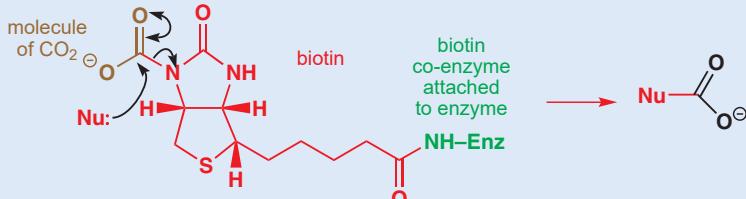
cycloaddition of azide and alkyne



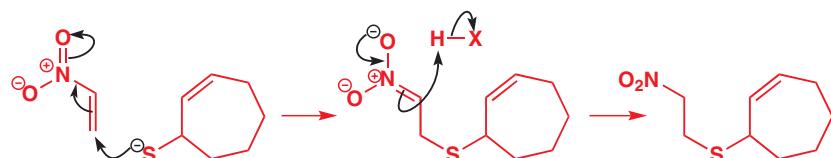
We shall end this section with the illustration of a beautiful intramolecular 1,3-dipolar cycloaddition that was used in the synthesis of the vitamin biotin. Starting at the beginning of the synthesis will allow you to revise some reactions from earlier chapters. The starting material is a simple cyclic allylic bromide that undergoes an efficient  $\text{S}_{\text{N}}2$  reaction with a sulfur nucleophile. In fact, we don't know (or care!) whether this is an  $\text{S}_{\text{N}}2$  or  $\text{S}_{\text{N}}2'$  reaction as the product of both reactions is the same. This sort of chemistry was discussed in Chapter 24 if you need to check up on it. Notice that it is the sulfur atom that does the attack—it is the soft end of the nucleophile and better at  $\text{S}_{\text{N}}2$  reactions. The next step is the cleavage of the ester group to reveal the thiolate anion.

### Biotin

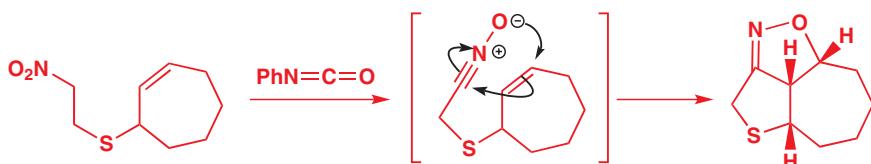
Biotin is an enzyme cofactor that activates and transports  $\text{CO}_2$  for use as an electrophile in biochemical reactions.



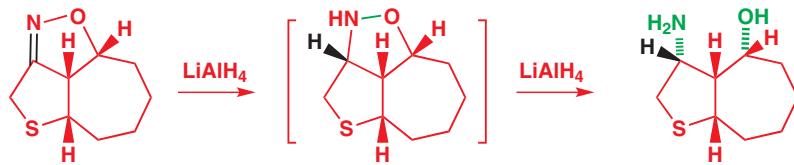
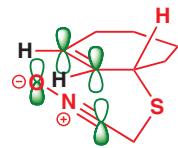
The nucleophilic thiolate anion does a conjugate addition (Chapter 22) on to a nitroalkene.



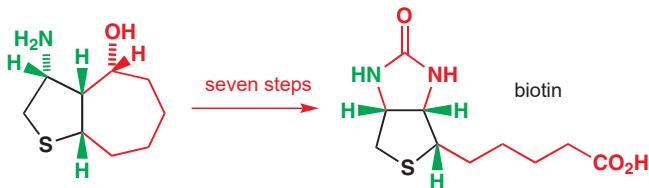
Now comes the exciting moment. The nitroalkene gives the nitrile oxide directly on dehydration with  $\text{PhN}=\text{C}=\text{O}$  and the cycloaddition occurs spontaneously in the only way it can, given the intramolecular nature of the reaction.



In the margin we show how this reaction works—the nitrile oxide comes up from the underside of the seven-membered ring, pushing the black hydrogen atoms upwards and making all the rings join up in a *cis* fashion. Next the cycloadduct is reduced completely with LiAlH<sub>4</sub> so that both the N—O and C=N bonds are cleaved. This step is very stereoselective so the C=N reduction probably precedes the N—O cleavage and the hydride has to attack from the outside (top) face of the molecule. These considerations are explored more thoroughly in Chapter 32.



The sulfur-containing ring and the stereochemistry of biotin are already defined. In the seven steps that follow, the rest of the molecule is assembled. The most important is the breaking open of the seven-membered ring by a Beckmann rearrangement (which you will meet in Chapter 36).

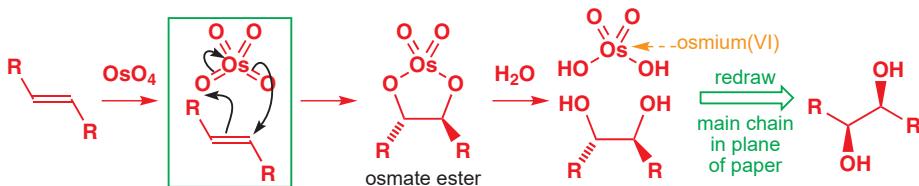


## Two very important synthetic reactions: cycloaddition of alkenes with osmium tetroxide and with ozone

We shall end this chapter with two very important reactions, both of which we have alluded to earlier in the book (Chapter 19). These reactions are very important not just because of their mechanisms, which you must be aware of, but even more because of their usefulness in synthetic chemistry, and in that regard they are second only to the Diels–Alder reaction when considering all the reactions in this chapter. They are both oxidations—one involves osmium tetroxide (OsO<sub>4</sub>) and one involves ozone (O<sub>3</sub>) and they both involve cycloaddition.

### OsO<sub>4</sub> adds two hydroxyl groups *syn* to a double bond

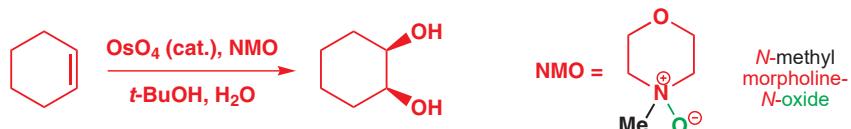
In Chapter 19 we emphasized the stereospecificity of this reaction but now we want to consider the nature of the first step (in the green frame). This is a cycloaddition between the osmium tetroxide and the alkene. You can treat the OsO<sub>4</sub> like a dipole, although it isn't drawn as one because osmium has plenty of orbitals to accommodate four double bonds. The reaction is a [3 + 2] cycloaddition or a 1,3-dipolar cycloaddition, whichever you prefer.



Interactive mechanism for dihydroxylation of alkenes

The osmate ester isn't the required product, and the reaction is usually done in the presence of water (the usual solvent is a *t*-BuOH-water mixture), which hydrolyses the osmate ester to the diol. Because both oxygen atoms were added in one concerted step during the cyclo-addition, their relative stereochemistry must remain *syn*.

Note that, in the cycloaddition, one arrow stops on osmium and another starts on the other side. Osmium therefore gains a lone pair of electrons and is reduced from Os(VIII) to Os(VI)—the reaction is therefore an oxidation, and it's one that is very specific to C=C double bonds (as we mentioned in Chapter 23). As written, it would involve a whole equivalent of the expensive, toxic, and heavy metal osmium, but it can be made catalytic by introducing a reagent to oxidize Os(VI) back to Os(VIII). The usual reagent is *N*-methylmorpholine-*N*-oxide (NMO) or Fe(III), and typical conditions for an osmylation, or dihydroxylation, reaction are shown in the scheme below.



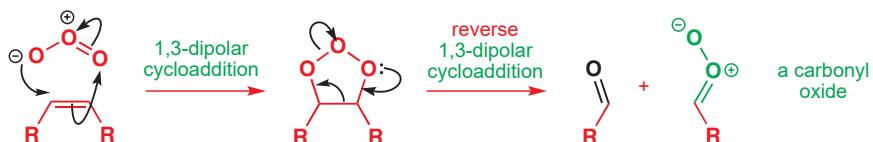
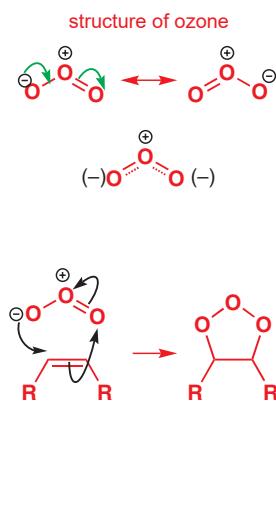
In behaviour that is typical of a 1,3-dipolar cycloaddition reaction,  $\text{OsO}_4$  reacts almost as well with electron-poor as with electron-rich alkenes.  $\text{OsO}_4$  simply chooses to attack the alkene HOMO or its LUMO, depending on which gives the best interaction. This is quite different from the electrophilic addition of *m*-CPBA or  $\text{Br}_2$  to alkenes.



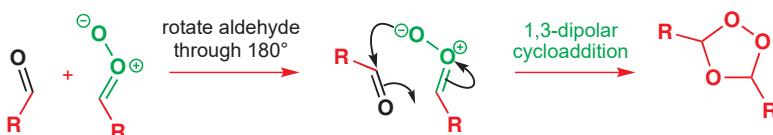
### A cycloaddition that destroys bonds: ozonolysis

Our last type of cycloaddition is most unusual. It starts as a 1,3-dipolar cycloaddition but eventually becomes a method of cleaving  $\pi$  bonds in an oxidative fashion so that they end up as two carbonyl groups. The reagent is ozone,  $O_3$ . Again, you met this reaction in Chapter 19, but we can now show you the full, remarkable details of the reaction mechanism.

Ozone is a symmetrical bent molecule with a central positively charged oxygen atom and two terminal oxygen atoms that share a negative charge. It is a 1,3-dipole and does typical 1,3-dipolar cycloadditions with alkenes. The product is a very unstable compound. The O–O single bond (bond energy 140 kJ mol<sup>-1</sup>) is a very weak bond—much weaker than the N–O bond (180 kJ mol<sup>-1</sup>) we have been describing as weak in previous examples—and this heterocycle has two of them. It immediately decomposes—by a *reverse* 1,3-dipolar cycloaddition.

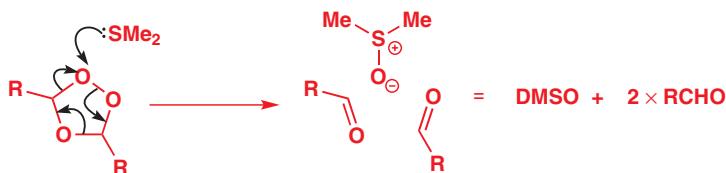


The products are a simple aldehyde on the left and a new, rather unstable looking molecule—a 1,3-dipole known as a carbonyl oxide—on the right. At least it no longer has any true O–O single bonds (the one that looks like a single bond is part of a delocalized system like the one in ozone). Being a 1,3-dipole, it now adds to the aldehyde in a third cycloaddition step. It might just add back the way it came, but it much prefers to add in the other way round, with the nucleophilic oxyanion attacking the carbon atom of the carbonyl group like this.



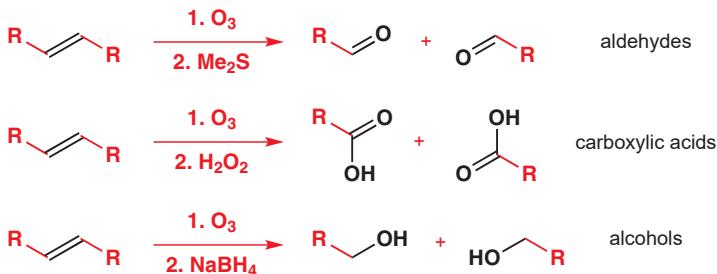
Interactive mechanism of ozonolysis

This compound—known as an ozonide—is the first stable product of the reaction with ozone. It is the culmination of two 1,3-dipolar cycloadditions and one reverse 1,3-dipolar cycloaddition. It is still not that stable and is quite explosive, so for the reaction to be of any use it needs decomposing. The way this is usually done is with dimethylsulfide or  $\text{Ph}_3\text{P}$ , which attacks the ozonide to give DMSO and two molecules of aldehyde.



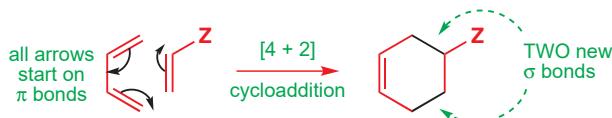
The ozonide will also react with oxidizing agents such as  $\text{H}_2\text{O}_2$  to give carboxylic acids, or with more powerful reducing agents such as  $\text{NaBH}_4$  to give alcohols. Here are the overall transformations—each cleaves a double bond—it is called an ozonolysis.

ozonolysis of alkenes to...



## Summary of cycloaddition reactions

- A cycloaddition is a one-step ring-forming reaction between two conjugated  $\pi$  systems in which two new  $\sigma$  bonds are formed, joining the two reagents at each end. The mechanism has one step with no intermediates, and all the arrows start on  $\pi$  bonds and go round in a ring.



- The cycloadditions are suprafacial—they occur on one face only of each  $\pi$  system—and for a thermally allowed reaction there should be  $4n + 2$  electrons in the mechanism, but  $4n$  in a photochemical cycloaddition. These rules are dictated by orbital symmetry.
- Cycloaddition equilibria generally lie over on the right-hand side in a thermal reaction because  $\text{C}-\text{C}$   $\sigma$  bonds are stronger than  $\text{C}-\text{C}$   $\pi$  bonds. In a photochemical cycloaddition the product loses its  $\pi$  bonds and therefore its means of absorbing energy. It is therefore the kinetic product of the reaction even if it has a strained four-membered ring.

- The stereochemistry of each component is faithfully reproduced in the product—the reactions are stereospecific—and the relationship between their stereochemistries may be governed by orbital overlap to give an *endo* product.

In the next chapter we meet two more classes of pericyclic reactions: electrocyclic reactions and sigmatropic rearrangements.

## Further reading

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For explanations of pericyclic reactions and other reactions, using the full molecular orbital treatment, consult: Ian Fleming, *Molecular Orbitals and Organic Chemical Reactions, Student Edition*, Wiley, Chichester 2009. There is also a more comprehensive edition intended for practicing chemists, called the *Library Edition*. He has also written an Oxford Primer: *Pericyclic Reactions*, OUP, Oxford, 1999.

For a comprehensive treatment of cycloadditions in the synthesis of nitrogen heterocycles, see P. Wyatt and S. Warren, *Organic Synthesis: Strategy and Control*, Wiley, Chichester, 2007, chapter 34.

The biotin synthesis on p. 904 is described by P. Confalone and his group, *J. Am. Chem. Soc.*, 1980, **102**, 1954.

## Check your understanding

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To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 周环反应 2: σ重排和电环化反应

35

## 联系

### 基础

- Cycloadditions and the principles of pericyclic reactions (essential reading!) ch34
- Acetal formation ch11
- Conformational analysis ch16
- Elimination reactions ch17
- Controlling alkene geometry and main group chemistry ch27
- The synthesis of aromatic heterocycles ch30

### 目标

- The second and third types of pericyclic reaction
- Stereochemistry from chair-like transition states
- What decides whether these pericyclic reactions go 'forwards' or 'backwards'
- Special chemistry of N, S, and P
- Why substituted cyclopentadienes are unstable
- What 'con'- and 'dis'-rotatory means

### 展望

- Rearrangements ch36
- Asymmetric synthesis ch41
- Natural products ch42

**Cycloadditions**, the subject of the last chapter, are just one of the three main classes of pericyclic reaction. In this chapter we consider the other two classes: **sigmatropic rearrangements** and **electrocyclic reactions**. We will analyse them in a way that is similar to our dealings with cycloadditions.

## Sigmatropic rearrangements

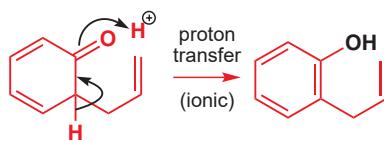
### The Claisen rearrangement was the first to be discovered

The original sigmatropic rearrangement occurred when an aryl allyl ether was heated without solvent and an *ortho*-allyl phenol resulted. This is the Claisen rearrangement. The first step in this reaction is a pericyclic reaction of a type that you will learn to call a [3,3]-sigmatropic rearrangement.

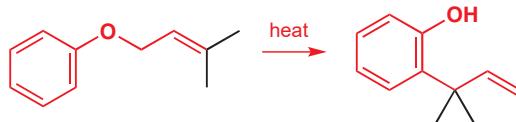


Interactive mechanism for aromatic Claisen rearrangement

This is a one-step mechanism without ionic intermediates or any charges, just like a cycloaddition. The arrows go round in a ring. The difference between this and a cycloaddition is that one of the arrows starts on a σ bond instead of on a π bond. The second step in the reaction is a simple ionic proton transfer to regenerate aromaticity.



How do we know that this is the mechanism? If the allyl ether is unsymmetrical, it turns ‘inside out’ during Claisen rearrangement, as required by the mechanism. Check for yourself that this is right.

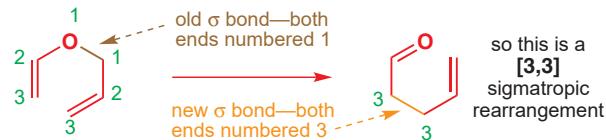


### The aliphatic Claisen rearrangement also occurs

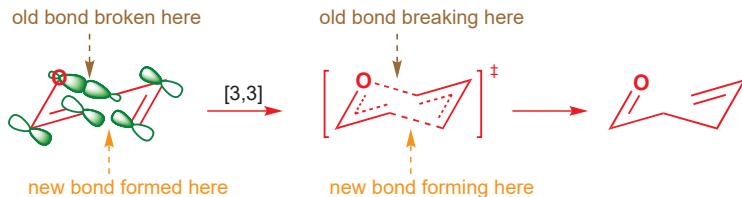


It was later found that the same sort of reaction occurs without the aromatic ring. This is called either the aliphatic Claisen rearrangement or the Claisen–Cope rearrangement. Here is the simplest possible example.

All these reactions are called sigmatropic because a  $\sigma$  bond appears to move from one place to another during the reaction. This particular reaction is called a [3,3]-sigmatropic rearrangement because the new  $\sigma$  bond has a 3,3 relationship to the old  $\sigma$  bond. You can see this if you number both ends of the old  $\sigma$  bond ‘1’ and count round in both directions to the ends of the new  $\sigma$  bond in the product. You will find that the ends of the new  $\sigma$  bond both have the number ‘3’.



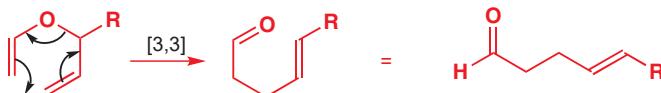
These [3,3]-sigmatropic rearrangements happen through a chair-like transition state, which allows us both to get the orbitals right and to predict the stereochemistry (if any) of the new double bond. The orbitals look something like this.



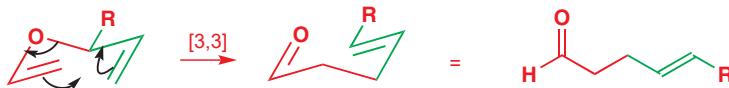
Note that these do not represent any specific frontier orbitals, they simply show that, in this conformation, the new  $\sigma$  bond is formed from two p orbitals that point directly at each other and that the two new  $\sigma$  bonds are formed from orbitals that are already parallel.

### Alkene stereochemistry in the Claisen rearrangement comes from a chair-like transition state

Stereochemistry may arise if there is a substituent on the saturated carbon atom next to the oxygen atom. If there is, the resulting double bond strongly favours the *trans* (*E*) geometry. This is because the substituent prefers an equatorial position on the chair transition state.

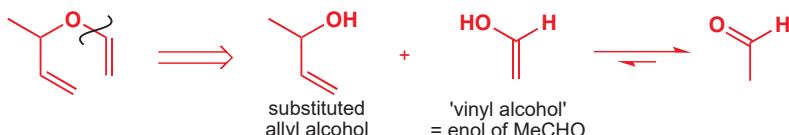


The substituent R prefers an equatorial position as the molecule reacts and R retains this position in the product. The new alkene bond is shown in green. Notice that the *trans* geometry of the alkene in the product is already there in the conformation chosen by the starting material and in the transition state.



Interactive aliphatic Claisen rearrangement mechanism

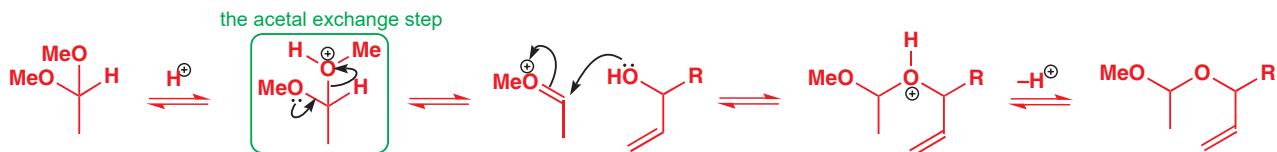
The starting material for these aliphatic Claisen rearrangements consists of ethers with one allyl and one vinyl group. We need now to consider how such useful molecules might be made. There is no problem about the allyl half—allylic alcohols are stable, easily made compounds. But what about the vinyl half? ‘Vinyl alcohol’ is just the enol of acetaldehyde (MeCHO).



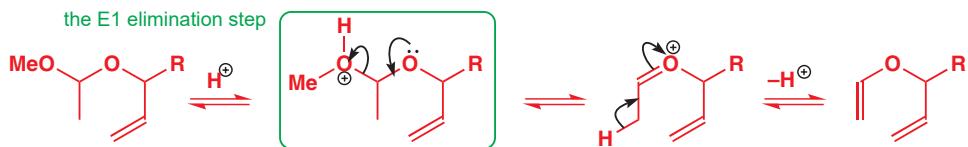
The solution is to use an acetal of the aldehyde in an acid-catalysed exchange process with the allylic alcohol. It is not necessary to isolate the allyl vinyl ether as long as some of it is formed and rearranges into the final product.



The acid catalyst usually used, propanoic acid, has a conveniently high boiling point so that the whole mixture can be equilibrated at high temperature. The first step is an acetal exchange in which the allylic alcohol displaces methanol.



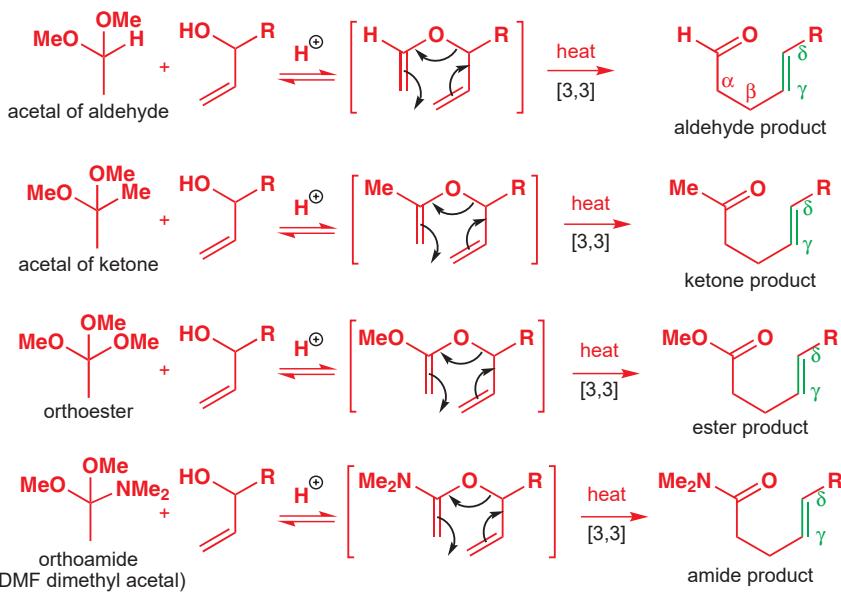
The methanol is distilled off as it is the most volatile of the components in this mixture. A second molecule of methanol is now lost in an acid-catalysed elimination reaction to give the vinyl group.



Note that the first molecule of methanol was displaced in an  $S_N1$  reaction and the second lost in an E1 reaction. The chemistry of acetals is dominated by the loss of protonated OR or OH groups in the steps with green boxes. Never be tempted to write  $S_N2$  mechanisms with acetals.

### The Claisen rearrangement is a general synthesis of $\gamma,\delta$ -unsaturated carbonyl compounds

The [3,3]-sigmatropic rearrangement itself can be carried out by heat as part of the same step or as a separate step depending on the compounds. This is a very flexible reaction sequence and can be used for aldehydes (as shown above), ketones, esters, or amides. In each case acetal-like compounds are used—acetals themselves for aldehydes and ketones; orthoesters and orthoamides for the other two (although the orthoamides are often called ‘amide acetals’).



The common feature in the products of these Claisen rearrangements is a  $\gamma\delta$ -unsaturated carbonyl group. If this is what you need in a synthesis, make it by a Claisen rearrangement.

## Orbital descriptions of [3,3]-sigmatropic rearrangements

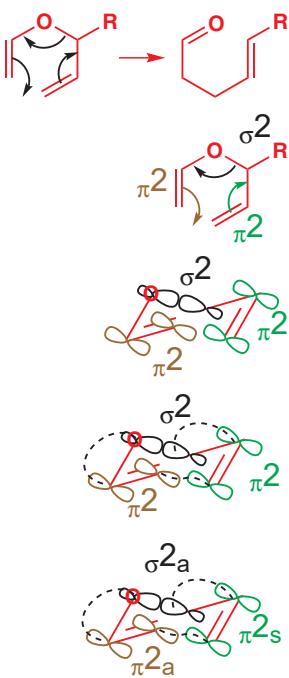
► If you need reminding of the meanings of the terms or symbols in this section please turn back to p. 892 of Chapter 34 now.

It is possible to give a frontier orbital description of a [3,3]-sigmatropic rearrangement but this is not a very satisfactory treatment because we don't have two separate reagents recognizing each other across space as we did in cycloadditions. There are *three* components in these reactions—two non-conjugated  $\pi$  bonds that do have to overlap across space and a  $\sigma$  bond in the chain joining the two  $\pi$  bonds. The Woodward–Hoffmann rules give a more satisfying description and we shall follow the routine outlined on p. 892 for cycloadditions. Note that for stage 3, we can use the three-dimensional diagram we have already made.

First a reminder of the Woodward–Hoffmann rules:

### ● The Woodward–Hoffmann rules

In a thermal pericyclic reaction the total number of  $(4q+2)_s$  and  $(4r)_a$  components must be odd.



1. Draw the mechanism for the reaction (we shall stay with a familiar one).
2. Choose the components. All the bonds taking part in the mechanism must be included and no others.
3. Make a three-dimensional drawing of the way the components come together for the reaction, putting in orbitals at the ends of the components (only!). Note that we have dropped the shading in the orbital from the previous diagrams earlier in the chapter.
4. Join up the components where new bonds are to be formed. Make sure you join orbitals that are going to form new bonds.
5. Label each component  $s$  or  $a$  depending whether new bonds are formed on the same or on opposite sides. See below for the  $\sigma$  bond symmetry.

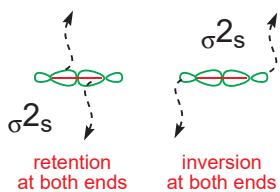
6. Add up the number of  $(4q + 2)_s$  and  $(4r)_a$  components. If the sum is odd, the reaction is allowed. Here there is:  
 one  $(4q + 2)_s$  component (one alkene) and  
 no  $(4r)_a$  components.

Total = 1, so this is an allowed reaction. As you saw in Chapter 34 (p. 893), the  $\pi_{2a}$  and  $\sigma_{2a}$  components have irrelevant symmetry and are not counted.

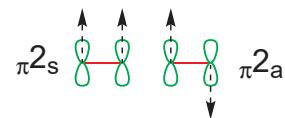
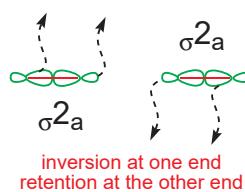
One new aspect of orbital symmetry has appeared in this diagram—how did we deduce a or s symmetry in the way the  $\sigma$  bond reacted? For  $\pi$  bonds it is simple—if both bonds are formed on the same side of the old  $\pi$  bond, it has reacted suprafacially; if on opposite sides, antarafacially.

With a  $\sigma$  bond the symmetry is not so obvious. We want to know if it does the *same* thing at each end (s) or a *different* thing (a). But what is the ‘thing’ it does? It reacts using the large lobe of the  $sp^3$  orbital (retention) or the small lobe (inversion). If it reacts with retention at both ends or inversion at both ends, it reacts suprafacially, while if it reacts with retention at one end and inversion at the other, it reacts antarafacially. There are four possibilities.

$\sigma$  bond reacting suprafacially

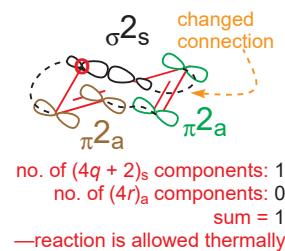


$\sigma$  bond reacting antarafacially



If you are interested in the frontier orbital approach to [3,3]-sigmatropic reactions, you could read about it in Ian Fleming (2009) *Molecular Orbitals and Organic Chemical Reactions, Student Edition*, Wiley-Blackwell. We shall use this approach when we come to [1,5]-sigmatropic rearrangements.

In the routine above, we chose to use our  $\sigma$  bond so that we got inversion at one end and retention at the other. That was why we identified it as an antarafacial component. If we had chosen another style we should have got different descriptions of the components, but the reaction would still have been allowed, for example changing just one connecting line, as in the margin, changes the symmetry of the  $\sigma$  bond so that it becomes a  $\sigma_{2s}$  component but it also changes the symmetry of one of the  $\pi$  bonds so that it becomes a  $\pi_{2a}$  component. The net result is still only one component of the Woodward–Hoffmann symmetry, the sum is still 1, and the reaction still allowed.



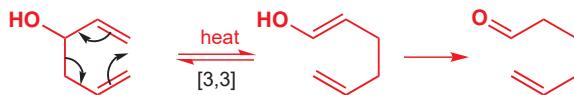
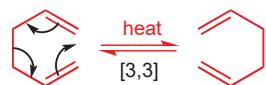
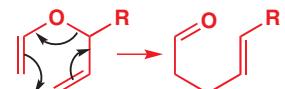
## The direction of [3,3]-sigmatropic rearrangements

Orbital symmetry tells us that [3,3]-sigmatropic rearrangements are allowed but says nothing about which way they will go. They are allowed in either direction. So why does the Claisen–Cope rearrangement always form the carbonyl-containing product? Think back to our discussion on enols (Chapter 20) and you may recall that the combination of a carbonyl group and a C–C  $\sigma$  bond made the keto form more stable than the enol form with its combination of a C=C  $\pi$  bond and a C–O  $\sigma$  bond. The same is true here. It is the stability of the carbonyl group that drives the reaction to the right.

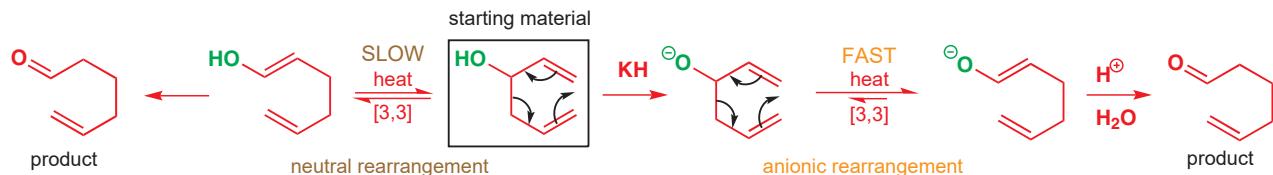
### Directing the Cope rearrangement by the formation of a carbonyl group

The Cope rearrangement is a [3,3]-sigmatropic rearrangement with only carbon atoms in the ring. In its simplest version it is not a reaction at all. The starting material and the product are the same.

We can drive this reaction too by the formation of a carbonyl group if we put an OH substituent in the right place.

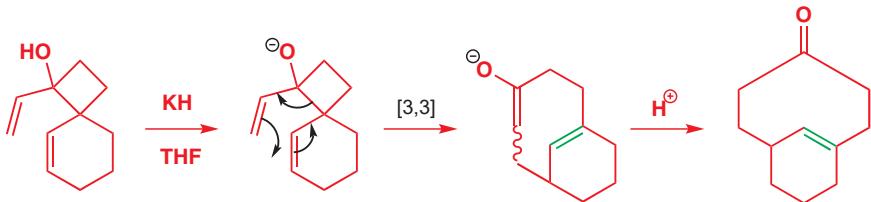


The product of the sigmatropic step is the enol of the final product. It turns out that the reaction is accelerated if the starting alcohol is treated with base ( $\text{KH}$  is the best) to make the alkoxide. The product is then the potassium enolate, which is more stable than the simple potassium alkoxide starting material. As the reaction proceeds, conjugation is growing between  $\text{O}^-$  and the new  $\pi$  bond.

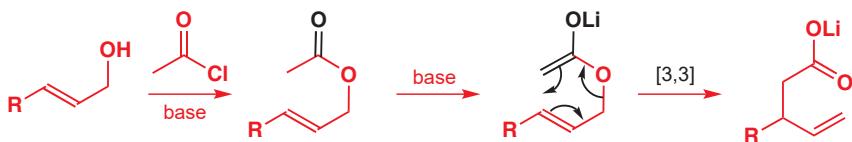


► Bredt's rule forbidding bridgehead alkenes and the reasons for it are discussed in Chapter 17.

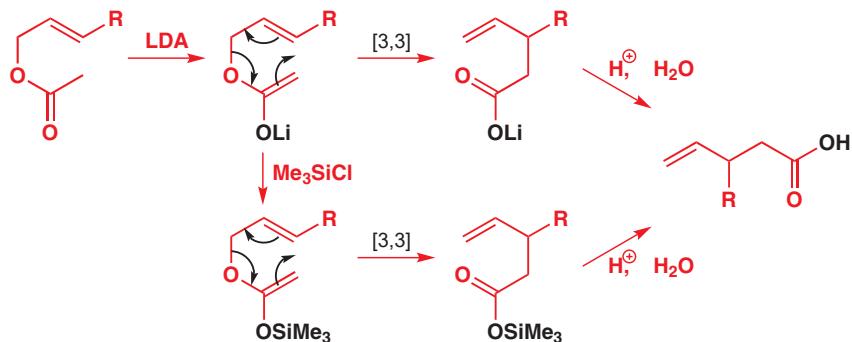
Some remarkable compounds can be made by this method. One of the strangest—a ‘bridge-head’ alkene—was made by a potassium alkoxide-accelerated Cope rearrangement in which a four-membered ring was expanded into an eight-membered ring containing a *trans* double bond (shown in green).



A combination of an oxygen atom in the ring and another one outside the ring is very powerful at promoting [3,3]-sigmatropic rearrangements and easy to arrange by making the lithium enolate of an allylic alcohol.

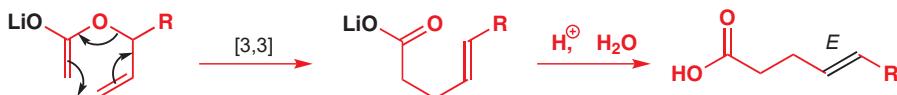


Sometimes it is better to convert the lithium enolate into the silyl enol ether before heating to accomplish the [3,3]-sigmatropic rearrangement. In any case, both products give the unsaturated carboxylic acid on work-up.



Interactive mechanism for Ireland-Claisen rearrangement

This reaction is known as the Ireland-Claisen rearrangement as it was a variation of the Claisen rearrangement invented by R. E. Ireland in the 1970s and widely used since. If the substituents are suitably arranged, it shows the same *E* selectivity as the simple Claisen rearrangement and for the same reason.

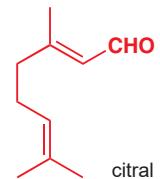
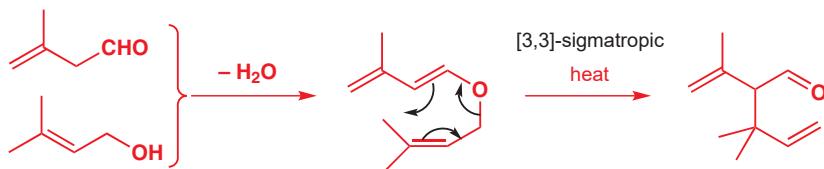


In some cases simple Cope rearrangements without any oxygen atoms at all can be directed by an unstable starting material or a stable product. The instability might be strain and the stability might simply be more substituents on the double bonds. In the next reaction the driving force is the breaking of a weak  $\sigma$  bond in a three-membered ring. This reaction goes in 100% yield at only just above room temperature, so it is very favourable. In the second example, the trisubstituted double bonds inside the five-membered rings of the product are more stable than the exomethylene groups in the starting material.



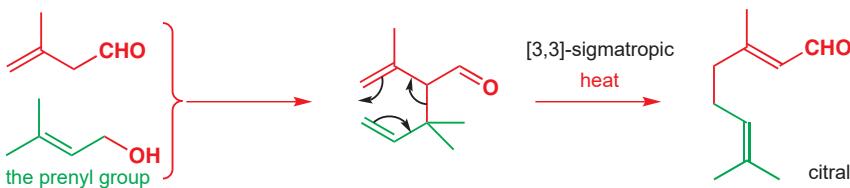
### An industrial synthesis of citral

'Citral' is a key intermediate in the synthesis of vitamin A, and it is manufactured by a remarkable process that involves two successive [3,3]-sigmatropic rearrangements, a Claisen followed by a Cope. The allyl vinyl ether needed for the Claisen rearrangement is an enol ether of an unsaturated aldehyde with an unsaturated alcohol. The two starting materials are themselves derived from a common precursor, making this a most efficient process! Heating the enol ether promotes [3,3]-sigmatropic rearrangement propelled by the formation of a carbonyl group.



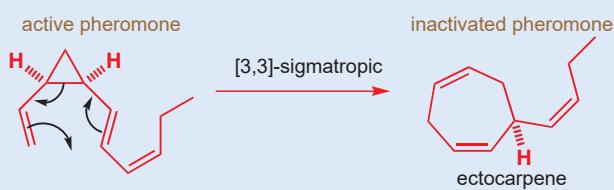
■ Notice that the product is a  $\gamma,\delta$ -unsaturated carbonyl compound.

But the product of this rearrangement is now set up for a second [3,3]-sigmatropic rearrangement, this time made favourable by a shift into conjugation and the formation of two tri-substituted double bonds from two terminal ones. Overall, the prenyl group walks from one end of the molecule to the other, inverting twice as it goes.



### Seaweed sex censored by a sigmatropic shift

In order to reproduce, the female gametes of marine brown algae must attract mobile male gametes. This they do by releasing a pheromone, long thought to be the cycloheptadiene ectocarpene. In 1995 results were published that suggested that, in fact, the pheromone was a cyclopropane, and that ectocarpene was ineffective as a pheromone.

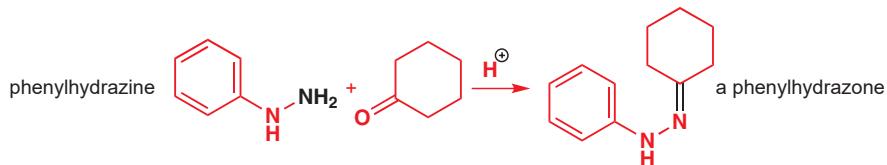


How had the confusion arisen? Well, the remarkable thing is that the cyclopropyl pheromone inactivates itself, with a half-life of several minutes at ambient temperature, by [3,3]-sigmatropic rearrangement to the cycloheptadiene, driven by release of strain from the three-membered ring. This not only confused the earlier pheromone chemists, but it also provides a marvellously precise way for the algae to signal their presence and readiness for reproduction without saturating the sea water with meaningless pheromone.

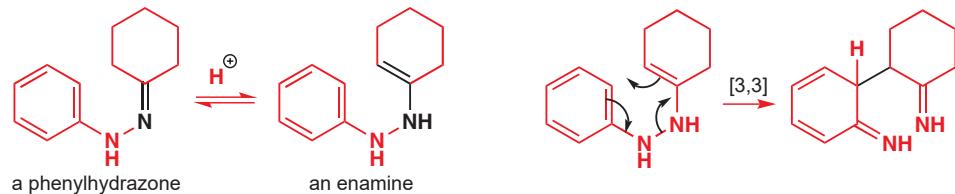
### Applications of [3,3]-sigmatropic rearrangements using other elements

There is no need to restrict our discussion to carbon and oxygen atoms. We shall finish this section with two useful reactions that use other elements. You met the most famous synthesis of indoles in Chapter 30—the Fischer indole synthesis—and we can now look in more detail at the key step of this remarkable reaction. Condensation of phenylhydrazine with a ketone in slightly acidic solution gives a phenylhydrazone.

► Hydrazones—the imine derivatives of hydrazines—appeared in Chapter 11.

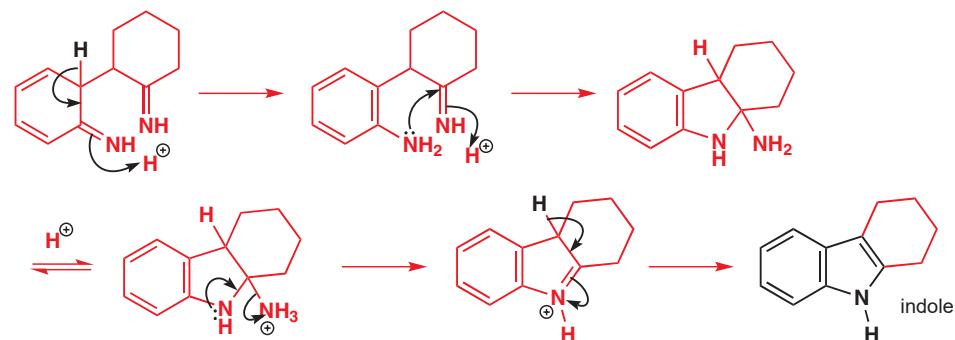


If the ketone is enolizable, this imine is in equilibrium with the corresponding enamine. The important bonds are given in black in the diagram. The enamine is ideally set up for a [3,3]-sigmatropic rearrangement in which the  $\sigma$  bond to be broken is the weak N–N  $\sigma$  bond and one of the  $\pi$  bonds is in the benzene ring.

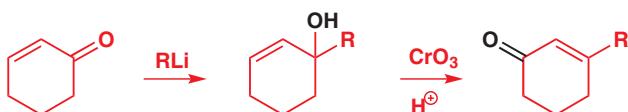


► Interactive mechanism for Fischer indole synthesis

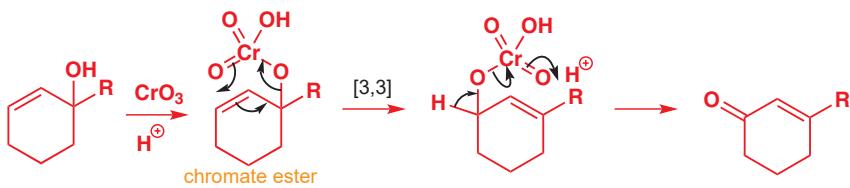
► A detailed discussion of this reaction as a synthesis of indoles appears in Chapter 30.



That was a [3,3]-sigmatropic reaction involving two nitrogens. There follows one with two oxygens and a chromium atom. When tertiary allylic alcohols are oxidized with  $\text{CrO}_3$  in acid solution, no direct oxidation can take place, but a kind of conjugate oxidation occurs.



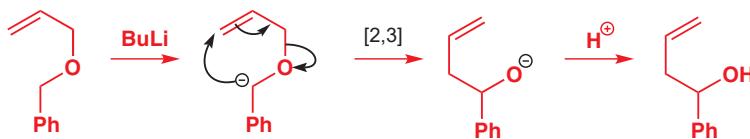
The first step in Cr(VI) oxidations can take place to give a chromate ester but this intermediate has no proton to lose so it transfers the chromate to the other end of the allylic system, where there is a proton. The chromate transfer can be drawn as a [3,3]-sigmatropic rearrangement. The final step is the normal oxidation in which chromium drops down from orange Cr(VI) to Cr(IV) and eventually by disproportionation to green Cr(III).



► Cr(VI) oxidations are described in Chapters 9 and 23.

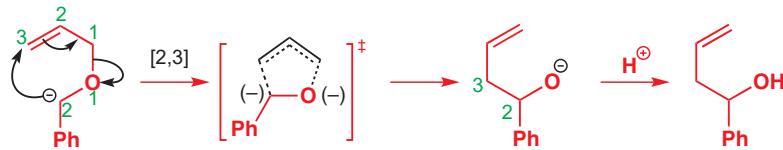
## [2,3]-Sigmatropic rearrangements

All [2,3]-sigmatropic rearrangements have six-membered cyclic transition states. It is no accident that the size of the ring is given by the sum of the two numbers in the square brackets and this is universally the case for sigmatropic rearrangements. We are now going to look at [2,3]-sigmatropic rearrangements so we will be needing five-membered cyclic transition states. There is a problem here. You cannot draw three arrows going round a five-membered ring without stopping or starting on an atom, not a bond. This can be OK if the atom is a carbanion.

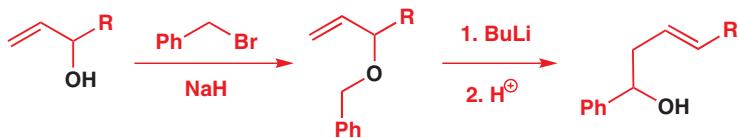


■ It can also be OK if the atom is a carbocation, or if it is an element that is happy to change oxidation state.

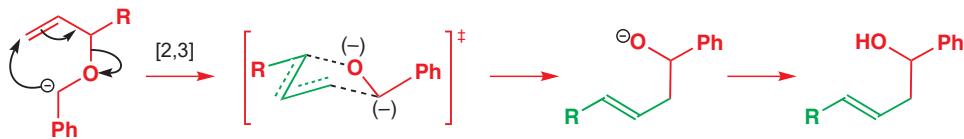
The starting material is a benzyl allyl ether and undergoes [2,3]-sigmatropic rearrangement to make a new C–C  $\sigma$  bond at the expense of a C–O  $\sigma$  bond—a bad bargain this as the C–O bond is stronger. The balance is tilted by the greater stability of the oxyanion in the product than of the carbanion in the starting material. The new bond has a 2,3 relationship to the old and the transition state is a five-membered ring.



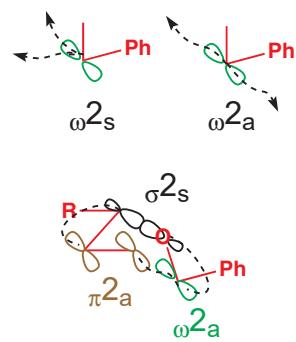
The transition state can be quite chair-like so that the new  $\pi$  bond will be *trans* if it has a choice. There will be a choice if the ether has been made from a substituted allyl alcohol.



We cannot draw a complete chair as we haven't got a six-membered ring, but the part that is to become the new  $\pi$  bond can be in a chair-like part of the five-membered ring. The substituent R prefers an equatorial position and the resulting *trans* arrangement of the groups is outlined in green.



We can use the same conformational diagram to show how the orbitals overlap as the new bond is formed. When we come to use the Woodward–Hoffmann rules on these [2,3]-sigmatropic rearrangements, we find something new. We have a  $\pi$  bond and a  $\sigma$  bond and a carbanion. How are we to represent a carbanion (or a carbocation) that is just a p orbital on an atom? The new symbol we use for a simple p orbital is  $\omega$  (lower case omega).



Much more sulfur chemistry is described in Chapter 27.

A carbanion is an  $\omega_2$  component and a carbocation is an  $\omega_0$  component as it has zero electrons. If the two new bonds are formed to the same lobe of the p orbital of the carbanion, we have an  $\omega_2s$  component, but if they are formed to different lobes we have an  $\omega_2a$  component.

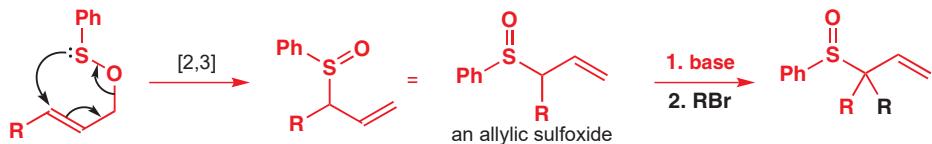
Without going through the whole routine again, the [2,3]-sigmatropic rearrangement we have been discussing can be described as an  $\omega_{2a} + \sigma_{2s} + \pi_{2a}$  reaction. There is one  $(4q+2)_s$  and no  $(4r)_a$  component so the reaction is thermally allowed.

### [2,3]-Sigmatropic rearrangements with S and Se

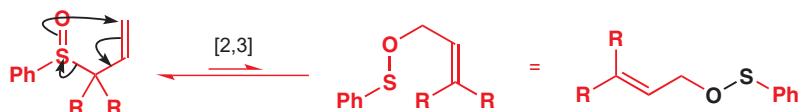
There are many [2,3]-sigmatropic rearrangements involving a variety of heteroatoms as well as carbon. The mechanism is common with elements that are prepared to change their oxidation state by two so that an arrow can both start and finish on that atom. The examples in this section involve sulfur and selenium, which can both form stable compounds at three oxidation states: S or Se(II), S or Se(IV), and S or Se(VI).



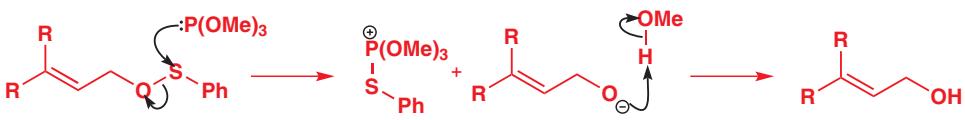
Reaction of an allylic alcohol with PhSCl gives an unstable sulfenate ester that rearranges on heating to an allylic sulfoxide by a [2,3]-sigmatropic rearrangement involving both O and S. Notice that arrows both start and stop on the sulfur atom, which changes from S(II) to S(IV) during the reaction. The new functional group with an S=O bond is a sulfoxide, and this is a good way of making allylic sulfoxides. The product forms an anion stabilized by sulfur, which can be alkylated.



We have said that all these sigmatropic rearrangements are reversible but now we can prove it. If this product is heated in methanol with a nucleophile such as  $(\text{MeO})_3\text{P}$  (trimethylphosphite), which has a liking for sulfur, the [2,3]-sigmatropic rearrangement runs backwards and a sulfenate ester is again formed.

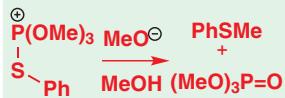


This is an unfavourable reaction because the equilibrium lies over on the sulfoxide side. But the nucleophile traps the sulfenate ester and the methanol ensures that the alkoxide ion formed is immediately protonated so that we get another allylic alcohol.



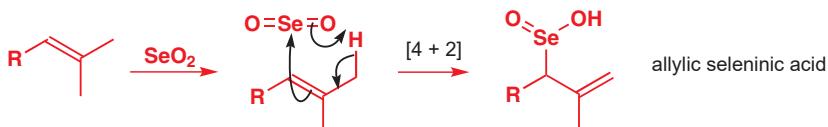
So what is the point of going round in circles like this? The net result is the alkylation of an allylic alcohol in a position where alkylation would not normally be considered possible.

The other products are actually  $\text{PhSMc}$  and  $(\text{MeO})_3\text{P}=\text{O}$ . You might like to work out a mechanism for these stages of the reaction.



A related reaction of selenium in its +4 oxidation state (as selenium dioxide,  $\text{SeO}_2$ ) allows us to make allylic alcohols and enals from simple alkenes. The overall reaction is the simple oxidation shown in the margin, but the route by which the compound gets there involves two successive pericyclic reactions.

Selenium dioxide will react with alkenes in a [4 + 2] cycloaddition reminiscent of the ene reaction.



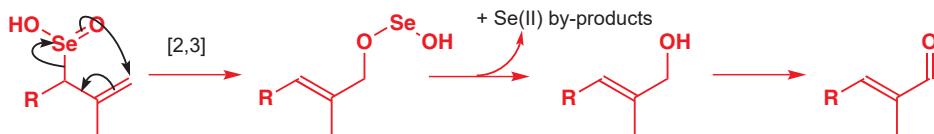
The initial product is an allylic seleninic acid—and just like an allylic sulfoxide (but more so because the C–Se bond is even weaker) it undergoes allylic rearrangement to give an unstable compound that rapidly decomposes to an allylic alcohol. In some cases, particularly this most useful oxidation of methyl groups, the oxidation continues to give an aldehyde or ketone.



► The ene reaction was introduced on p. 894.

■ In a very few special cases, this seleninic acid intermediate has been isolated.

Interactive mechanism for allylic oxidation

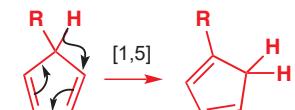
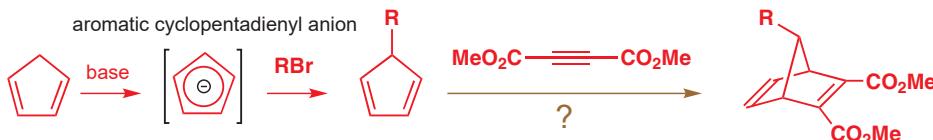


Overall,  $\text{CH}_3$  has been replaced by  $\text{CH}_2\text{OH}$  or  $\text{CH}=\text{O}$  in an allylic position, a transformation similar to the allylic bromination reaction with NBS that you met in Chapter 24, but with a very different mechanism. The by-product of the oxidation is a selenium(II) compound, and it can be more practical to carry out the reaction with only a catalytic amount of  $\text{SeO}_2$ , with a further oxidizing agent, *t*-butyl hydroperoxide, to reoxidize the  $\text{Se(II)}$  after each cycle of the reaction. This eliminates the need to get rid of large amounts of selenium-containing products, which are toxic and usually smelly.

## [1,5]-Sigmatropic hydrogen shifts

When one of the numbers in square brackets is '1', the old and new  $\sigma$  bonds are to the same atom, so we are dealing with the migration of a group around a conjugated system. In the case of a [1,5]-sigmatropic rearrangement the transition state is a six-membered ring (remember—just add together the numbers in square brackets). There is an important example in the margin. Let us first check that this is indeed a [1,5]-sigmatropic rearrangement by numbering the position of the new  $\sigma$  bond with respect to the old. Note that we must go the long way round the five-membered ring because that is the way the mechanism goes.

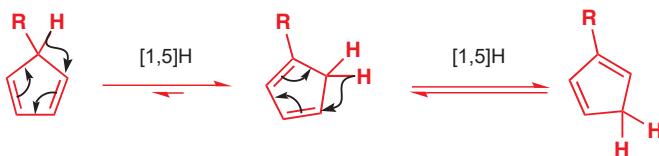
It is a [1,5]-sigmatropic rearrangement. The figure '1' in the square brackets shows that the same atom is at one end of the new  $\sigma$  bond as was at one end of the old  $\sigma$  bond. One atom has moved in a 1,5 manner and these are often called [1,5]-sigmatropic shifts. This is often abbreviated to [1,5]H shift to show which atom is moving. This particular example is important because sadly it prohibits a most attractive idea. The aromatic cyclopentadienyl anion is easily formed, stable, and readily alkylated. This sequence of alkylation and Diels–Alder reaction looks very good.



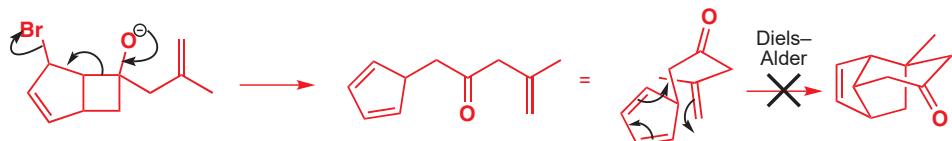
Interactive mechanism for a [1,5]-sigmatropic shift on cyclopentadiene

But sadly this sequence is, in fact, no good at all. A mixture of three Diels–Alder adducts is usually obtained resulting from addition to the three cyclopentadienes present in solution as

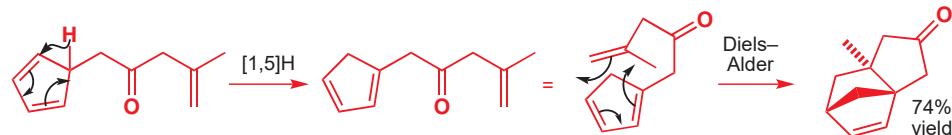
the result of rapid [1,5]H shifts. The one drawn above is a minor product because there is more of the other two dienes, which have an extra substituent on the double bonds.



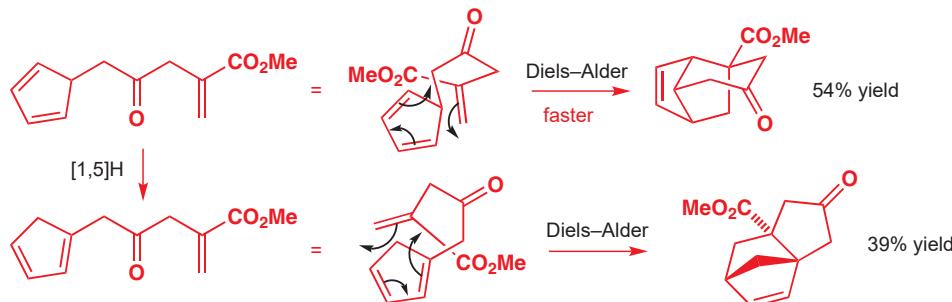
An excellent example comes from the intramolecular Diels–Alder reactions explored by Dreiding in 1983. One particular substituted cyclopentadiene was made by a fragmentation reaction (see Chapter 36). It might have been expected to give a simple Diels–Alder adduct.



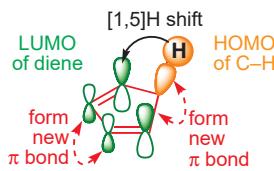
There is nothing wrong with this reaction—indeed, the product looks beautifully stable—but it is not formed because the [1,5]H shift is too quick and gives a more stable cyclopentadiene with more substituents on a double bond. Then it does the Diels–Alder reaction.



Notice that in these compounds the ketone is not conjugated to any of the alkenes and so does not influence the reaction. If we increase the reactivity of the dienophile by putting an ester group in conjugation with it, most of the compound does the Diels–Alder reaction *before* it does the [1,5]H shift.



### Orbital description for the [1,5]H sigmatropic shift



You should satisfy yourself that the other frontier orbital combination—HOMO of the diene and LUMO of the C–H bond—works equally well.

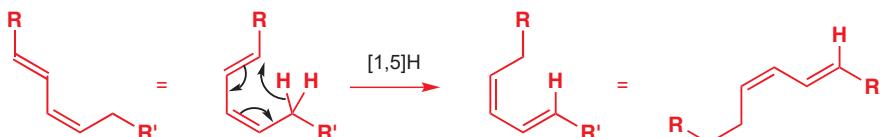
It is equally satisfactory to use frontier orbitals or the Woodward–Hoffmann rules for these reactions. We can take the diene as one component (HOMO or LUMO or  $\pi_4$ ) and the C–H bond as the other (LUMO or HOMO or  $\sigma_2$ ). Let us start by using the LUMO of the diene ( $\psi_3$ ) and the HOMO of the C–H bond (its filled  $\sigma$  orbital), as shown in the margin. If the circle around the H atom surprised you, perhaps it will also remind you that hydrogen has only a 1s orbital, which is spherical. You can probably see already that all the orbitals are correctly lined up for the reaction.

The hydrogen atom slides across the top face of the planar cyclopentadiene ring. We call this a suprafacial migration, meaning that the migrating group leaves from one face of the  $\pi$  system and rejoins that same face (the top face in this example). Antarafacial migration would mean leaving the top face and rejoining the bottom face—a clear impossibility here.

If you use the Woodward–Hoffmann rules, you need to note that the hydrogen atom must react with retention. The 1s orbital is spherically symmetrical and has no node, so wherever you draw the dotted line from that orbital it always means retention. Choosing the components is easy—the diene is a  $\pi_4$  and the C–H bond a  $\sigma_2$  component.

The easiest way to join them up is to link the hydrogen atom's 1s orbital to the top lobe of the p orbital at the back of the diene and the black  $sp^3$  orbital to the top lobe at the front of the diene. This gives us  $\pi_4$ s and  $\sigma_2$ s components and there is one  $(4q+2)_s$  and no  $(4r)_a$  components so the sum is odd and the reaction is allowed. Both approaches give us the same picture—a suprafacial migration of the hydrogen atom with (inevitably) retention at the migrating group.

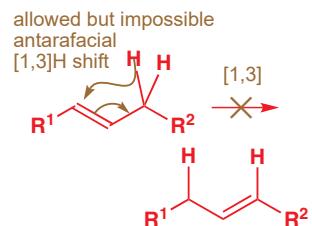
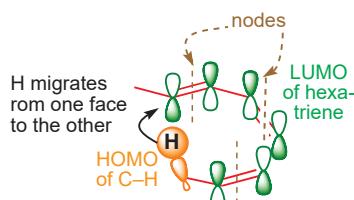
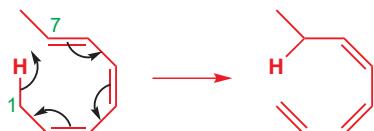
These [1,5]-sigmatropic shifts are not restricted to cyclopentadienes. In Chapter 34 we bemoaned the lack of Diels–Alder reactions using *E,Z* dienes. One reason for the shortage of examples is that such dienes undergo [1,5]H shifts rather easily and mixtures of products result.



The consequences of orbital symmetry for sigmatropic hydrogen shifts are simple. In thermal reactions, [1,5]H shifts occur suprafacially but [1,3]H and [1,7]H shifts must be antarafacial. Antarafacial [1,3]H shifts are impossible, even though they are allowed, because a rigid three-carbon chain is too short to allow the H atom to transfer from the top to the bottom—the H atom just can't reach. This is just as well, as otherwise double bonds would just wander around molecules by repeated [1,3]H shifts.

When we come to [1,7]H shifts, the situation is different. Now the much longer chain is just flexible enough to allow antarafacial migration. The hydrogen atom leaves the top side of the triene and adds back in on the bottom side. The diagram shows this in orbital terms: the LUMO of hexatriene has three nodes. Antarafacial [1,7]H migration is allowed and possible.

allowed and possible antarafacial [1,7]H shift



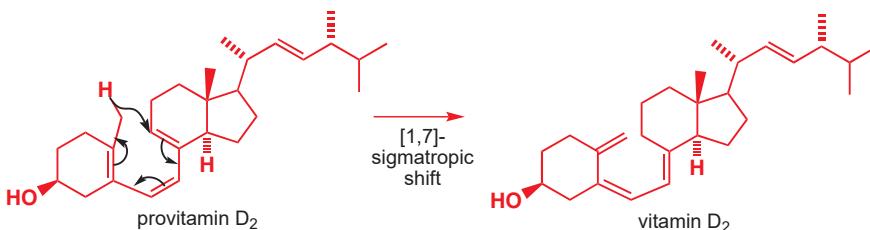
### ● Summary of thermal sigmatropic migrations of hydrogen

	[1,3]H shift	[1,5]H shift	[1,7]H shift
stereochemistry	antarafacial	suprafacial	antarafacial
feasibility	impossible	easy	possible

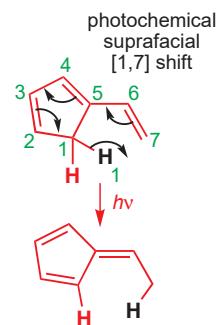
### Photochemical [1,n] H sigmatropic shifts follow the opposite rules

As you should by now expect, all this is reversed in photochemical reactions. The margin shows an example of a [1,7]H shift that cannot occur antarafacially because the molecule is a rigid ring, but that can and does occur photochemically in a suprafacial manner.

A [1,7]H shift occurs in the final stages of the human body's synthesis of vitamin D from cholesterol. Here is the last step of the biosynthesis.

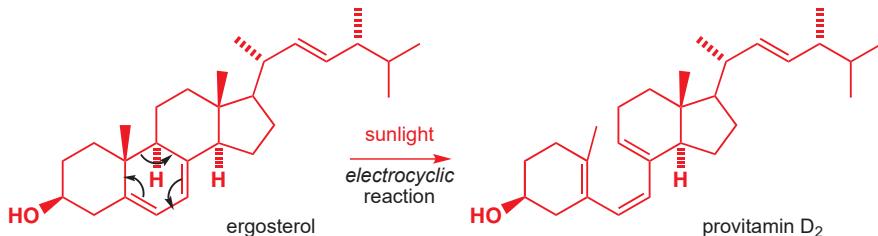


→ The reversal of the rules of orbital symmetry when you move from thermal to photochemical reactions was described on p. 896.



This step happens spontaneously, without the need for light, so the [1,7]H shift must be antarafacial. That's no problem in this triene system—there is enough flexibility for the hydrogen atom to migrate from the top to the bottom face.

Why, then, does the body famously need sunlight to make vitamin D? The reason is the previous step, which can only occur when light shines on the skin.

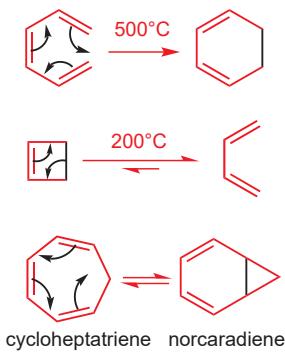
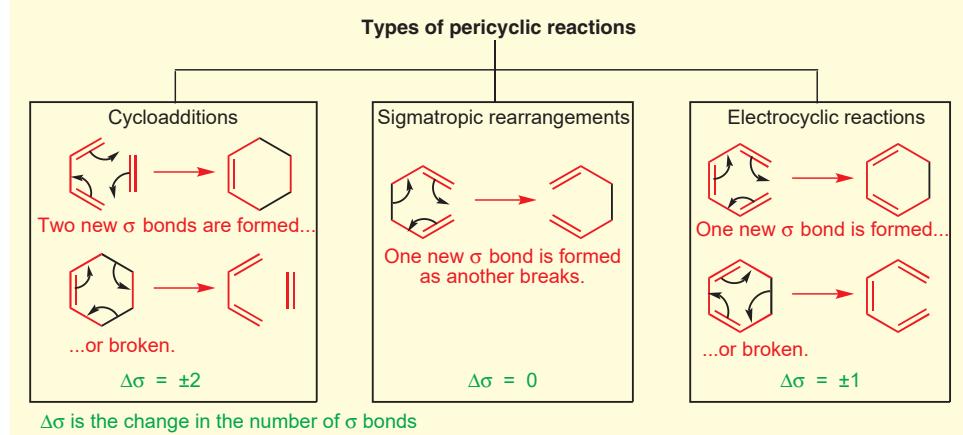


This ring opening is clearly pericyclic—the electrons go round in a ring, and the curly arrows could be drawn either way—but it is neither a cycloaddition (only one  $\pi$  system is involved) nor a sigmatropic rearrangement (a  $\sigma$  bond is broken rather than moved). It is, in fact, a member of the third and last kind of pericyclic reaction, an *electrocyclic reaction*.

## Electrocyclic reactions

In an electrocyclic reaction a ring is always broken or formed. Rings may, of course, be formed by cycloadditions as well, but the difference with electrocyclic reactions is that just one new  $\sigma$  bond is formed (or broken) across the ends of a single conjugated  $\pi$  system. In a cycloaddition, two new  $\sigma$  bonds are always formed (or broken), and in a sigmatropic rearrangement one  $\sigma$  bond forms while one breaks.

- The types of pericyclic reactions are distinguished by the number of  $\sigma$  bonds made or broken



One of the simplest electrocyclic reactions occurs when hexatriene is heated to 500 °C. It is a pericyclic reaction because the electrons go round in a ring (you could equally draw the arrows going the other way); it's electrocyclic because a new  $\sigma$  bond is formed across the ends of a  $\pi$  system. The reaction goes because the  $\sigma$  bond that is formed is stronger than the  $\pi$  bond that is lost.

The opposite is true for the electrocyclic opening of cyclobutene—ring strain in the four-membered ring means that the reverse (ring-opening) reaction is preferred to ring closure.

In one famous case, the release of ring strain is almost exactly counterbalanced by the formation of a  $\sigma$  bond at the expense of a  $\pi$  bond. Cycloheptatriene exists in equilibrium with a bicyclic isomer known as norcaradiene. Usually cycloheptatriene is the major component of the equilibrium, but the norcaradiene structure is favoured with certain substitution patterns.

## Rules for electrocyclic reactions

Whether they go in the direction of ring opening or ring closure, electrocyclic reactions are subject to the same rules as all other pericyclic reactions. With most of the pericyclic reactions you have seen so far, we have given you the choice of using either HOMO–LUMO reasoning or the Woodward–Hoffmann rules. With electrocyclic reactions, you really have to use the Woodward–Hoffmann rules because (at least for the ring closures) there is only one molecular orbital involved.

In the same way, the Woodward–Hoffmann rules apply both to cycloadditions and to reverse cycloadditions, as you saw in Chapter 34.

### • Electrocyclic reactions

- An electrocyclic reaction is the formation of a new  $\sigma$  bond across the ends of a conjugated polyene or the reverse.

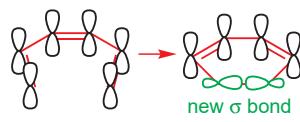
It is important that you do not confuse electrocyclic reactions with pericyclic reactions. Pericyclic is the name for the whole family of reactions involving no charged intermediates in which the electrons go round the outside of the ring. *Electrocyclic reactions, cycloadditions, and sigmatropic rearrangements are the three main classes of pericyclic reactions.*

Let's start with the hexatriene ring closure from the beginning of this section, first looking at the orbitals and then following the same procedure that we taught you for cycloadditions and sigmatropic rearrangements to see what the Woodward–Hoffmann rules have to say about the reaction.

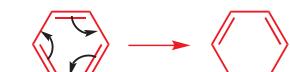
Hexatriene is, of course, a  $6\pi$  electron ( $\pi_6$ ) conjugated system and, on forming cyclohexadiene, the end two orbitals must rotate through  $90^\circ$  to form a  $\sigma$  bond.

So, now for the Woodward–Hoffmann treatment.

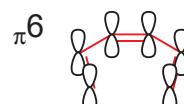
1. Draw the mechanism for the reaction.



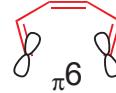
2. Choose the components. All the bonds taking part in the mechanism must be included and no others.



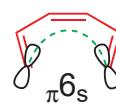
3. Make a three-dimensional drawing of the way the components come together for the reaction, putting in orbitals at the ends of the components (only!).



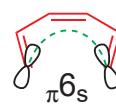
4. Join up the components where new bonds are to be formed. Make sure you join orbitals that are going to form new bonds.



5. Label each component  $s$  or  $a$  depending on whether new bonds are formed on the same or on opposite sides. We called this reaction ' $s$ ' because the top halves of the two  $\pi$  orbitals join together.

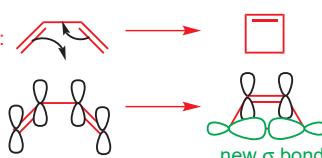
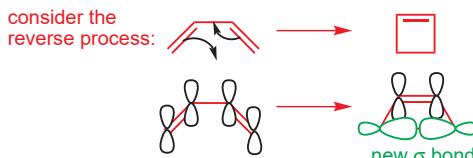


6. Add up the number of  $(4q + 2)_s$  and  $(4r)_a$  components. If the sum is odd, the reaction is allowed. Here there is one  $(4q + 2)_s$  component and no  $(4r)_a$  components. Total = 1 so this is an allowed reaction.

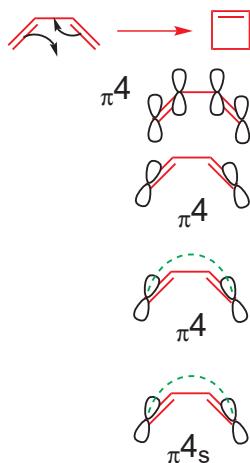


We can give the same treatment to the cyclobutene ring-opening reaction—the Woodward–Hoffmann rules tell us nothing about which way the reaction will go, only if the reaction is allowed, and it is usually easier with electrocyclic reactions to consider the ring-closing reaction even if ring opening is favoured thermodynamically. This is the process we need to consider:

**Reminder.** In a thermal pericyclic reaction the total number of  $(4q + 2)_s$  and  $(4r)_a$  components must be odd.

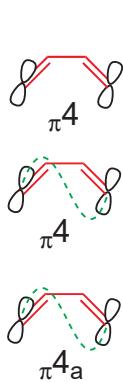


And the Woodward–Hoffmann treatment again.



1. Draw the mechanism for the reaction.
2. Choose the components. All the bonds taking part in the mechanism must be included and no others.
3. Make a three-dimensional drawing of the way the components come together for the reaction, putting in orbitals at the ends of the components (only!).
4. Join up the components where new bonds are to be formed. Make sure you join orbitals that are going to form new bonds.
5. Label each component  $s$  or  $a$  depending on whether new bonds are formed on the same or on opposite sides.
6. Add up the number of  $(4q + 2)_s$  and  $(4r)_a$  components. If the sum is odd, the reaction is allowed. There are no  $(4q + 2)_s$  components and no  $(4r)_a$  components. Total = 0 so this is a disallowed reaction.

Oh dear! We know that the reaction works, so something must be wrong. It certainly isn't Woodward and Hoffmann's Nobel-prize-winning rules—it's our way of drawing the orbital overlap that is at fault. We were fine up to stage 3 (we had no choice till then)—but see what happens if we make the orbitals overlap in a different way.

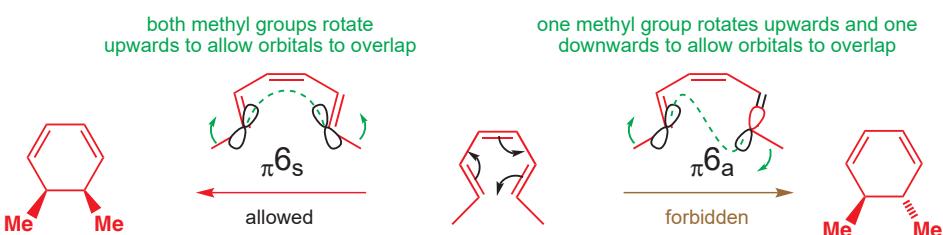


1. As before.
2. As before.
3. Make a three-dimensional drawing of the way in which the components come together for the reaction, putting in orbitals at the ends of the components (only!).
4. Join up the components where new bonds are to be formed. Make sure you join orbitals that are going to form new bonds.
5. Label each component  $s$  or  $a$  depending on whether new bonds are formed on the same or on opposite sides.
6. Add up the number of  $(4q + 2)_s$  and  $(4r)_a$  components. If the sum is odd, the reaction is allowed. There are no  $(4q + 2)_s$  components and one  $(4r)_a$  component. Total = 1 so this is an allowed reaction.

Now it works! In fact, extension of this reasoning to other electrocyclic reactions tells you that they are *all* allowed—provided you choose to make the conjugated system react with itself suprafacially for  $(4n + 2)\pi$  systems and antarafacially for  $(4n)\pi$  systems. This may not seem particularly informative, since how you draw the dotted line has no effect on the reaction product in these cases. But it can make a difference. Here is the electrocyclic ring closure of an octatriene, showing the product from (a) suprafacial reaction and (b) antarafacial reaction.

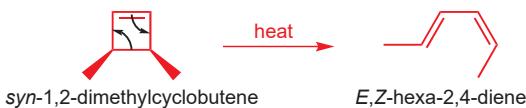
■ The green arrows in this and subsequent diagrams are merely mechanical devices to show the way in which the substituents move. They are nothing to do with real mechanistic curly arrows.

Interactive mechanism for disrotatory ring closure of hexatrienes

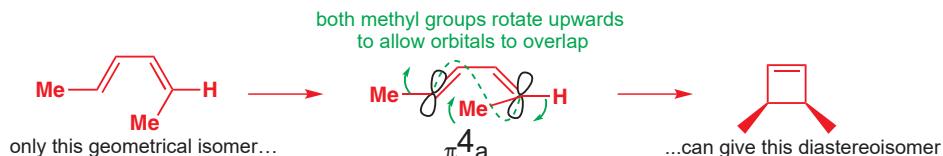


## Conrotatory and disrotatory reactions

Whether the reaction is supra- or antarafacial ought to be reflected in the relative stereochemistry of the cyclized products—and indeed it is. The reaction above gives solely the diastereoisomer on the left, with the methyl groups *syn*—clear proof that the reaction is supra-facial. This is a difficult result to explain without the enlightenment provided by the Woodward–Hoffmann rules! This electrocyclic cyclobutene ring opening also gives the product as a single stereoisomer.



Again, if we draw the reverse reaction, we can see that the reaction required has to be antarafacial for the stereochemistry to be right.



Interactive mechanism for conrotatory opening of cyclobutenes

We have drawn little green arrows on the diagrams to show how the methyl groups move as the new  $\sigma$  bonds form. For the allowed suprafacial reaction of the  $6\pi$  electron system they rotate in opposite directions so the reaction is called **disrotatory** (yes, they both go up, but one has to rotate clockwise and one anticlockwise) while for the allowed antarafacial reaction of the  $4\pi$  electron system they rotate in the same direction so the reaction is called **conrotatory** (both clockwise as drawn, but they might equally well have both gone anticlockwise). We can sum up the course of all electrocyclic reactions quite simply using these words.

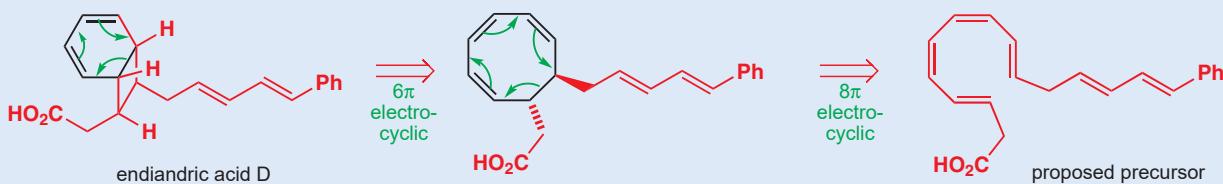
### • Rules for electrocyclic reactions

- All electrocyclic reactions are allowed.
- Thermal electrocyclic reactions involving  $(4n + 2)\pi$  electrons are **disrotatory**.
- Thermal electrocyclic reactions involving  $(4n)\pi$  electrons are **conrotatory**.
- In **conrotatory** reactions the two groups rotate in the *same* turning sense: *both* clockwise or *both* anticlockwise.
- In **disrotatory** reactions, *one* group rotates *clockwise* and *one* anticlockwise.

This rotation is the reason why you must carefully distinguish electrocyclic reactions from all other pericyclic reactions. In cycloadditions and sigmatropic rearrangements there are small rotations as bond angles adjust from  $109^\circ$  to  $120^\circ$  and vice versa, but in electrocyclic reactions rotations of nearly  $90^\circ$  are required as a planar polyene becomes a ring or vice versa. These rules follow directly from application of the Woodward–Hoffmann rules—you can check this for yourself.

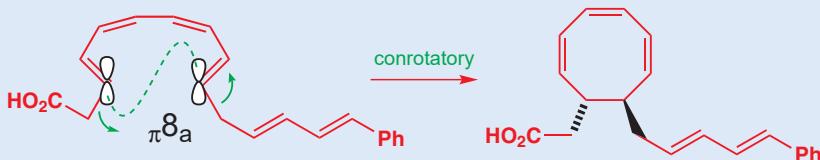
### Electrocyclic reactions in nature: the endiandric acids

A beautiful example of electrocyclic reactions at work is provided by the chemistry of the endiandric acids. This family of natural products, of which endiandric acid D is one of the simplest, is remarkable in being racemic—most chiral natural products are enantiomerically pure (or at least enantiomerically enriched) because they are made by enantiomerically pure enzymes (we discuss all this in Chapter 42). So it seemed that the endiandric acids were formed by non-enzymatic cyclization reactions, and in the early 1980s their Australian discoverer, Black, proposed that their biosynthesis might involve a series of electrocyclic reactions, starting from an acyclic polyene precursor.

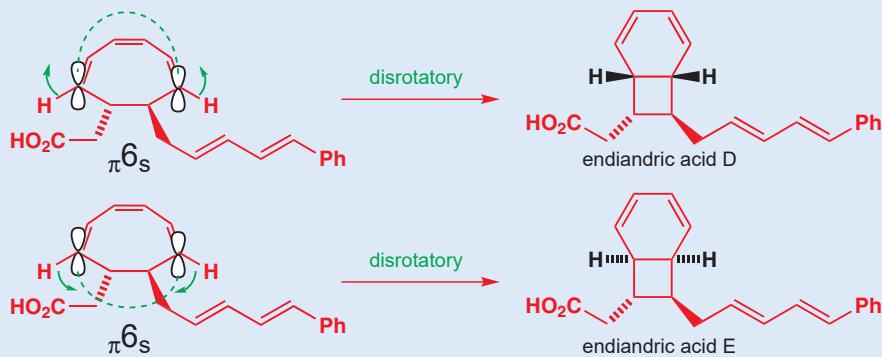


What made his proposal so convincing was that the stereochemistry of the endiandric acid D is just what you would expect from the requirements of the

Woodward–Hoffmann rules. The first step from the precursor is an  $8\pi$  electrocyclic reaction, and would therefore be conrotatory.

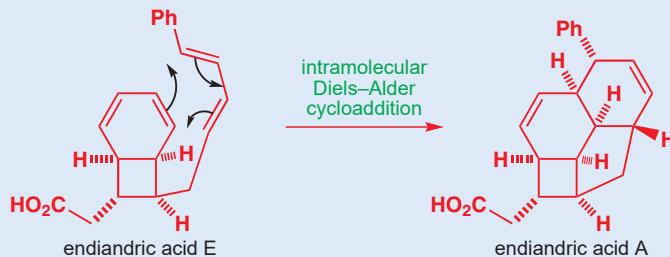


This sets up a new  $6\pi$  system, which can undergo an electrocyclic reaction in disrotatory fashion. Because there are already chiral centres in the molecule, there are, in fact, two possible diastereoisomeric products from this reaction,



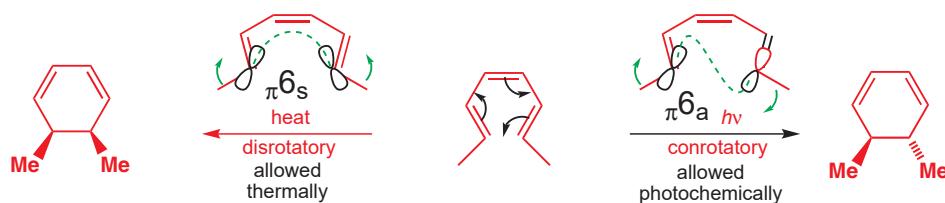
Of course, this was only a hypothesis—until in 1982 K.C. Nicolaou's group synthesized the proposed endiandric acid precursor polyene—and in one step made both endiandric acids D and E, plus endiandric acid A, which arises from a further pericyclic reaction—an intramolecular Diels–Alder cycloaddition

tion of the acyclic diene on to the cyclohexadiene as dienophile. Endiandric acid A has four rings and eight stereogenic centres, and yet a series of pericyclic reactions produce it in one step from an acyclic polyene!

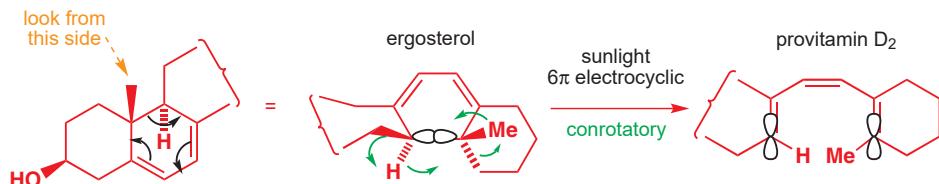


### Photochemical electrocyclic reactions

After your experience with cycloadditions and sigmatropic rearrangements, you will not be surprised to learn that, in photochemical electrocyclic reactions, the rules regarding conrotatory and disrotatory cyclizations are reversed.



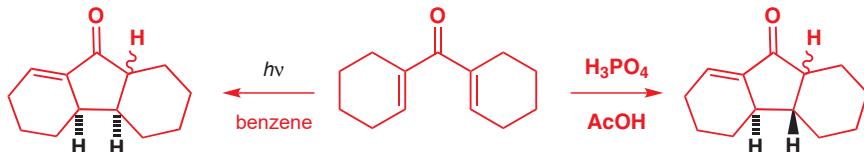
We can now go back to the reaction that introduced this section—the photochemical electrocyclic ring opening of ergosterol to give provitamin D<sub>2</sub>. By looking at the starting material and product we can deduce whether the reaction is conrotatory or disrotatory.



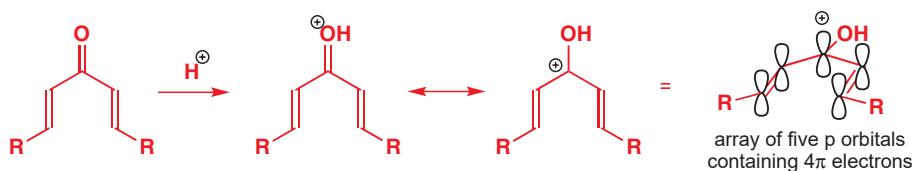
It's clearly conrotatory, and a little more thought will tell you why it has to be—a disrotatory thermal  $6\pi$  cyclization would put an impossible *trans* double bond into one of the two six-membered rings. Vitamin D deficiency is endemic in those parts of the world where sunlight is scarce for many months of the year—and all because of orbital symmetry.

### Cations and anions

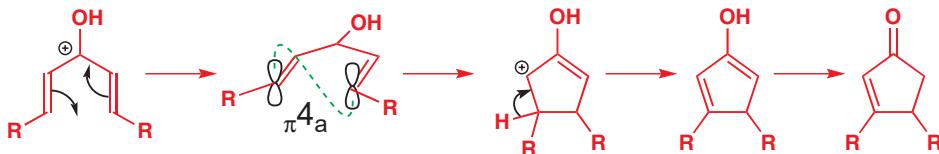
What we have just been telling you should convince you that the two reactions below are electrocyclic reactions, not least because the stereochemistry reverses on going from thermal to photochemical reaction.



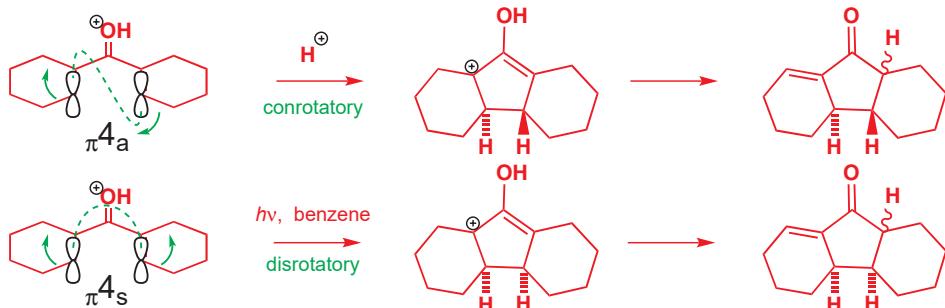
They are examples of what is known, after its Russian discoverer, as the Nazarov cyclization. In its simplest form, the Nazarov cyclization is the ring closure of a doubly  $\alpha,\beta$ -unsaturated ketone to give a cyclopentenone. Nazarov cyclizations require acid, and protonation of the ketone sets up the conjugated  $\pi$  system required for an electrocyclic reaction.



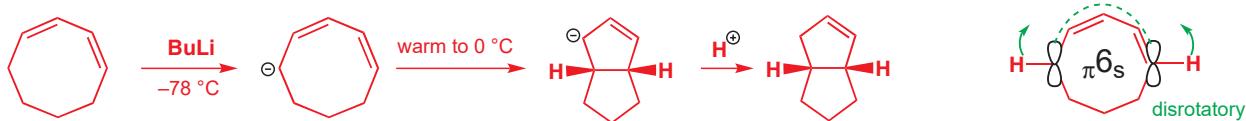
One of the five  $\pi$  orbitals involved is empty—so the cyclization is a  $4\pi$  electrocyclic reaction, and the orbitals forming the new  $\sigma$  bond must interact antarafacially. Loss of a proton and tautomerism gives the cyclopentenone.



The example below confirms that the reaction is thermally conrotatory and photochemically disrotatory.



Dienyl cations and dienyl anions both undergo electrocyclic ring closure—a nice example occurs when this cyclooctadiene is deprotonated with butyllithium. There are still five p orbitals involved in the cyclization, but now there are six  $\pi$  electrons, so the reaction is disrotatory.



In this case, it is the conrotatory *photochemical* cyclization that is prevented by strain (it was tried—cyclooctadienyl anion is stable for at least a week at  $-78^\circ C$  in broad daylight) as the product would be a 5,5 *trans*-fused system. The same strain prevents thermal electrocyclic ring closure of cyclooctadienyl *cations*.

### ● All electrocyclic reactions are allowed

It would be a good point here to remind you that, although all electrocyclic reactions are allowed both thermally and photochemically providing the rotation is right, the steric requirements for con- or disrotatory cyclization or ring opening may make one or both modes impossible.

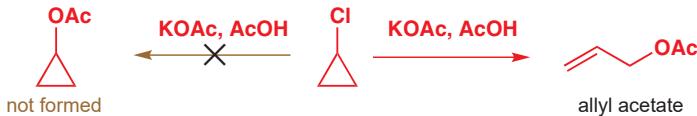
### Small rings are opened by electrocyclic reactions

► You saw allyl cations as intermediates in substitution reactions in Chapters 15 and 24.

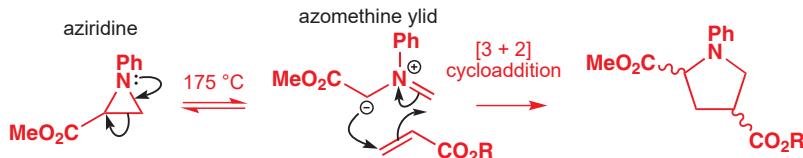
Ring strain is important in preventing a reaction that would otherwise change your view of a lot of the chemistry you know. Allyl cations are conjugated systems containing  $2\pi$  electrons, so if you knew no other chemistry than what is in this chapter you might expect them to cyclize via disrotatory electrocyclic ring closure. The product would be a cyclopropyl cation.



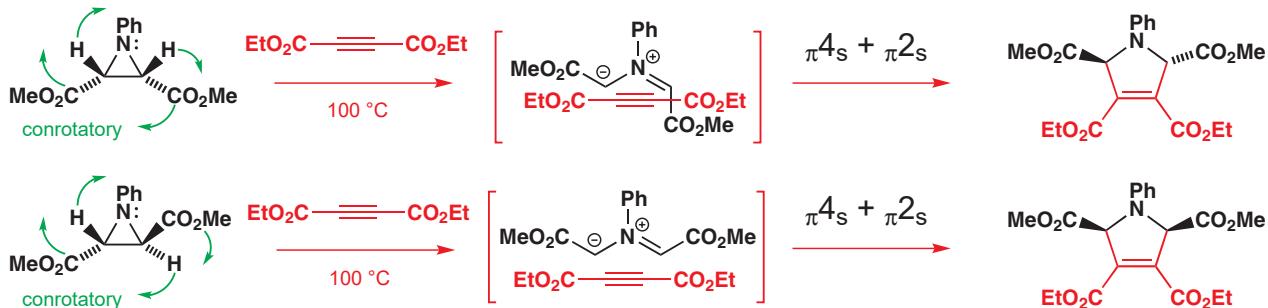
In fact, it is the cyclopropyl cations that undergo this reaction (very readily indeed—cyclopropyl cations are virtually unobservable) because ring strain encourages them to undergo electrocyclic ring opening to give allyl cations. The instability of cyclopropyl cations means that, even as they start to form as intermediates, they spring open to give allyl cation-derived products. Try nucleophilic substitution on a cyclopropane ring and this happens.



Electrocyclic ring opening of one type of three-membered ring tells us about the stereochemistry of the process. Many aziridines are stable compounds, but those bearing electron-withdrawing groups are unstable with respect to electrocyclic ring opening. The products are azomethine ylids and can be trapped by [3 + 2] cycloaddition reactions with dipolarophiles.



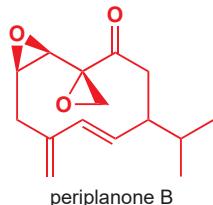
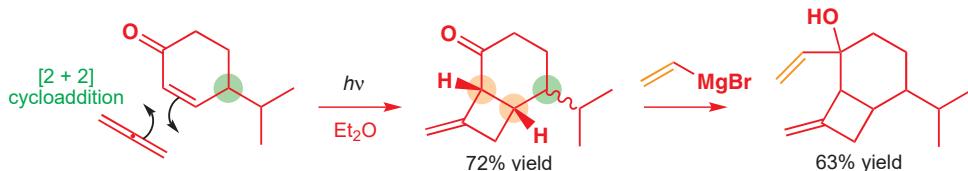
Because the cycloaddition is stereospecific (suprafacial on both components), the stereochemistry of the products can tell us the stereochemistry of the intermediate ylid, and confirms that the ring opening is conrotatory (the ylid is a  $4\pi$  electron system).



### The synthesis of a cockroach pheromone using pericyclic reactions

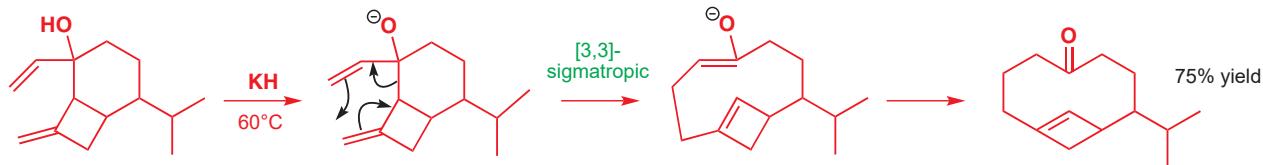
We finish this pair of chapters about pericyclic reactions with a synthesis whose simplicity is outclassed only by its elegance. Periplanone B is a remarkable bis-epoxide that functions as the sex pheromone of the American cockroach. Insect sex pheromones often have economic importance because they can form the key to remarkably effective traps for insect pests.

In 1984, Schreiber published a synthesis of the pheromone in which the majority of steps involve pericyclic reactions. Make sure you understand each one as it appears—re-read the appropriate part of Chapter 34 or this chapter if you have any problems. The first step is a photochemical [2 + 2] cycloaddition. You could not have predicted the regiochemistry, but it is typical of the cycloaddition of allenes with unsaturated ketones.



The product is a mixture of diastereoisomers because of the chiral centre already in the molecule (ringed in green), but it is, of course, fully stereospecific for the two new orange chiral centres in the four-membered ring. The next step adds vinylmagnesium bromide to the ketone—again a mixture of diastereoisomers results.

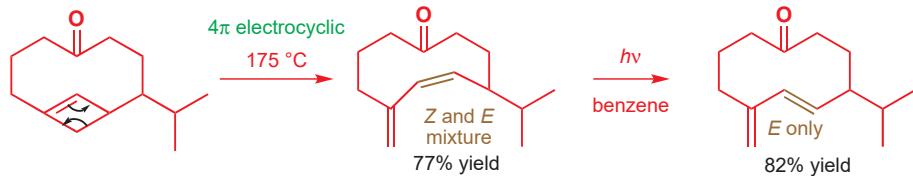
All the carbon atoms in the 12-membered ring are now present, and they are sorted out by the two steps that follow. The first is a Cope rearrangement: a [3,3]-sigmatropic rearrangement, accelerated as we have described (p. 914) by the presence of an alkoxide substituent.



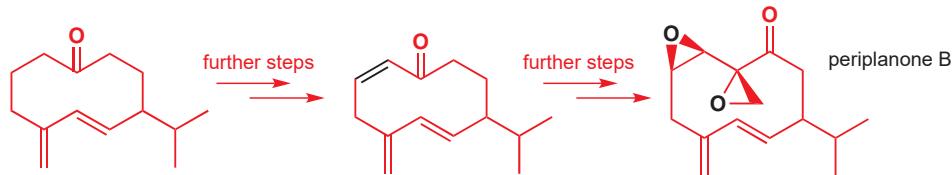
You met 1,3-dipolar cycloadditions in Chapter 34, see p. 901.

■ There are two things to note here—firstly the geometry of the double bond is nothing to do with whether the reaction is conrotatory or disrotatory. As you know this  $4\pi$  electron electrocyclic ring opening must be conrotatory but as there is no substituent on the other end of the diene product we can't tell. Secondly notice that in this 12-membered ring a *trans* double bond is not only possible but probably preferred. We introduced irradiation as a means of interconverting double bond isomers in Chapter 27.

The six-membered ring has expanded to a ten-membered ring. Now for a second ring-expansion step—heating the compound to 175 °C makes it undergo electrocyclic ring opening of the four-membered ring, giving the 12-membered ring we want. Or rather not quite—the new double bond in the ring is formed as a mixture of *cis* and *trans* isomers, but irradiation isomerizes the less stable *cis* to the more stable *trans* double bond.



The remaining steps in the synthesis involve the insertion of another *Z* alkene and two epoxides. Pericyclic reactions are particularly valuable in the synthesis and manipulation of rings.



We must now take our leave of this trio of pericyclic reactions and move on to two reaction classes that have appeared frequently in these two chapters, but that also involve mechanisms other than pericyclic ones and deserve a chapter of their own: *rearrangements* and *fragmentations*.

## Further reading

For explanations of pericyclic reactions and other reactions, using the full molecular orbital treatment, consult: Ian Fleming, *Molecular Orbitals and Organic Chemical Reactions, Student Edition*, Wiley, Chichester 2009. There is also a more comprehensive edition intended for practicing chemists, called the *Library Edition*. He has also written an Oxford Primer: *Pericyclic Reactions*, OUP, Oxford, 1999.

For a comprehensive treatment of sigmatropic and electrocyclic reactions in the synthesis of nitrogen heterocycles, see P. Wyatt and S. Warren, *Organic Synthesis: Strategy and Control*, Wiley, Chichester, 2007, chapter 34.

The synthesis of periplanone appears in S. L. Schreiber and C. Santini, *J. Am. Chem. Soc.*, 1984, **106**, 4038.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 参与、重排和碎片化

## 联系

### 基础

- Nucleophilic substitution at saturated carbon [ch15](#)
- Conformational analysis [ch16](#)
- Elimination reactions [ch17](#)
- Electrophilic aromatic substitution [ch21](#)
- Controlling stereochemistry [ch14, ch32, & ch33](#)
- Main group chemistry [ch27](#)
- Stereoelectronics [ch31](#)
- Sigmatropic rearrangements [ch35](#)

### 目标

- Participation: nucleophiles that are already part of the molecule
- Participation may mean rearrangement
- Participating groups can have lone pairs or  $\pi$  electrons
- Carbocations often rearrange by alkyl migration
- How to work out the mechanism of a rearrangement
- Ring expansion by rearrangement
- Using rearrangements in synthesis
- Insertion of O, N, or C next to a ketone
- How fragmentation splits molecules into three pieces by C–C bond cleavage
- Controlling rearrangements and fragmentations
- Control of fragmentations by stereochemistry

### 展望

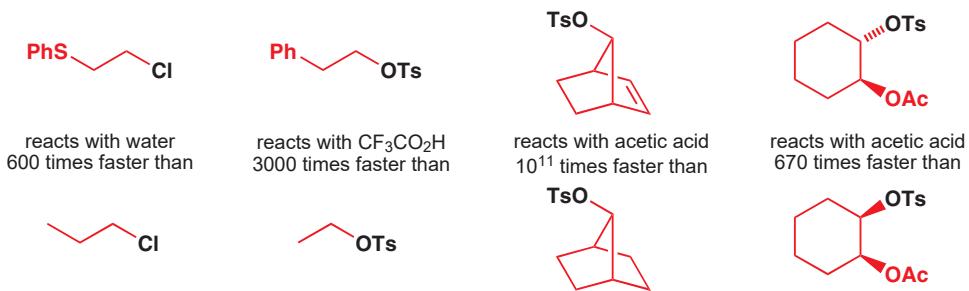
- Carbene chemistry [ch38](#)
- Determination of mechanism [ch39](#)
- The chemistry of life [ch42](#)

The last two chapters introduced **pericyclic reactions**, and the next one will cover reactions of **radicals**. Together with the **ionic reactions** which have been the subject of most of this book, these three classes cover all organic mechanisms. But before we move on to consider radicals, we need to fill a gap in our coverage of ionic reactions. You have met the most important types of ionic reactions—additions, substitutions, and eliminations. But two remain and they are closely related. In **rearrangements** the molecule changes its carbon skeleton and in **fragmentations** the carbon skeleton splits into pieces. We lead up to these types of reaction by looking at a phenomenon known as **participation**.

## Neighbouring groups can accelerate substitution reactions

Compare the rates of the following substitution reactions. Each is a substitution of the leaving group (OTs or Cl) by solvent, known as a solvolysis.

■ A solvolysis was defined in Chapter 15 as ‘a reaction in which the solvent is also the nucleophile’.

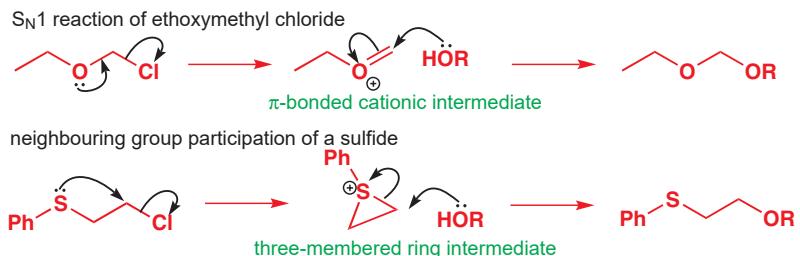


Nearby groups can evidently increase the rate of substitution reactions significantly. Now, you may be thinking back to Chapter 15 and saying ‘yes, yes, we know that’—when we were discussing the mechanisms of substitution reactions we pointed out that a cation-stabilizing group at the reaction centre makes S<sub>N</sub>1 reactions very fast, for example:



In the four examples above, though, it is not at the reaction centre itself that the functional groups change but at the carbon *next* to the reaction centre, and we call these groups *neighbouring groups*. The mechanism by which they speed up the reactions is known as *neighbouring group participation*. Compare the reaction of this ether and this sulfide with an alcohol.

■ Neighbouring group participation is occasionally called **anomeric assistance** (Greek *anchi* = neighbouring; *mer* = part).



In both cases, ionization of the starting material is assisted by the lone pair of an electron-rich functional group. The ether in the first example assists by forming a  $\pi$  bond, the sulfide assists by forming a  $\sigma$  bond in a three-membered ring, and a common feature of all mechanisms involving neighbouring group participation is the formation of a cyclic intermediate.

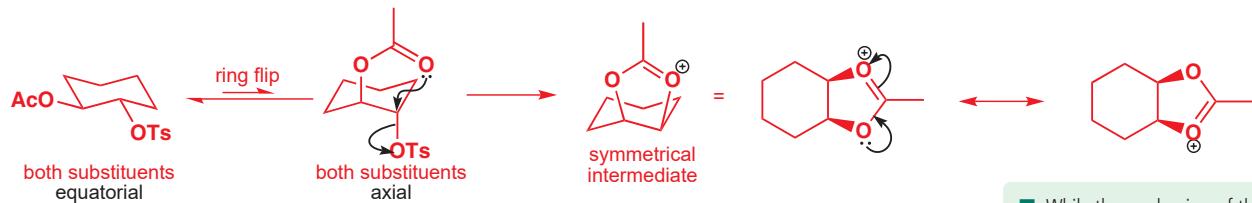
### Stereochemistry can indicate neighbouring group participation

How do we know that neighbouring group participation is taking place? Well, the first bit of evidence is the *increase in rate*. The neighbouring groups become involved only if they can increase the rate of the substitution reaction—otherwise the mechanism will just follow the ordinary S<sub>N</sub>2 pathway. But more important information comes from reactions where stereochemistry is involved, and one of these is the last of the four examples at the start of the chapter. Here it is again in more detail. Not only does the first of these reactions go faster than the second—it’s stereochemical course is different too.



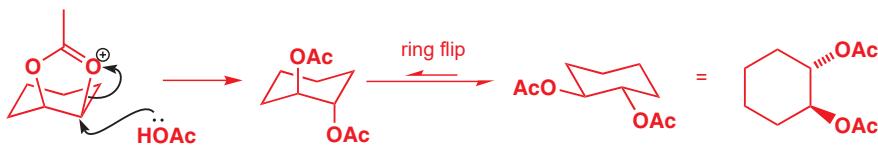
Although one starting material has *syn* and the other *anti* stereochemistry, the products have the same (*anti*) stereochemistry—one substitution goes with retention and one goes with

inversion. Again, neighbouring group participation is the reason. To explain this, we should first draw the six-membered rings in their real conformation. For the *anti* compound, both substituents can be equatorial. However, not much can happen in this conformation—but, if we allow the ring to flip, you can see immediately that the acetate substituent is ideally placed to participate in the departure of the tosylate group.



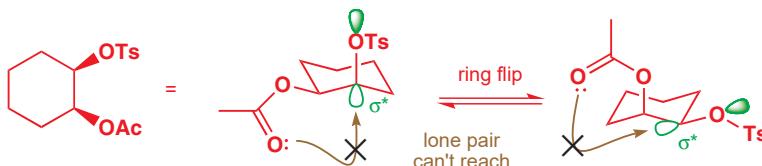
What results is an entirely symmetrical intermediate—the positive charge on one of the oxygens is, of course, delocalized over both of them. The intramolecular  $S_N2$  reaction takes place with inversion, as required by the orbitals, so now the junction of the two rings is *cis*.

The next step is attack of acetic acid on the intermediate. This is another  $S_N2$  reaction, which also proceeds with inversion and gives back a *trans* product.



Overall, we have *retention* of stereochemistry. As you know,  $S_N2$  reactions go with inversion and  $S_N1$  reactions with loss of stereochemical information, so this result is possible only if we have two sequential  $S_N2$  reactions taking place—in other words neighbouring group participation.

Why, then, does the other diastereoisomer react with inversion of stereochemistry? Well, try drawing the mechanism for intramolecular displacement of the tosyl group. Whether you put the tosylate or the acetate group equatorial doesn't matter; there is no way in which the acetate oxygen's lone pair can reach the  $\sigma^*$  orbital of the tosylate C–O bond.



Neighbouring group participation is impossible, and substitution goes simply by intermolecular displacement of OTs by AcOH. Just one  $S_N2$  step means overall inversion of configuration, and no participation means a slower reaction.

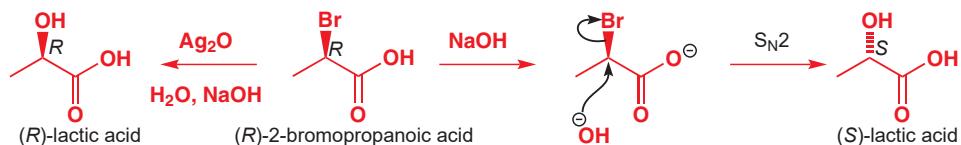


If you are unsure what we are talking about, go back and read Chapter 16 now!

Interactive mechanism for unexpected retention of stereochemistry

### Retention of configuration is an indication of neighbouring group participation

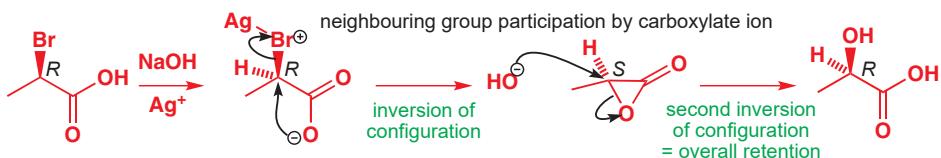
Enantiomerically pure (*R*)-2-bromopropanoic acid reacts with concentrated sodium hydroxide to give (*S*)-lactic acid. The reaction goes with inversion and is a typical  $S_N2$  reaction—and a good one too, since the reaction centre is adjacent to a carbonyl group (see Chapter 15). If, on the other hand, the reaction is run using  $Ag_2O$  and a low concentration of sodium hydroxide, (*R*)-lactic acid is obtained—there is overall *retention* of stereochemistry.



■ Lactones (that is, cyclic esters) don't usually react with hydroxide by this mechanism, and you might expect this intermediate (which is a cyclic ester) to hydrolyse by attack of hydroxide at the C=O group. You might like to think about why this doesn't happen in this case.

Interactive mechanism for  $\alpha$ -lactone formation

Nucleophilic substitution reactions that go with retention of stereochemistry are rather rare and mostly go through two successive inversions with neighbouring group participation, like the example you saw in the last section. This time the neighbouring group is carboxylate: the silver oxide is important because it encourages the ionization of the starting material by acting as a halogen-selective Lewis acid. A three-membered ring intermediate forms, which then gets opened by hydroxide in a second  $S_N2$  step.



#### ● Retention suggests participation

If you see a substitution reaction at a stereogenic saturated carbon atom that goes with retention of stereochemistry, look for neighbouring group participation!

Why does the carboxylate group participate only at low  $\text{HO}^-$  concentration and in the presence of  $\text{Ag}^+$ ? You can think of the situation in these two reactions in terms of the factors that favour  $S_N1$  and  $S_N2$  reactions. In the first, we have conditions suited to an  $S_N2$  reaction: a very good nucleophile ( $\text{HO}^-$ ) and a good leaving group ( $\text{Br}^-$ ). Improve the leaving group by adding  $\text{Ag}^+$  ( $\text{Ag}^+$  assists  $\text{Br}^-$ 's departure much as  $\text{H}^+$  assists the departure of  $\text{OH}^-$  by allowing it to leave as  $\text{H}_2\text{O}$ ) and worsen the nucleophile ( $\text{H}_2\text{O}$  instead of  $\text{HO}^-$ , of which there is now only a low concentration), and we have the sorts of conditions that would favour an  $S_N1$  reaction. The trouble is, without neighbouring group participation, the cation here would be rather unstable—right next to a carbonyl group. The carboxylate saves the day by participating in the departure of the  $\text{Br}^-$  and forming the lactone. The key thing to remember is that a reaction always goes by the mechanism with the fastest rate.

#### ● Neighbouring groups participate only if they speed up the reaction.

### What sorts of groups can participate?

You've already met the most important ones—sulfides, esters, carboxylates. Ethers and amines (you will see some of these shortly) can also assist substitution reactions through neighbouring group participation. The important thing that they have in common is an electron-rich heteroatom with a lone pair that can be used to form the cyclic intermediate. Sulfides are rather better than ethers—this sulfide reacts with water much faster than  $n\text{-PrCl}$  but the ether reacts with acetic acid four times more slowly than  $n\text{-PrOSO}_2\text{Ar}$ .

sulfide participation



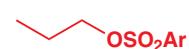
reacts with  $\text{H}_2\text{O}$   
600 times faster than



ether participation?



reacts with  $\text{AcOH}$   
4 times slower than



The OMe group slows the reaction down just because it is electronegative more than it accelerates it by participation. A more distant OMe group can participate: this 4-MeO alkyl sulfonate reacts with alcohols 4000 times faster than the  $n\text{-Bu}$  sulfonate.

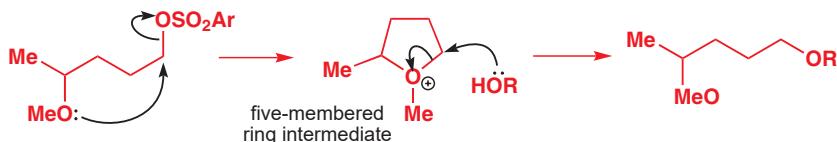
ether participation



reacts with  $\text{ROH}$   
4000 times faster than

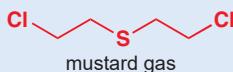


Again neighbouring group participation is involved, but this time through a five- rather than a three-membered ring. Participation is most commonly through three- and five-membered rings, less often six-membered ones, and very rarely four- or more than seven-membered ones.



### Mustard gas

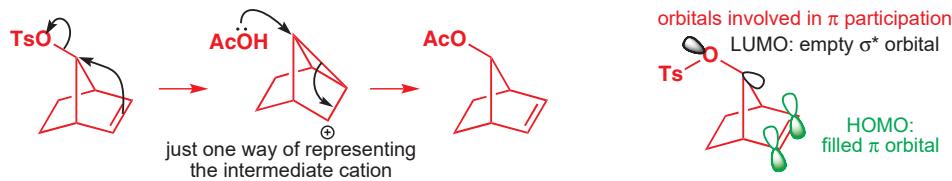
Participation of sulfides through three-membered rings was used to gruesome effect in the development of mustard gas during the Second World War. Mustard gas itself owes its toxicity to the neighbouring group participation of sulfur, which accelerates its alkylation reactions.



■ Why these ring sizes? Well, the underlying reasons are the same as those we discussed in Chapter 31 when we talked about the kinetics (rates) of formation and thermodynamics (stability) of different ring sizes: three- and five-membered rings form particularly rapidly in any reaction.

### Not all participating groups have lone pairs

Another of the four examples we started with shows that even the  $\pi$  electrons of a C=C double bond can participate. Retention of stereochemistry in the product (the starting tosylate and product acetate are both *anti* to the double bond) and the extremely fast reaction ( $10^{11}$  times that of the saturated analogue) are tell-tale signs of neighbouring group participation.

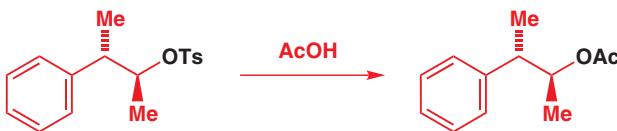


### What is the structure of the intermediate?

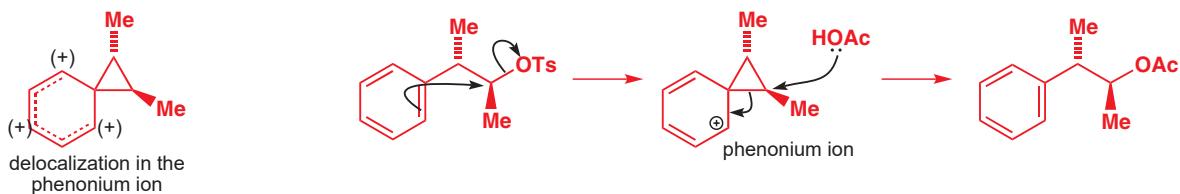
During the 1950s and 1960s, this sort of question provoked a prolonged and acrimonious debate, which we have no intention of stirring up, and all we will do is point out that the intermediate in this reaction is not fully represented by the structure we have here: it is symmetrical and could be represented by two structures with three-membered rings or by a delocalized structure in which two electrons are shared between three atoms. The difference need not concern us.



Finally, an example with a neighbouring phenyl group. Participation is suggested by the retention of relative stereochemistry.

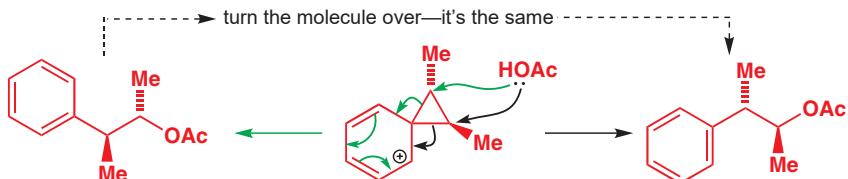


Again,  $\pi$  electrons are involved, but the reaction is now electrophilic aromatic substitution (Chapter 21) rather like an intramolecular Friedel–Crafts alkylation with a delocalized intermediate often termed a phenonium ion.



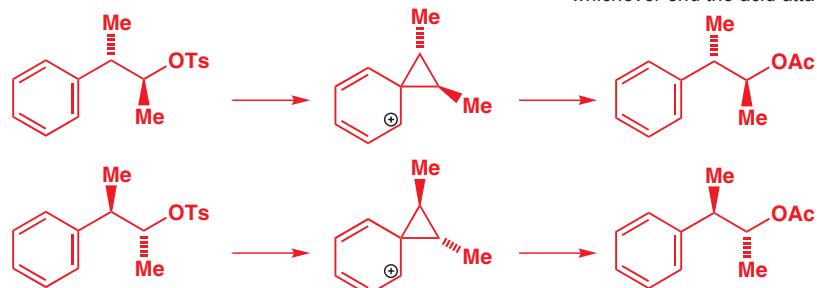
### More stereochemical consequences of neighbouring group participation

The phenonium ion is symmetrical. The acetic acid can attack either atom in the three-membered ring to give the same product.



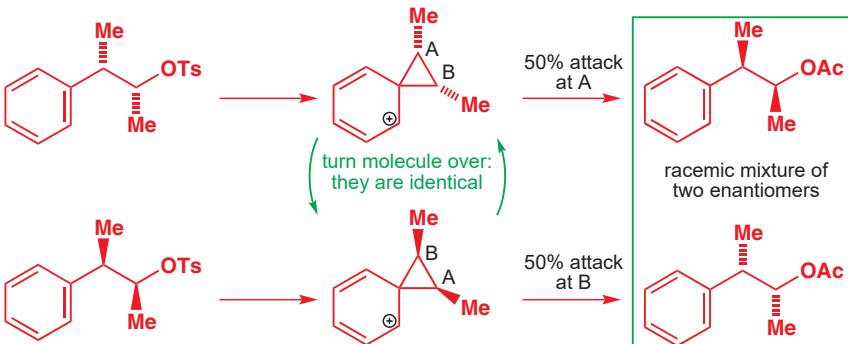
The phenonium ion is nonetheless still chiral, since it has an axis (and not a plane or centre) of symmetry, so if we use an enantiomerically pure starting material we get an enantiomerically pure product.

from this enantiomer of tosylate . . . we get this phenonium ion . . . and this enantiomer of product  
whichever end the acid attacks



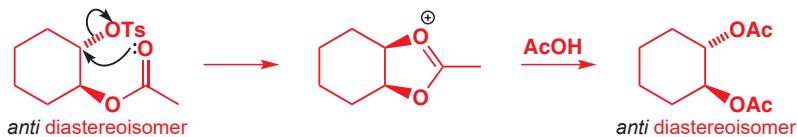
Not so with the other diastereoisomer of this compound! Now, the phenonium ion is symmetrical with a plane of symmetry—it is therefore achiral, and the same whichever enantiomer we start from. Attack on each end of the phenonium ion gives a different enantiomer, so whichever enantiomer of starting material we use we get the same racemic mixture of products. You can compare this reaction with the loss of stereochemical information that occurs during an  $S_N1$  reaction of enantiomerically pure compounds. Both reactions pass through an achiral intermediate.

from either enantiomer . . . we get the same achiral phenonium ion . . . and therefore racemic product

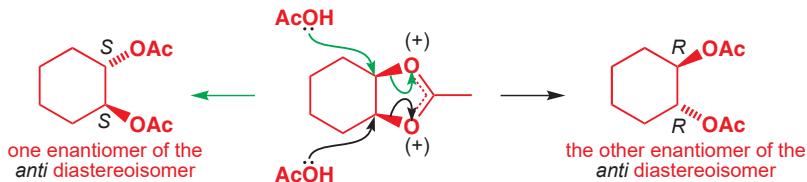


There is a subtlety here that you should not overlook and that makes this study, which was carried out by Cram in 1949, exceedingly elegant. Reactions of both of these diastereoisomers are stereospecific: the relative stereochemistry of the products depends on the relative stereochemistry of the starting materials. Yet, while the absolute stereochemistry of the starting materials is retained in one case (we get a single enantiomer of a single diastereoisomer), it is lost in the other (we get a racemic mixture of both enantiomers of a single diastereoisomer). These are important distinctions, and if you are in any doubt about these terms, re-read Chapters 14 and 33. Donald Cram (1919–2001) of UCLA was awarded the Nobel prize in 1987 jointly with Jean-Marie Lehn (1939–) of Strasbourg and Paris, and Charles Pedersen (a Norwegian born in Korea in 1904) of DuPont for ‘their development and use of molecules with structure-specific interactions of high selectivity’.

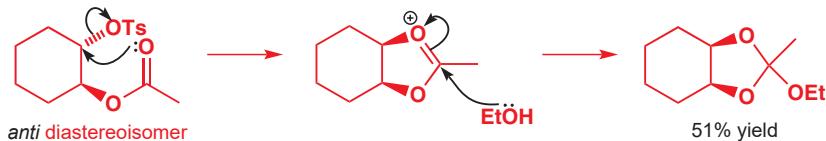
The same loss of absolute stereochemical information (but retention of relative stereochemistry) occurs in another reaction that you met at the start of this chapter. We then emphasized two features: the acceleration in rate and the retention of stereochemistry.



The intermediate oxonium ion is delocalized and achiral. If a single enantiomer of the starting material is used, racemic product is formed through this achiral intermediate. Attack at one carbon atom gives one enantiomer; attack at the other gives the mirror image.



In this case the neighbouring group can be caught in the act—when the rearrangement is carried out in ethanol, the intermediate is trapped by attack at the central carbon atom. It is as though someone switched the light on while the acetate's fingers were in the biscuit tin. The product is an orthoester and is achiral too. This chemistry should remind you of the formation of acetals, as described in Chapter 11.



## Rearrangements occur when a participating group ends up bonded to a different atom

Because the intermediates in these examples are symmetrical, 50% of the time one substituent ends up moving from one carbon atom to another during the reaction. This is clearer in the following example: the starting material is prepared such that the carbon atom carrying the phenyl group is an unusual isotope—carbon-14. This doesn't affect the chemistry, but means that the two carbon atoms are easily distinguishable. Reacting the compound with trifluoroacetic acid scrambles the label between the two positions: the intermediate is symmetrical and, in the 50% of reactions with the nucleophile that take place at the labelled carbon atom, the phenyl ends up migrating to the unlabelled carbon atom in a rearrangement reaction.

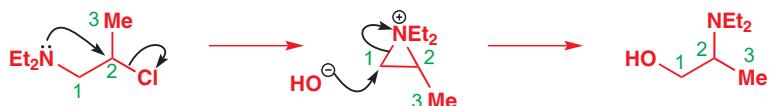


Now, consider this substitution reaction, in which OH replaces Cl but with a change in the molecular structure. The substitution goes with complete rearrangement—the amine ends up attached to a different carbon atom. We can easily see why if we look at the mechanism. The reaction starts off looking like a neighbouring group participation of the sort you are now familiar with (the carbon atoms are numbered for identification).

■ Labelling an atom with an unusual isotope is a standard way to probe the details of a reaction. Radioactive  $^3\text{H}$  (tritium) or  $^{14}\text{C}$  used to be used but, with the advent of high-field NMR, non-radioactive  $^2\text{H}$  (deuterium) and  $^{13}\text{C}$  are more versatile and less hazardous. These methods are examined more thoroughly in Chapter 39.

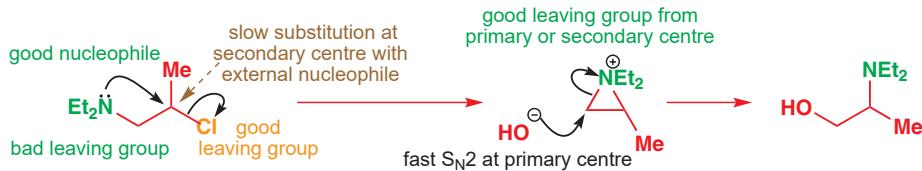


The intermediate is an aziridinium ion (aziridines are three-membered rings containing nitrogen—the nitrogen analogues of epoxides). The hydroxide ion chooses to attack only the less hindered terminal carbon 1, and a rearrangement results—the amine has migrated from carbon 1 to carbon 2.



Interactive mechanism for migration of participating group

We should just pause here for a moment to consider why this rearrangement works. We start with a secondary alkyl chloride that contains a very bad leaving group ( $\text{Et}_2\text{N}$ ) and a good one ( $\text{Cl}^-$ )—but the good one is hard for  $\text{HO}^-$  to displace because it is at a secondary centre (remember—secondary alkyl halides are slow to react by  $\text{S}_{\text{N}}1$  or  $\text{S}_{\text{N}}2$ ). But the  $\text{NEt}_2$  can participate to make an aziridinium intermediate—now there is a good leaving group ( $\text{RNEt}_2$  without the negative charge) at the primary as well as the secondary carbon, so  $\text{HO}^-$  does a fast  $\text{S}_{\text{N}}2$  reaction at the primary carbon.

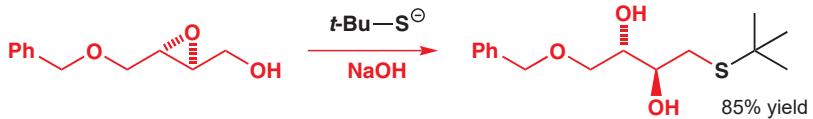


Another way to look at this reaction is to see that the good internal nucleophile  $\text{Et}_2\text{N}$  will compete successfully for the electrophile with the external nucleophile  $\text{HO}^-$ . Intramolecular reactions are usually faster than bimolecular reactions.

- Intramolecular reactions (including participation of a neighbouring group) that give three-, five-, or six-membered rings are usually faster than intermolecular reactions.

### The Payne rearrangement

The reaction of an epoxy alcohol in base does not always give the expected product.



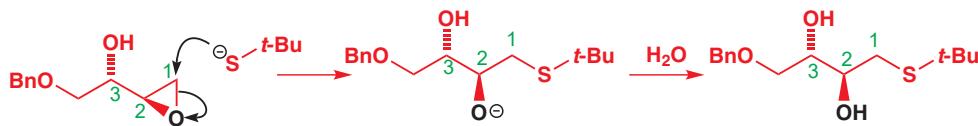
The thiolate nucleophile has not opened the epoxide directly, but instead *appears* to have displaced  $\text{HO}^-$ —a very bad leaving group. Almost no nucleophile will displace  $\text{OH}^-$ , so we need an alternative explanation. This comes in the form of another rearrangement, this time involving oxygen, but otherwise rather similar to the ones you have just met. Again, our epoxide, although reactive as an electrophile, suffers from being secondary at both electrophilic centres.  $t\text{-BuS}^-$  is a bulky nucleophile, so direct attack on the epoxide is slow. Instead, under the basic conditions of the reaction, the neighbouring alkoxide group attacks intramolecularly to make a new, rearranged epoxy alcohol. This is called the Payne rearrangement.

Interactive mechanism for Payne rearrangement

the Payne rearrangement



Now we do have a reactive, primary electrophilic site, which undergoes an  $S_N2$  reaction with the  $t\text{-BuS}^-$  under the conditions of the rearrangement. Notice how the black OH, which started on the carbon labelled 1, has ended up on carbon 2.



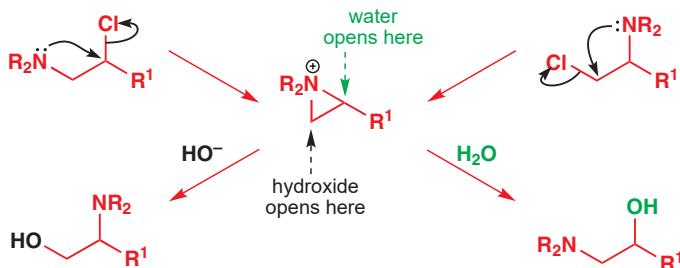
### The direction of rearrangement can depend on the nucleophile

Compare these reactions: you saw the first on p. 938 but the second is new.



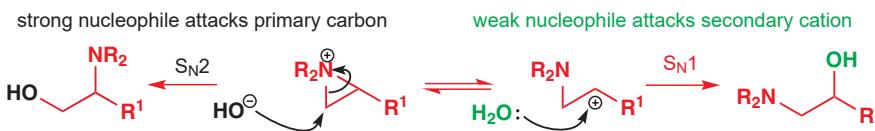
In the first reaction, the amine migrates from the primary to the secondary position; in the other from secondary to primary. Both go through very similar aziridinium intermediates, so the difference must be due to the regioselectivity with which this aziridinium ion opens in each case.

The only important difference is the nucleophile used in the reaction. Hydroxide opens the aziridinium at the less hindered end; water opens the aziridinium ion at the more hindered (more substituted) end. Why?



When a group migrates from a primary to a secondary carbon, we say the rearrangement has a primary **migration origin** and a secondary **migration terminus**. The migrating group moves from the migration origin to the migration terminus.

We can think of the aziridinium ion as a compound containing two alternative leaving groups—one from a primary centre and one from a secondary one. Primary centres can take part in fast  $S_N2$  reactions, but cannot undergo  $S_N1$ . Secondary centres can undergo either  $S_N1$  or  $S_N2$  reactions, but, in general, do neither very well. Now, the rate of an  $S_N2$  reaction depends on the nucleophile, so a good nucleophile (like  $\text{HO}^-$ ) can do fast  $S_N2$  reactions, while a bad one (like  $\text{H}_2\text{O}$ ) cannot. The fastest reaction  $\text{HO}^-$  can do then is  $S_N2$  at the primary centre (remember: you see only the reaction that goes by the fastest mechanism). Water, on the other hand, takes part only reluctantly in substitution reactions—but this does not matter if they are  $S_N1$  reactions because their rates are independent of nucleophile.  $\text{H}_2\text{O}$  waits until the leaving group has left of its own accord to give a cation, which rapidly grabs *any* nucleophile—water will do just as well as  $\text{HO}^-$ . This can happen *only* at the secondary centre because the primary cation is too unstable to form.



Interactive mechanism showing the effect of different nucleophiles

All the rearrangements you have met so far occurred during substitution reactions. All happened because reaction *with* rearrangement is faster than reaction *without* rearrangement—in other words, rearrangement occurs because of a kinetic preference for the rearrangement pathway. You could see these reactions as ‘special case’ examples of neighbouring group participation—in both participation and rearrangement the neighbouring group speeds up the

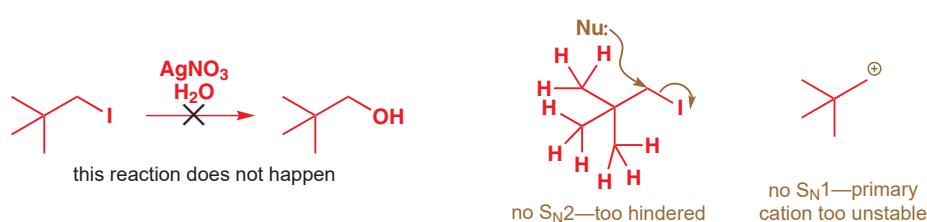
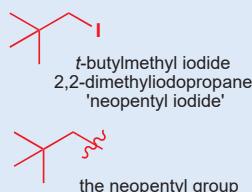
reaction, but in rearrangement reactions the neighbouring group gets rather more than it bargained for, and ends up elsewhere in the molecule. Both proceed through a cyclic transition state or intermediate, and it is simply the way in which that transition state or intermediate collapses that determines whether rearrangement occurs.

### Rearrangement can involve migration of alkyl groups

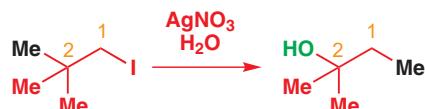
This example is a nucleophilic substitution under conditions ( $\text{Ag}^+$ ,  $\text{H}_2\text{O}$ ) designed to encourage  $\text{S}_{\text{N}}1$  reactions (excellent leaving group, poor nucleophile). First of all, this is what does not happen (and indeed without  $\text{Ag}^+$  nothing happens at all).

#### Neopentyl

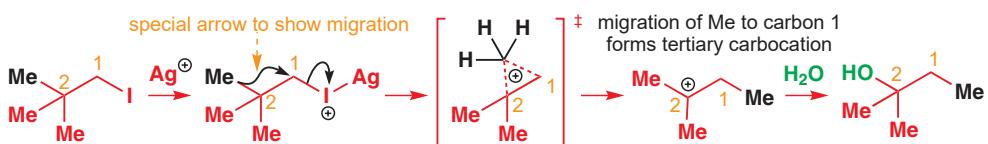
The *t*-butylmethyl group is also called 'neopentyl'.



Compounds like this, with a *t*-butyl group next to the electrophilic centre, are notoriously slow to undergo substitution reactions. They can't do  $\text{S}_{\text{N}}2$ , they are too hindered; they can't do  $\text{S}_{\text{N}}1$ , the cation you would get is primary. In fact, a rearrangement occurs. One of the methyl groups moves ('migrates') from carbon 2 to carbon 1, the new OH group taking its place at carbon 2.



How has this happened? Well, firstly, our principle (p. 934) tells us that it has happened because  $\text{S}_{\text{N}}1$  and  $\text{S}_{\text{N}}2$  are both so slow that this new rearrangement mechanism is faster than either. Adding  $\text{Ag}^+$  makes  $\text{I}^-$  desperate to leave, but unassisted this would mean the formation of a primary carbocation. The molecule does the only thing it can to stop this happening and uses the electrons in an adjacent C–C bond to assist the departure of  $\text{I}^-$ . Having participated, the methyl group continues to migrate to carbon 1 because by doing so it allows the formation of a stable tertiary carbocation, which then captures water in a step reminiscent of the second half of an  $\text{S}_{\text{N}}1$  reaction. Note the cyclic transition state where the migrating group is partially bonded to two carbon atoms.

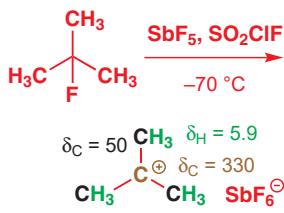


In the migration step we used a slightly unusually S-shaped curly arrow to represent the movement of a group (Me) along a bond taking its bonding electrons with it. We shall use this type of arrow when a group migrates from one atom to another during a rearrangement.

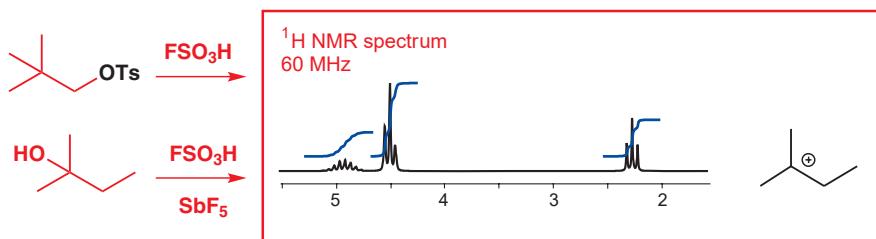
### Carbocations readily rearrange

In Chapter 15 we showed you that it is possible to run the NMR spectra of carbocations by using a polar but non-nucleophilic solvent such as liquid  $\text{SO}_2$  or  $\text{SOCIF}$ . Treating an alkyl halide RX with the powerful Lewis acid  $\text{SbF}_5$  under these conditions gives a solution of carbocation: the carbocation reacts neither with solvent nor the  $\text{SbF}_5\text{X}^-$  counterion because neither is nucleophilic. We know, for example, that the chemical shifts in both the  $^{13}\text{C}$  and  $^1\text{H}$  NMR spectra of the *t*-butyl cation are very large, particularly the  $^{13}\text{C}$  shift at the positively charged centre.

■ Some of the cyclic species you have seen so far (aziridinium ions, epoxides) are intermediates; the intermediate cyclic cation here is probably only a transition state.



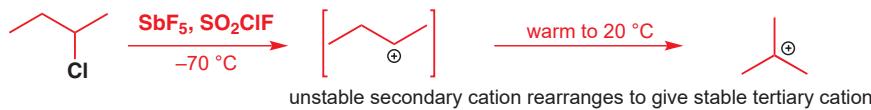
NMR can be used to follow the course of rearrangement reactions involving carbocations too. We can illustrate this with an experiment that tries to make the neopentyl cation by the substitution reaction you have just seen. This time the starting material and solvent are slightly different, but the outcome is nonetheless most revealing. Dissolving neopentyl tosylate in fluorosulfonic acid (a strong, non-nucleophilic acid) at  $-77^{\circ}\text{C}$  gives a 77% yield of a cation whose spectrum is shown below. Assigning the peaks is not hard once you know that the same spectrum is obtained when 2,2-dimethyl-2-butanol is dissolved in fluorosulfonic acid with  $\text{SbF}_5$  added.



■ Notice how the methyl groups appear as triplets due to coupling to  $\text{CH}_2$  through the empty p orbital.

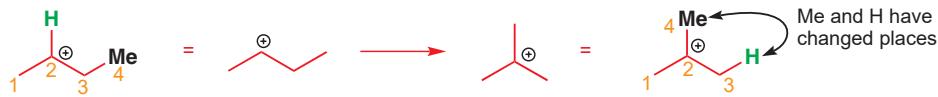
Clearly, the spectrum is the tertiary 2-methylbutyl cation and the neopentyl cation never saw the light of day. The reaction is the same rearrangement that you saw in the substitution reaction of neopentyl iodide, but here the rate of rearrangement can be measured and it is extremely fast. Neopentyl tosylate reacts to form a cation under these conditions about  $10^4$  times as fast as ethyl tosylate, even though both tosylates are primary. This massive rate difference shows that if migration of an alkyl group can allow rearrangement to a more stable carbocation, it will happen, and happen rapidly.

Primary cations can never be observed by NMR—they are too unstable. But secondary cations can, provided the temperature is kept low enough. *sec*-Butyl chloride in  $\text{SO}_2\text{ClF}$  at  $-78^{\circ}\text{C}$  gives a stable, observable cation. But, as the cation is warmed up, it rearranges to the *t*-butyl cation. Now this rearrangement truly is a carbocation rearrangement: the starting material is an observable carbocation and so is the product, and we should just look at the mechanism in a little more detail.



■ In fact, all seven possible isomers of pentyl alcohol ( $\text{C}_5\text{H}_{11}\text{OH}$ ) give this same spectrum under these conditions at temperatures greater than  $-30^{\circ}\text{C}$ .

With rearrangements like this it is best to number the C atoms so you can see clearly what moves where. If we do this, we see that the methyl group we have labelled 4 and the H on C3 have changed places. (Note that C3 starts off as a  $\text{CH}_2$  group and ends up as  $\text{CH}_3$ .)

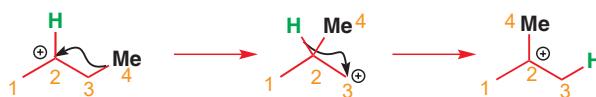


■ The reason we say 'truly' is a carbocation rearrangement' here is quite subtle and need not detain us long. We know that a secondary cation is formed in this case because we can see it by NMR; it subsequently rearranges to a tertiary cation. As we can never see primary cations, we don't know that they are ever formed, and the most reasonable explanation for rearrangements of the type you saw on p. 937 is that migration of the alkyl group begins *before* the leaving group is fully gone. This has been proved in a few cases, but we will from now on not distinguish between the two alternatives.

### Top tip for rearrangements

Number the carbon atoms in the starting material and product before you try to work out the mechanism.

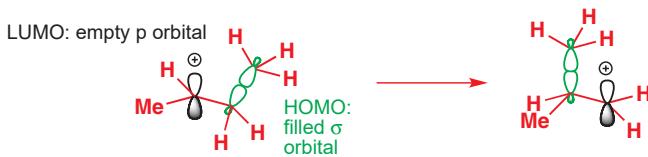
Using the sort of arrows we introduced on p. 940, we can draw a mechanism for this in which first the Me migrates, and then the hydride. We say hydride migration rather than hydrogen (or proton) because the H atom migrates with its pair of electrons.



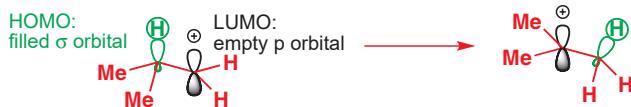
■ You will see why Me has to migrate first if you try drawing the mechanism out with H migrating first instead.

As these rearrangements are a new type of reaction, we should just spend a moment looking at the molecular orbitals that are involved. For the first step, migration of the methyl group,

the LUMO must clearly be the empty p orbital of the cation, and the HOMO is the C–C  $\sigma$  bond, which is about to break.

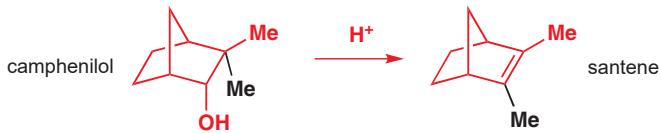


The methyl group can slide smoothly from one orbital to another—there are bonding interactions all the way. The next step, migration of H, is just the same—except that the HOMO is now a C–H  $\sigma$  bond. The methyl migration is thermodynamically unfavourable as it transforms a secondary cation into an unstable primary cation but the hydride migration puts that right as it gives a stable tertiary cation. The whole reaction is under thermodynamic control.

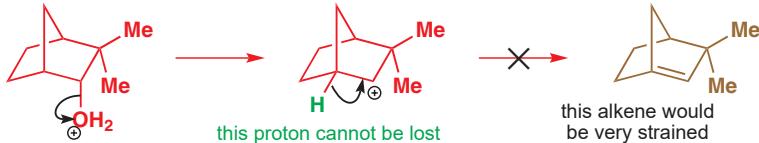


### Wagner–Meerwein rearrangements

Carbocation rearrangements involving migration of H or alkyl groups don't just happen in NMR machines. They happen during normal reactions too. For example, acid-catalysed dehydration of the natural product camphenilol gives the alkene santene (a key component of the fragrance of sandalwood oil) in a reaction involving migration of a methyl group.



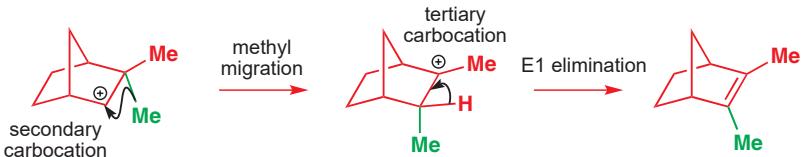
The mechanism shows why the rearrangement happens: the first-formed cation cannot eliminate  $\text{H}^+$  in an E1 reaction because loss of the only available proton would give a very strained bridgehead alkene (make a model and see!).



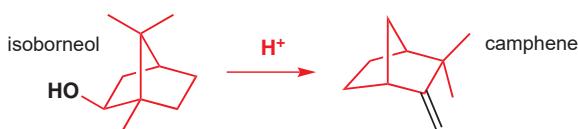
► The impossibility of bridgehead alkenes (Bredt's rule) was discussed in Chapter 17, p. 389.

Interactive mechanism for Wagner–Meerwein rearrangements

However, migration of a methyl group both stabilizes the cation—it becomes tertiary instead of secondary—and allows E1 elimination of  $\text{H}^+$  to take place to give a stable alkene.

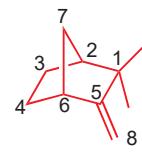
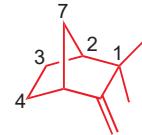
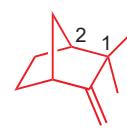
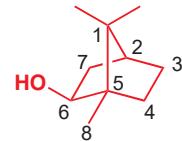


The migration of an alkyl group to a cationic centre is known as a Wagner–Meerwein rearrangement or Wagner–Meerwein shift, and this migration is, of course, a synthetic manifestation of the rearrangement we have just been looking at in NMR spectra. Wagner–Meerwein shifts have been studied extensively in the class of natural products to which both of these natural products belong—terpenes. For the moment, though, we will just illustrate this type of reaction with one more example—another acid-catalysed dehydration, of isoborneol to give camphene.



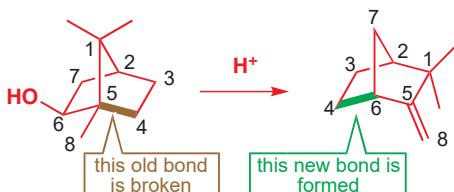
This one *seems* much more complicated—but, in fact, only one alkyl migration is involved. To see what has happened, remember the ‘top tip’—number the carbons. You can number the starting material any way you choose—we’ve started with the gem-dimethyl group because it will be easy to spot in the product. The numbers just follow round the ring, with C8 being the methyl group attached to C5.

Now for the hard bit—we need to work out which carbon in the starting material becomes which carbon in the product. The best thing is just to have a go—mistakes will soon become obvious and you can always try again.



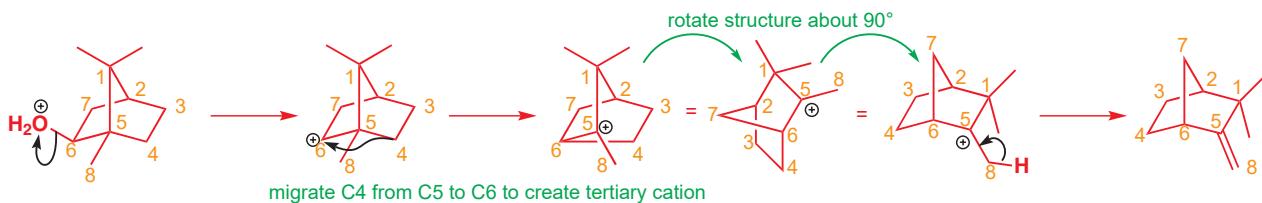
- Use the substituents to help you—some will have changed, but most will be the same or similar, for example C1 is still easy to spot as the carbon carrying the dimethyl group.
- Use connectivity to help you—again, a C–C bond or two may have broken or formed, but most of the C–C bonds in the starting material will be there in the product. C1 and C2 will probably still be next door to one another—C2 was a bridgehead carbon in the starting material, and there is a bridgehead C attached to C1 in the product; assume that’s C2.
- C3 and C4 were unsubstituted carbons in the starting material, and are identifiable in the product too. The other easily spotted atom is C7—an unsubstituted C attached to C2.
- C5, C6, and C8 are harder. We can assume that C8 is the =CH<sub>2</sub> carbon—it was a methyl group but perhaps has become involved in an elimination. C5 was attached to C1, C4, C6, and C8: one of the remaining carbons is attached to C1 and C8, so that seems more likely to be C5, which leaves C6 as the bridgehead, attached as before to C7 and C5.

Now we have the whole picture and we can assess what has happened in the reaction—which old bonds have broken and which new bonds have formed.



Numbering the atoms this way identifies the likely point of rearrangement—the only bond broken is between C4 and C5. Instead we have a new one between C4 and C6: C4 appears to have migrated from C5 to C6.

Now for the mechanism. The first step will, of course, be loss of water to generate a secondary cation at C6. The cation is next to a quaternary centre, and migration of any of three bonds could generate a more stable tertiary carbocation. But we know that the new bond in the product is between C4 and C6, so let’s migrate carbon 4. Manipulating the diagrams a bit turns up a structure remarkably similar to our product, and all we need to do is lose a proton from C8.



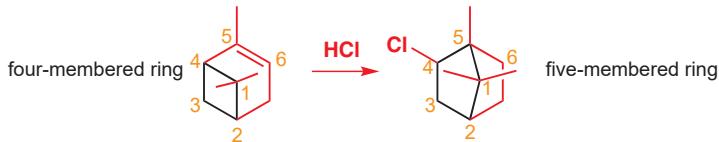
If you are observant, you may ask why the alkyl group migrated in this example and not the methyl group, or the other alkyl group—all three possibilities give similar tertiary carbocations. The reason involves the *alignment* of the orbitals involved, which we will discuss at the end of the chapter.

Although migration of an alkyl group that forms part of a ring leads to much more significant changes in structure than simple migration of a methyl group, the reason why it happens is still just the same.

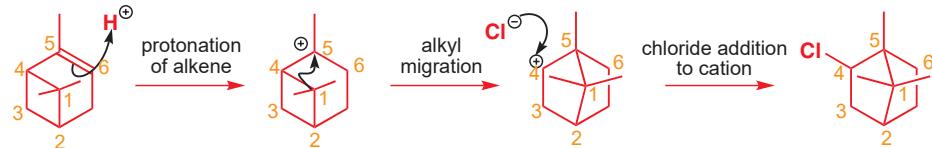
● Alkyl migrations occur in order to make a carbocation more stable.

### Ring expansion means rearrangement

'More stable' usually means 'more substituted', but cations can also be made *more stable* if they become *less strained*. So, for example, four-membered rings adjacent to cations readily rearrange to five-membered rings in order to relieve ring strain.

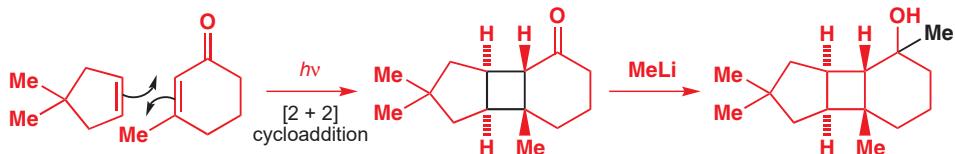


This time the cation is formed by protonation of an alkene, not departure of a leaving group, but writing a mechanism should now be a straightforward matter to you.

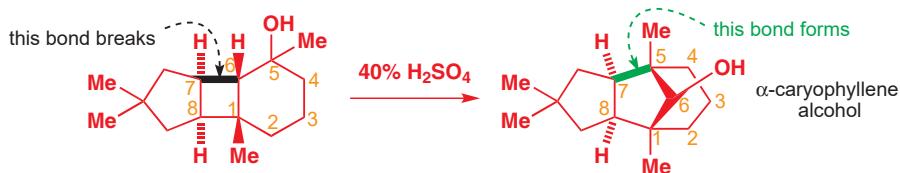


Interactive mechanism for cation-mediated ring expansion

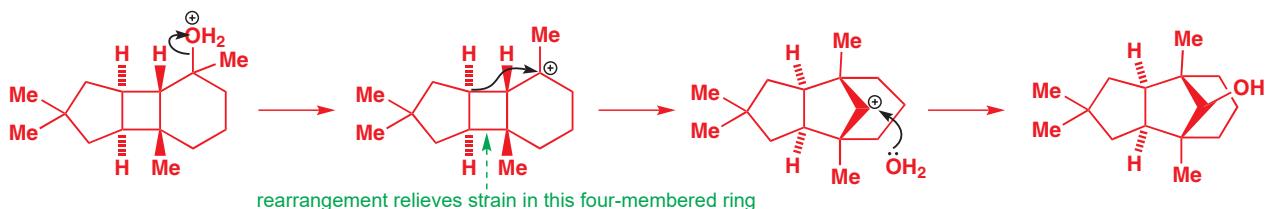
Although the rearrangement step transforms a stable tertiary cation into a less stable secondary cation, relief of strain in expansion from a four- to a five-membered ring makes the alkyl migration favourable. A synthesis of the natural product  $\alpha$ -caryophyllene alcohol makes use of a similar ring expansion. Notice the photochemical [2 + 2] cycloaddition (Chapter 34) in the synthesis of the starting material.



Rearrangement of this tertiary alcohol in acid gives the target natural product. The four-membered ring has certainly disappeared but it may not be obvious at first what has taken its place.

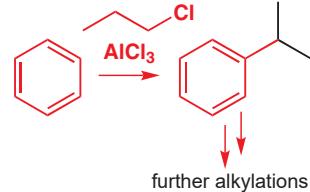


As usual, numbering the atoms makes clear what has happened: carbon 7 has migrated from carbon 6 to carbon 5. Loss of water gives a tertiary carbocation that undergoes rearrangement to a secondary carbocation with expansion of a four- to a five-membered ring.



### Carbocation rearrangements: blessing or curse?

Well, that depends. You have now seen a few useful carbocation rearrangements that give single products in high yield. But you have also met at least one reaction that *cannot* be done because of carbocation rearrangements: as we mentioned in Chapter 15, Friedel–Crafts alkylation using primary alkyl halides leads to products derived from rearranged cations. The alkylation in the margin illustrates the problems of trying to use carbocation rearrangements to make single products in high yield. We can give three guidelines to spotting this type of reaction.

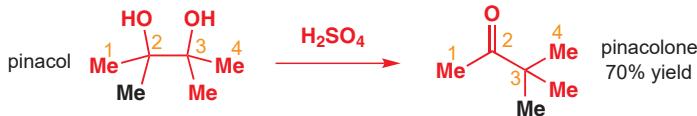


1. The rearrangement must be fast so that other reactions do not compete.
2. The product cation must be sufficiently more stable than the starting one so that the rearrangement happens in high yield.
3. Subsequent trapping of the product cation must be reliable: cations are high-energy intermediates, and are therefore unselective about how they react.

A reaction is no good if the cation reacts in more than one way—it may react with a nucleophile, eliminate, or undergo further rearrangement—but it must do only one of these! For the rest of the chapter, we will address only reactions that, unlike this Friedel–Crafts reaction, follow these guidelines. The reactions we will talk about all happen in good yield.

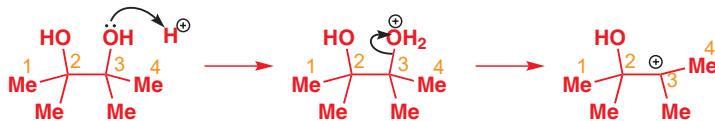
## The pinacol rearrangement

When the 1,2-diol pinacol is treated with acid, a rearrangement takes place.



Pinacol, the trivial name for the starting material, which is made from acetone by a reaction you will meet in Chapter 37, gives its name to this class of rearrangements, and to the product, 'pinacolone'.

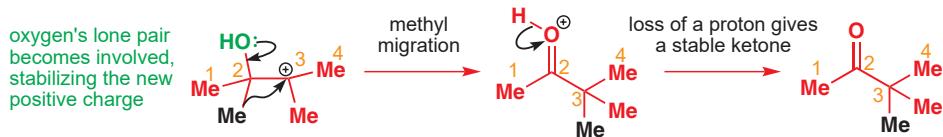
Whenever you see a rearrangement, especially in acid, you should now think 'carbocation'. Here, protonation of one of the hydroxyl groups allows it to leave as water, giving the carbocation.



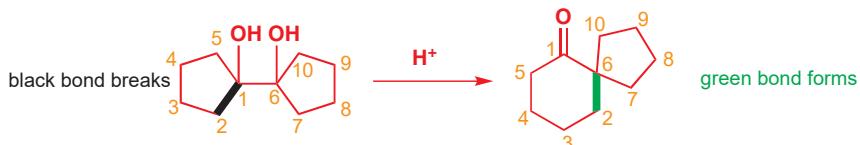
You now know that carbocations rearrange by alkyl shifts to get as stable as they can be—but this carbocation is already tertiary, and there is no ring strain, so why should it rearrange? Well, here we have another source of electrons to stabilize the carbocation: lone pairs on an oxygen atom. We pointed out early in the chapter that oxygen is very good at stabilizing a positive charge on an adjacent atom, and somewhat less good at stabilizing a positive charge two atoms away. By rearranging, the first-formed carbocation gets the positive charge into a position where the oxygen can stabilize it, and loss of a proton from oxygen then gives a stable ketone.

 Interactive mechanism for pinacol rearrangement

- Spirocycles are pairs of rings joined at a single carbon atom (Chapter 32).

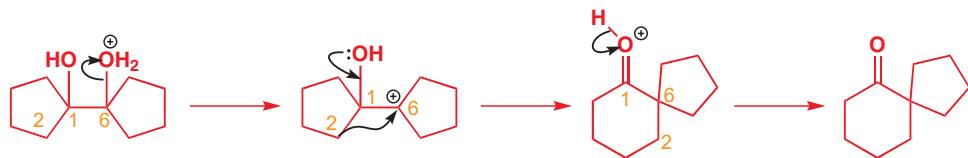


You can view the pinacol as a rearrangement with a ‘push’ and a ‘pull’. The carbocation left by the departure of water ‘pulls’ the migrating group across at the same time as the oxygen’s lone pair ‘pushes’ it. A particularly valuable type of pinacol rearrangement forms spirocyclic ring systems. You may find this one harder to follow, although the mechanism is identical with that of the last example. Our ‘top tip’ of numbering the atoms should help you to see what has happened: atom 2 has migrated from atom 1 to atom 6.



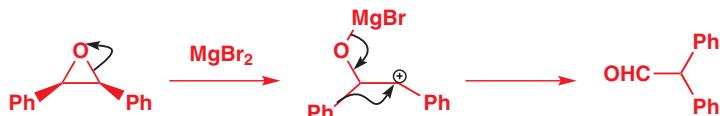
- Of course, it doesn’t matter how you number the atoms, but the numbering must be consistent. Usually, your initial impression of a greatly changed molecule will come down to just one or two atoms changing their substitution pattern, and numbering will help you to work out which ones they are.

When drawing the mechanism it doesn’t matter which hydroxyl group you protonate or which adjacent C–C bond migrates—they are all the same. One five-membered ring expands to a six-membered ring but the reason this reaction happens is the formation of a carbonyl group, as in all pinacol rearrangements.



### Epoxides rearrange with Lewis acids in a pinacol fashion

The intermediate cation in a pinacol rearrangement can equally well be formed from an epoxide, and treating epoxides with acid, including Lewis acids such as  $MgBr_2$ , promotes the same type of reaction.



Rearrangement of epoxides with magnesium salts means that opening epoxides with Grignard reagents can give surprising results.



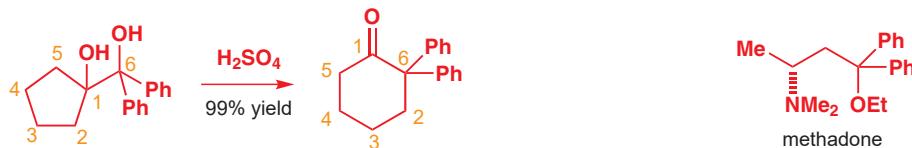
The alkyllithium reaction is quite straightforward as long as the alkyllithium is free of lithium salts. A clue to what has happened with the Grignard reagents comes from the fact that treating this epoxide with just  $MgBr_2$  (not  $RMgBr$ ) gives an aldehyde.



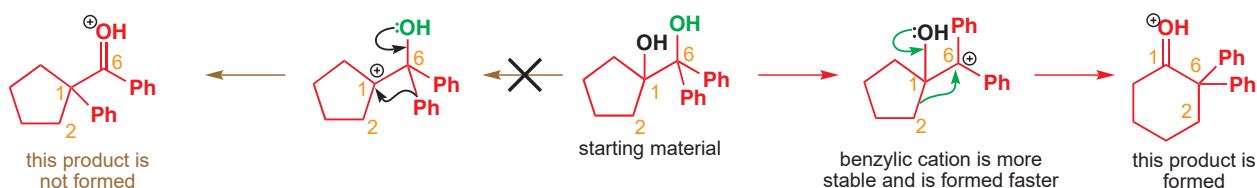
With a Grignard reagent, rearrangement occurs faster than addition to the epoxide, and then the Grignard reagent adds to the aldehyde.

### Some pinacol rearrangements have a choice of migrating group

With these symmetrical diols and epoxides, it does not matter which hydroxyl group is protonated and leaves, nor which end the epoxide opens, nor which group migrates. When an unsymmetrical diol or epoxide rearranges, it *is* important which way the reaction goes. Usually, the reaction leaves behind the more stable cation. So, for example, this unsymmetrical diol gives the ring-expanded ketone, a starting material for the synthesis of analogues of the drug methadone.



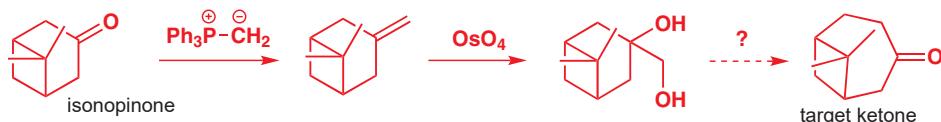
This product is formed because the green OH group leaves more readily than the black as the carbocation stabilized by two phenyl groups forms more readily than the carbocation stabilized by two alkyl groups. The migration step which follows has no choice: both alkyl groups on the black alcohol are the same.



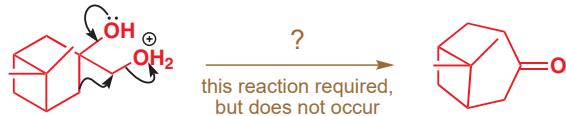
Most unsymmetrical diols or epoxides give mixtures of products on rearrangement. The problem is that there is a choice of two leaving groups and two alternative rearrangement directions, and only for certain substitution patterns is the choice clear-cut.

### Semipinacol rearrangements are pinacol reactions with no choice about which way to go

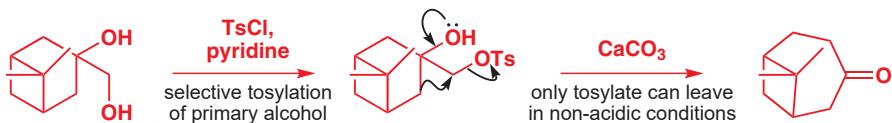
For some work on perfume compounds, this seven-membered cyclic ketone was needed. A reasonable starting material to use is the diol shown because it can be made in two steps from the natural product isonopinone.



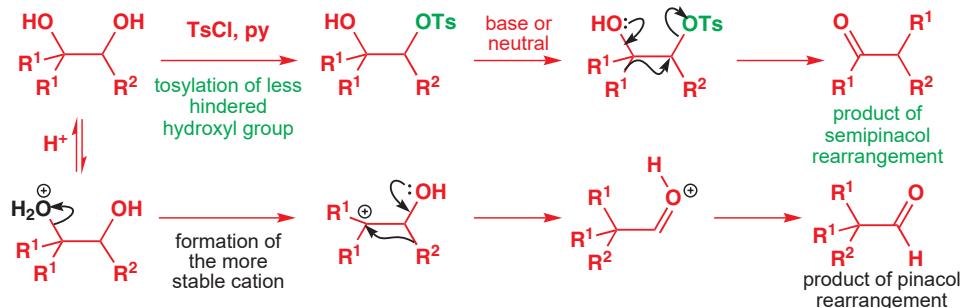
The reaction needed for the last stage is a pinacol rearrangement—the *primary* hydroxyl group needs persuading to leave as the ring expands. The problem is, of course, that the tertiary hydroxyl group is much more likely to leave since it leaves behind a more stable carbocation.



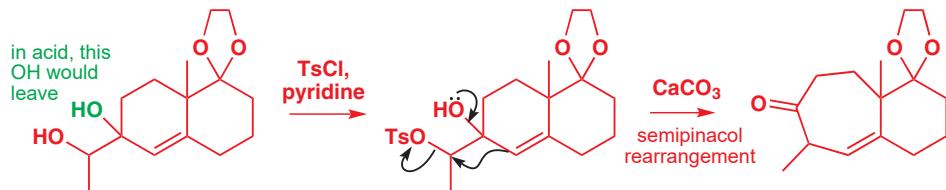
The solution to this problem is to force the primary hydroxyl group to be the leaving group by making it into a tosylate. The primary hydroxyl group reacts more rapidly with  $\text{TsCl}$  than the tertiary one because it is less hindered. A weak base is now all that is needed to make the compound rearrange in what is known as a semipinacol rearrangement.



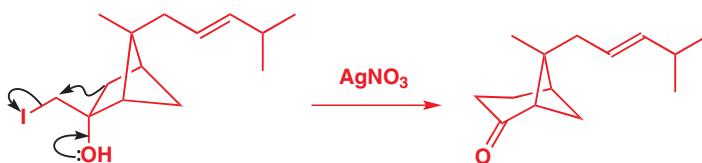
Semipinacol rearrangements are rearrangements in which a hydroxyl group provides the electrons to ‘push’ the migrating group across, but the ‘pull’ comes from the departure of leaving groups other than water—tosylate in this example, but typically also halide or nitrogen ( $N_2$ ). Since tosylation occurs at the *less* hindered hydroxyl group of a diol, not only can semipinacol rearrangements be more regioselective than pinacol rearrangements, but their regioselectivity may be in the opposite direction.



Corey exploited this in a synthesis of the natural product longifolene. He needed to persuade an easily made 6,6-fused ring system to undergo rearrangement to a ring-expanded ketone. Again, a normal acid-catalysed pinacol rearrangement is no good—the tertiary, allylic hydroxyl group is much more likely to ionize, and the acid-sensitive protecting group would be hydrolysed too. Tosylation of the secondary alcohol in the presence of the tertiary is possible, and semipinacol rearrangement gives the required ketone.



The leaving group need not be tosylate: in the following example, part of a synthesis of bergamotene (a component of valerian root oil and the aroma of Earl Grey tea), a 2-iodo alcohol rearranges.

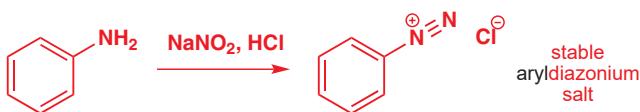


### Semipinacol rearrangements of diazonium salts

You saw in Chapter 21 how aromatic amines can be converted to diazonium salts by treatment with acidic sodium nitrite.

■ Treating 2-halo alcohols with base is, of course, a good way to make epoxides. Using  $AgNO_3$  to improve iodide’s leaving ability without increasing the nucleophilicity of the hydroxyl group favours rearrangement at the expense of epoxide formation. There would certainly be a danger of epoxide formation in strong base.

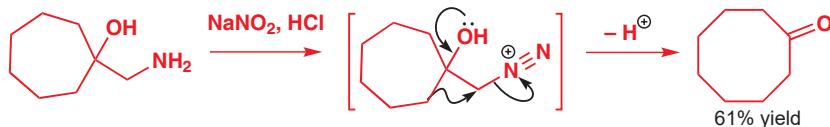
■ It might be an idea to review pp. 520–523 of Chapter 22 to be sure you understand the mechanism of this reaction.



Aryldiazonium salts are stable but alkyldiazonium salts are not: nitrogen gas is the world's best leaving group, and, when it goes it leaves behind a carbocation.



One of the 'further reactions' this carbocation can undergo is rearrangement. If the starting amine is a 2-amino alcohol, the cation can be stabilized by a semipinacol rearrangement.

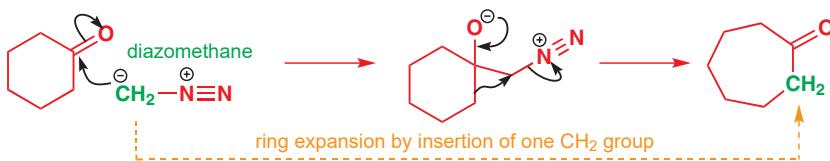


■ Semipinacol rearrangements of diazonium salts derived from 2-amino alcohols are sometimes called **Tiffeneau–Demjanov rearrangements**.

Interactive mechanism for Tiffeneau–Demjanov rearrangement

While alkyldiazonium salts are unstable, their conjugate bases, diazoalkanes, are stable enough to be prepared and are nucleophilic towards carbonyl compounds. Diazoalkanes are neutral compounds having one fewer proton than diazonium salts, and are delocalized structures with a central sp nitrogen atom.

When diazomethane (a compound we will investigate in more detail in Chapter 38) adds to a ketone, the product undergoes a ring expansion by rearrangement of the same type of intermediate.

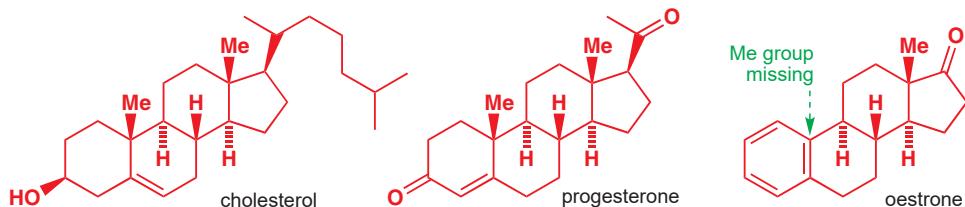


Interactive mechanism for semipinacol rearrangements of diazonium salts

The problem with reactions like this is that both the starting material and product are ketones, so they work cleanly only if the starting material is more reactive than the product. Cyclohexanone is more reactive as an electrophile than either cyclopentanone or cycloheptanone, so it ring expands cleanly to cycloheptanone. But expansion of cyclopentanone to cyclohexanone is messy and gives a mixture of products.

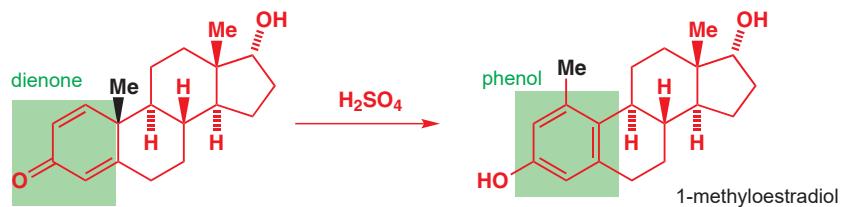
## The dienone-phenol rearrangement

The female sex hormone oestrone is the metabolic product of another hormone, progesterone, itself made in the body from cholesterol.

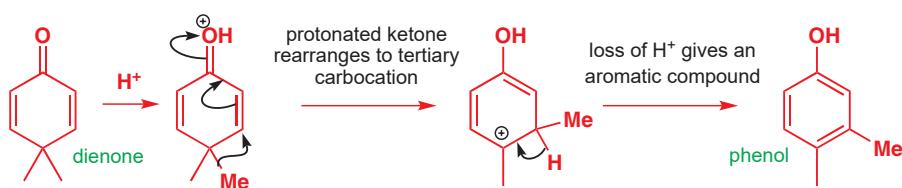


Oestrone lacks one of progesterone's methyl groups, probably removed in the body as  $\text{CO}_2$  after oxidation. In 1946, Carl Djerassi, a man whose work led directly to the invention of the contraceptive pill, showed that another derivative of cholesterol could be rearranged to the oestrone analogue 1-methyoestradiol—notice how the methyl group has this time migrated to an adjacent carbon atom. At the same time, the dienone has become a phenol.

Carl Djerassi, an American born in Vienna in 1923, worked chiefly at Ciba, at Syntex in Mexico, and at Stanford. He developed syntheses of human steroids from compounds in plants, was a pioneer of mass spectrometry, and is a colourful campaigner for peace and disarmament, along with being a playwright and novelist.

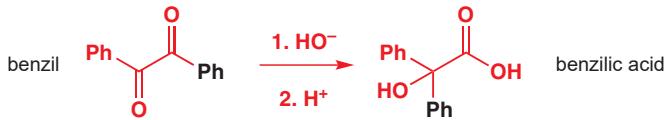


This type of rearrangement is known helpfully as a dienone-phenol rearrangement, and we can consider it quite simply as a type of *reverse* pinacol rearrangement. Pinacol and semipinacol rearrangements are driven by the formation of a carbonyl group. The rearranged cation is stabilized by being next to oxygen and it can rapidly lose  $H^+$  to give a carbonyl compound. In the key step of a dienone-phenol rearrangement, a protonated carbonyl compound rearranges to a tertiary carbocation. The reaction is driven from dienone to phenol because the product cation can rapidly undergo elimination of  $H^+$  to become aromatic.

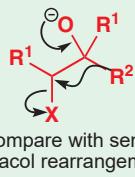


## The benzilic acid rearrangement

You have seen rearrangements in which carbonyl groups form at the migration origin: the migrating group in the pinacol and semipinacol rearrangements is ‘pushed’ by the oxygen’s lone pair as it forms the new carbonyl group. You have also seen carbonyl groups being destroyed at the migration terminus: the migrating group in the dienone-phenol rearrangement is ‘pulled’ towards the protonated carbonyl group. The first rearrangement reaction ever to be described has both of these at once.

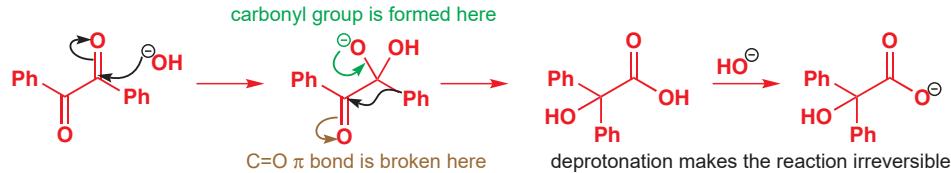


You may find it helpful to think of the benzilic acid rearrangement as a semipinacol rearrangement in which we have a breaking  $C=O \pi$  bond instead of a leaving group.



compare with semi-pinacol rearrangement

In 1838, Justus von Liebig found that treating ‘benzil’ (1,2-diphenylethan-1,2-dione) with hydroxide gave, after acid quench, 2-hydroxy-2,2-diphenylacetic acid, which he called ‘benzilic acid’. The mechanism of this benzilic acid rearrangement starts with attack of hydroxide on one of the carbonyl groups. The tetrahedral intermediate can collapse in a reaction reminiscent of a semipinacol rearrangement.



deprotonation makes the reaction irreversible

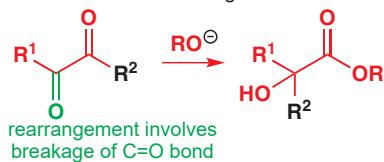
## The Favorskii rearrangement

We hope you have appreciated the smooth mechanistic progression so far in this chapter, from Wagner–Meerwein to pinacol and semipinacol through dienone-phenol to benzilic acid.

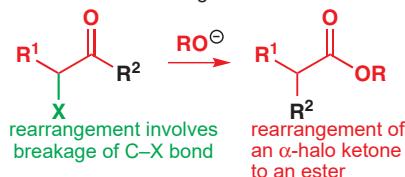
Interactive mechanism for benzilic acid rearrangement

Our aim is to help you gain an overall view of the types of rearrangements that take place (and why) and not to present you with lots of disconnected facts. It is at this point, however, that our mechanistic journey takes a hairpin bend. The bend comes as a surprise because when we show you the next rearrangement, the Favorskii, you would be forgiven for thinking that surely it's just a variant of the benzilic acid rearrangement?

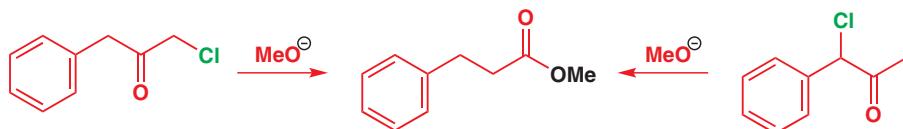
the benzilic acid rearrangement



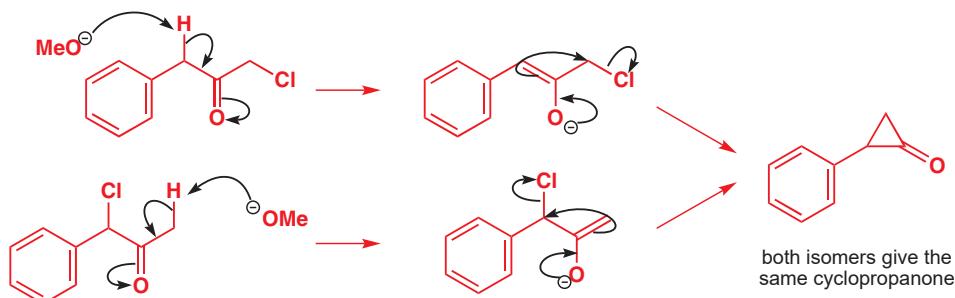
the Favorskii rearrangement



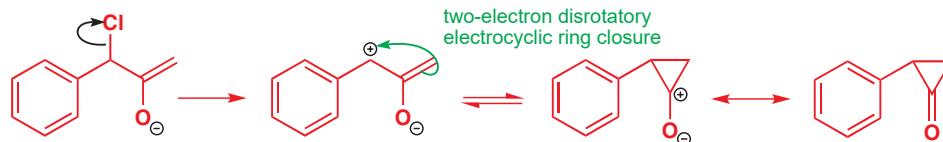
Well, this is what chemists thought until 1944, when some American chemists found that two isomeric  $\alpha$ -chloro ketones gave exactly the same product on treatment with methoxide. They suggested that both reactions went through the same intermediate.



That intermediate is a three-membered cyclic ketone, a cyclopropane: the alkoxide acts not as a nucleophile (its role in the benzilic acid rearrangement) but as a base, enolizing the ketone. The enolate can alkylate itself intramolecularly in a reaction that looks bizarre but that many chemists think is not unreasonable. The intermediate is the same cyclopropanone in each case.

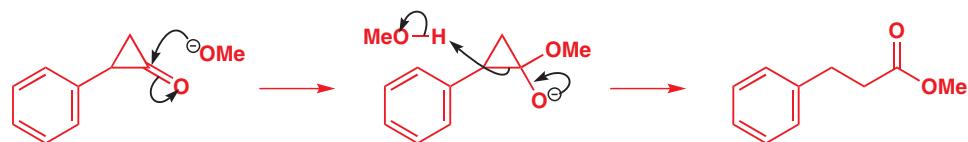


There is also a pericyclic mechanism for the ring-closure step. The enolate simply loses chloride to give an 'oxyallyl cation'—a dipolar species with an oxyanion and a delocalized allylic cation. This species can cyclize in a two-electron disrotatory electrocyclic reaction (Chapter 35) to give the same cyclopropanone.



Cyclopropanones are very reactive towards nucleophiles, and the tetrahedral intermediate arising from the attack of methoxide springs open to give the ester product. The more stable carbanion leaves: although the carbanion is not actually formed as a free species, there must be considerable negative charge at the carbon atom as the three-membered ring opens. Here the benzyl group is the better leaving group.

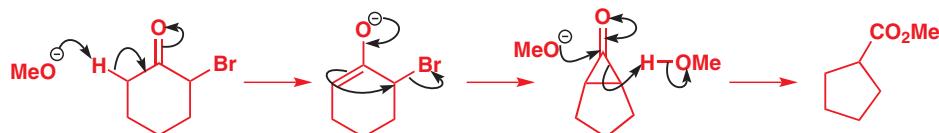
Cyclopropanones and cyclobutanones are very reactive, rather like epoxides, because, while the 60° or 90° angle in the ring is nowhere near the tetrahedral angle (108°), it is nearer 108° than the 120° preferred by the  $sp^2$  C of the C=O group. Conversely, the small ring ketones are resistant to enolization because that would place two  $sp^2$  carbon atoms in the ring.



Favorskii rearrangement of cyclic 2-bromoketones leads to ring contraction and this has become one of the most fruitful uses of the rearrangement in synthesis. Bromination of cyclohexanone (Chapter 20) and treatment with methoxide gives the methyl ester of cyclopentane carboxylic acid in good yield.



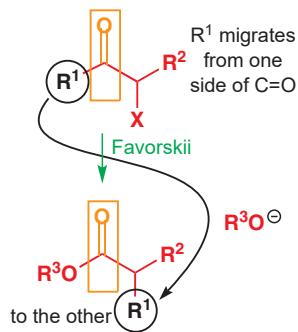
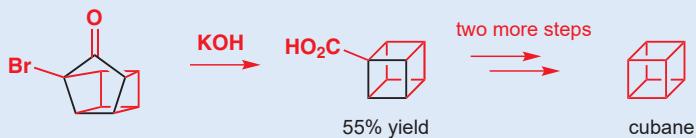
Enolization occurs on the side of the ketone away from the bromine atom and the enolate cyclizes as before but the cyclopropanone intermediate is symmetrical so that the product is the same whichever C–C bond breaks after nucleophilic attack by the methoxide ion.



Interactive mechanism for the Favorskii rearrangement

### Cubane from a Favorskii rearrangement

In 1964, two American chemists synthesized for the first time a remarkable molecule, cubane. Two of the key steps were Favorskii rearrangements, which allowed the chemists to contract five-membered rings to four-membered rings. Here is one of them. Two more steps decarboxylate the product to give cubane itself.

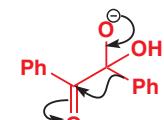
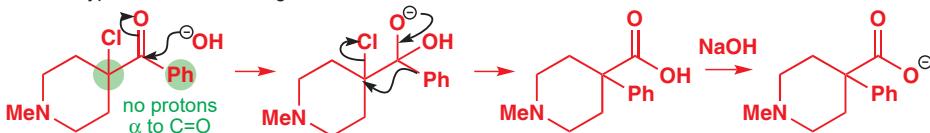


The overall consequence of the Favorskii rearrangement is that an alkyl group is transferred from one side of a carbonyl group to the other. This means that it can be used to build up heavily branched esters and carboxylic acids—the sort that are hard to make by alkylation (Chapter 25) because of the problems of hindered enolates and unreactive secondary alkyl halides. Heavily substituted acids, where CO<sub>2</sub>H is attached to a tertiary carbon atom, would be hard to make by any other method.



The Favorskii rearrangement is also a key step in the synthesis of the powerful obstetric painkiller pethidine. But try writing a mechanism for this last reaction and you run into a problem—there are no acidic protons so the ketone cannot be enolized! Yet the Favorskii rearrangement still works. Despite our warnings against confusing the mechanisms of the Favorskii and benzilic acid rearrangements, the Favorskii rearrangement may, in fact, follow a benzilic-type rearrangement mechanism, if there are no acidic hydrogens available.

benzilic-type Favorskii rearrangement of an un-enolizable ketone

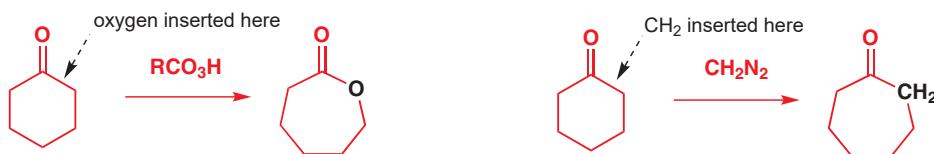


compare the migration step with this benzilic acid rearrangement

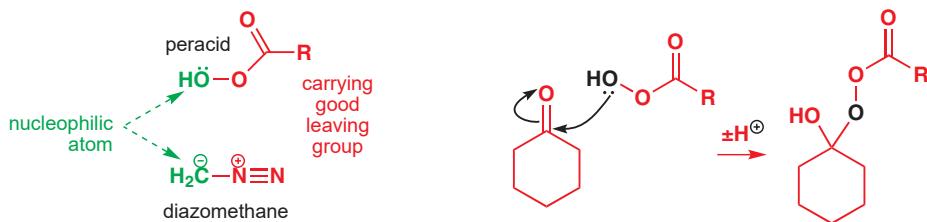
## Migration to oxygen: the Baeyer–Villiger reaction

In 1899, two Germans, A. Baeyer and V. Villiger, found that treating a ketone with a peracid ( $\text{RCO}_3\text{H}$ ) can produce an ester. An oxygen atom is ‘inserted’ next to the carbonyl group. You saw a similar ‘insertion’ reaction earlier in the chapter, and the mechanism here is not dissimilar.

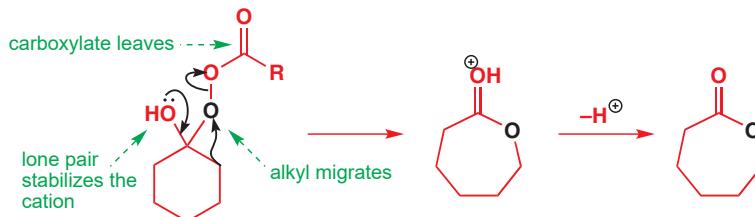
You have seen peracids used to make epoxides (Chapter 19); this is another important application.



Both peracids and diazomethane contain a nucleophilic centre that carries a good leaving group, and addition of peracid to the carbonyl group gives a structure that should remind you of a semipinacol intermediate with one of the carbon atoms replaced by oxygen.



Carboxylates are not such good leaving groups as nitrogen, but the oxygen–oxygen single bond is very weak. Once the peracid has added, loss of carboxylate is concerted with a rearrangement driven by formation of a carbonyl group.

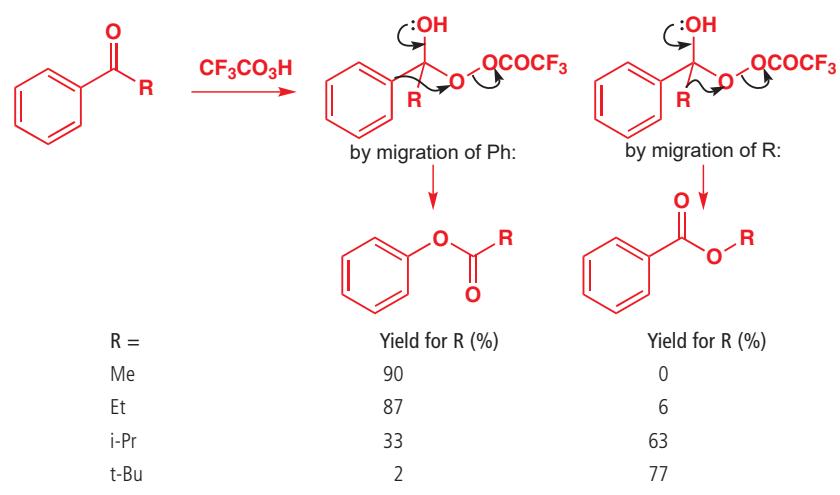


Interactive mechanism for the Baeyer–Villiger rearrangement

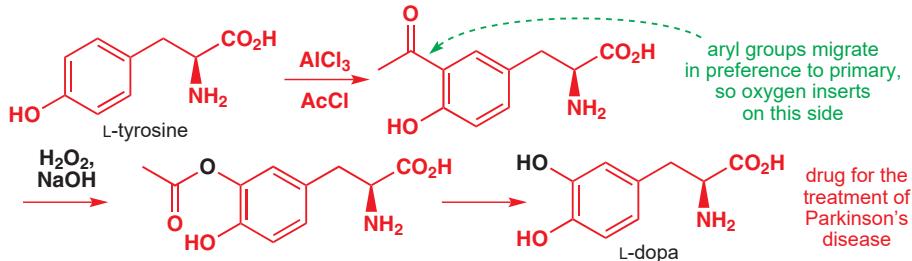
Baeyer–Villiger reactions are among the most useful of all rearrangement reactions, and the most common reagent is *m*-CPBA (*meta*-chloroperbenzoic acid) because it is commercially available.

### Which group migrates? (I): the facts

A question we have deliberately avoided up to this point is this: when there is a competition between two migrating groups, *which group migrates?* This question arises in pinacol, semipinacol, and dienone–phenol rearrangements and in Baeyer–Villiger reactions (in the benzilic acid and Favorskii rearrangements, there is no choice) and the awkward fact is that the answer is different in each case! However, let’s start with the Baeyer–Villiger reaction because here the question is always valid except when the ketone being oxidized is symmetrical. Here are some examples; you can probably begin to draw up guidelines for yourself.



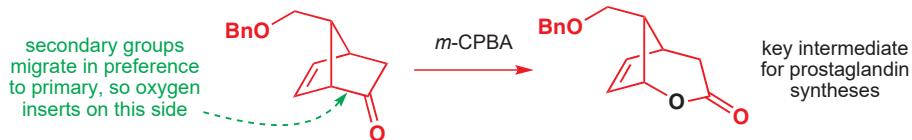
The order, with *tert*-alkyl the best at migrating, then *sec*-alkyl closely followed by Ph, then Et, then Me, *very roughly* follows the order in which the groups are able to stabilize a positive charge. Primary groups are much more reluctant to undergo migration than secondary ones or aryl groups, and this makes regioselective Baeyer–Villiger reactions possible.



The Baeyer–Villiger reaction has solved a regioselectivity problem here. L-tyrosine, a relatively cheap amino acid, can be converted to the important drug L-dopa provided it can be hydroxylated *ortho* to the OH group. This is where electrophilic substitutions of the phenol take place, but electrophilic substitutions with ‘ $\text{HO}^+$ ’ are not possible. However, after a Friedel–Crafts acylation, the acyl group can be converted to hydroxyl by the Baeyer–Villiger reaction and hydrolysis. The Baeyer–Villiger reaction means that  $\text{MeCO}^+$  can be used as a synthetic equivalent for ‘ $\text{HO}^+$ ’. Note the unusual use of the less reactive  $\text{H}_2\text{O}_2$  as oxidizing agent in this reaction. This is possible only when the migrating group is an electron-rich aromatic ring; these reactions are sometimes called Dakin reactions.

### Unsaturated ketones may epoxidize or undergo Baeyer–Villiger rearrangement

Peracids may epoxidize alkenes faster than ketones take part in Baeyer–Villiger reactions, so unsaturated ketones are not often good substrates for Baeyer–Villiger reactions. The balance is rather delicate. The two factors that matter are: how *electrophilic* is the ketone and how *nucleophilic* is the alkene? You might like to consider why this reaction *does* work, and why the C=C double bond here is particularly unreactive.

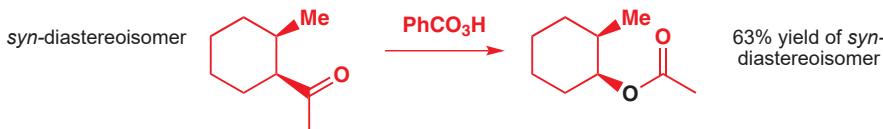


Small-ring ketones can relieve ring strain by undergoing Baeyer–Villiger reactions—this cyclobutanone (an intermediate in a synthesis of the perfumery compound *cis*-jasmine) is

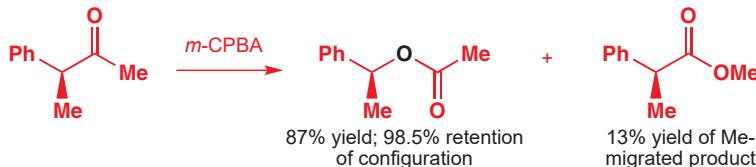
made by a ketene [2 + 2] cycloaddition, and is so reactive that it needs only  $\text{H}_2\text{O}_2$  to rearrange. Unlike  $\text{CF}_3\text{CO}_3\text{H}$  or *m*-CPBA,  $\text{H}_2\text{O}_2$  will not epoxidize double bonds unless they are electron-deficient (see Chapter 22).



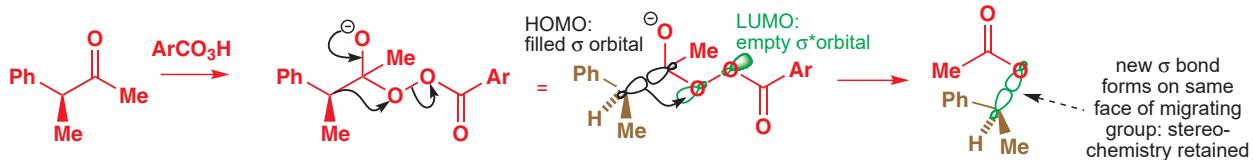
One point to note about both of the last two reactions is that the insertion of oxygen goes with retention of stereochemistry. You may think this is unsurprising in a cyclic system like this and, indeed, the first of the two cannot possibly go with inversion. However, this is a general feature of Baeyer–Villiger reactions, even when inversion would give a more stable product.



Even when you might imagine that racemization would occur, as in this benzylic ketone, retention is the rule.



By looking at the orbitals involved, you can see why this must be so. The  $\text{sp}^3$  orbital of the migrating carbon just slips from one orbital to the next with the minimum amount of structural reorganization. The large lobe of the  $\text{sp}^3$  orbital is used so the new bond forms to the same face of the migrating group as the old one, and stereochemistry is retained.

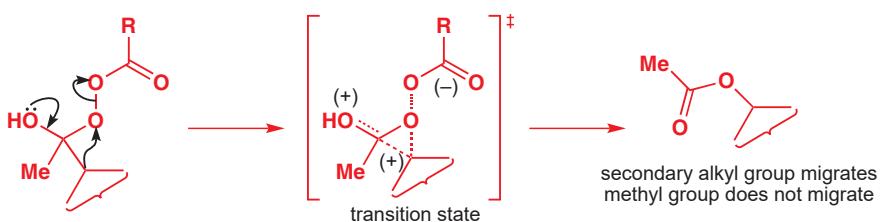


The orbital interactions in all 1,2-migrations are similar, and the migrating group retains its stereochemistry in these too. In the more familiar  $\text{S}_{\text{N}}2$  reaction, inversion occurs because the antibonding  $\sigma^*$  orbital rather than the bonding  $\sigma$  orbital is used. In the  $\text{S}_{\text{N}}2$  reaction, carbon undergoes *nucleophilic* attack with *inversion*; in rearrangements the migrating carbon atom undergoes *electrophilic* attack with *retention* of configuration.

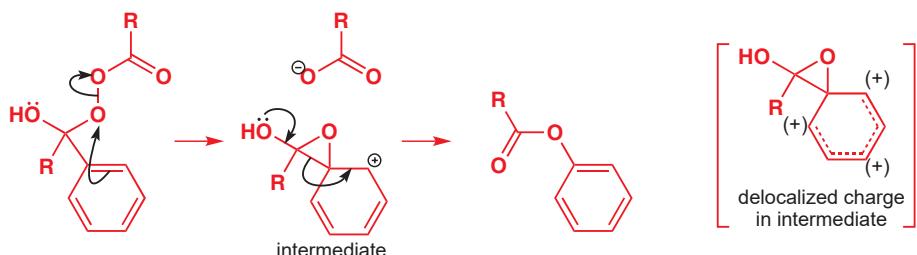
- In 1,2-migrations, the migrating group retains its stereochemistry.

### Which group migrates? (II): the reasons

Why does the more substituted group migrate in the Baeyer–Villiger reaction? The transition state has a positive charge spread out over the molecule as the carboxylate leaves as an anion. If the migrating group can take some responsibility for the positive charge the transition state will be more stable. The more stable the charge, the faster the rearrangement.



When a benzene ring migrates,  $\pi$  participation is involved as the benzene ring acts as a nucleophile and the positive charge can be spread out even further. Note that the Ph is stabilizing the charge here in the way that it stabilizes the intermediate in an electrophilic aromatic substitution reaction—like a pentadienyl cation rather than like a benzylic cation. What was a transition state in alkyl migration becomes an intermediate in phenyl migration.



The situation in other rearrangements is much more complicated—and indeed more complicated than many textbooks would have you believe. We shall look just briefly at the dienone-phenol rearrangement again, this time considering reactions in which there is competition between two different migrating groups. As in the Baeyer–Villiger reaction, the transition state is cationic, so you would expect cation-stabilizing groups to migrate more readily. This appears to be true for Ph versus Me, but is most definitely not true for Ph versus CO<sub>2</sub>Et. The cation *destabilizing* group CO<sub>2</sub>Et migrates even though Ph is much better at stabilizing a positive charge!



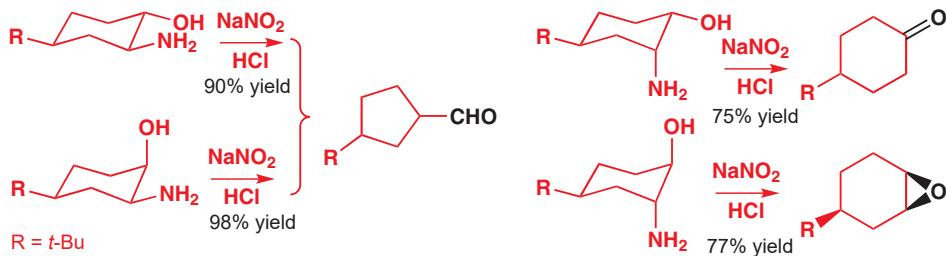
The reason is that CO<sub>2</sub>Et is so cation *destabilizing* that it prefers to migrate rather than be left behind next door to a cation. In this case, then, it is the cation-stabilizing ability of the group that *does not* migrate that matters most.



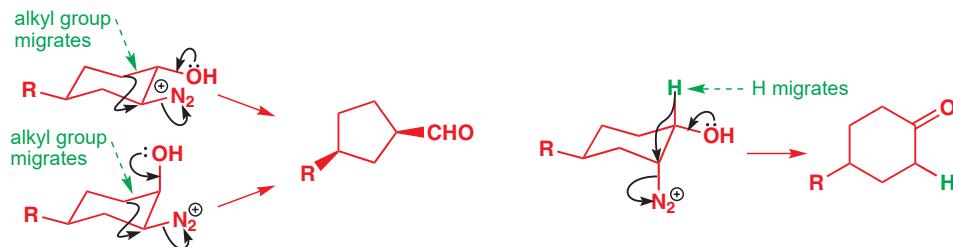
### Which group migrates? (III): stereochemistry matters too

Selectivity in rearrangement reactions is affected by the electronic nature of *both* the group that migrates *and* the group that is left behind. But there is more! *Stereochemistry* is important too. The outcome of diazotization and semipinacol rearrangement (Tiffeneau–Demjanov

rearrangement, p. 949) of this amino-alcohol depends entirely on the diastereoisomer you start with. There are four diastereoisomers, and we have drawn each one in the only conformation it can reasonably adopt, with the *t*-butyl group equatorial.

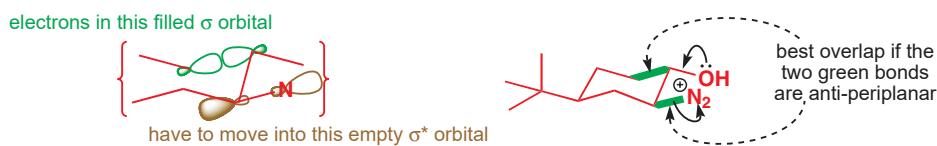


In all of these reactions, the OH group provides the electronic ‘push’. In the first two reactions, the ring contracts by an alkyl migration from the secondary alcohol, while in the third it is H that migrates from the same position.

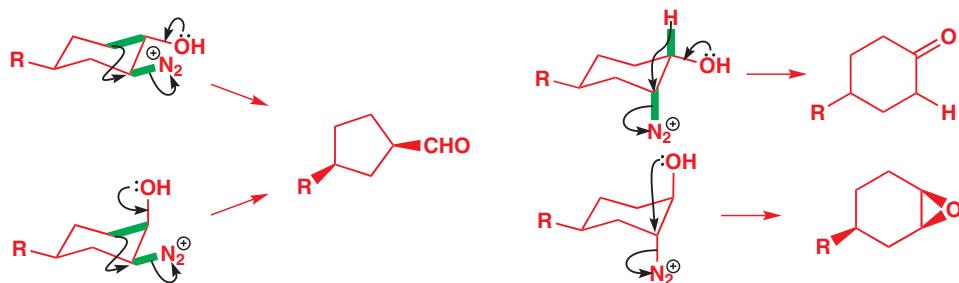


The only difference between the compounds is stereochemistry and, if we look at the orbitals involved in the reactions, we can see why this is so important. As the  $\text{N}_2^+$  leaving group departs, electrons in the bond to the migrating group have to flow into the  $\text{C}-\text{N} \sigma^*$  orbital—we discussed this on p. 949. But what we didn’t talk about then was the fact that best overlap between these two orbitals ( $\sigma$  and  $\sigma^*$ ) occurs if they are anti-periplanar to one another—just as in an E2 elimination reaction.

Interactive explanation of the stereochemistry of rearrangements



For the first two compounds, with the  $-\text{N}_2^+$  group equatorial, the group best placed to migrate is the alkyl group that forms the ring; for the third reaction, there is a hydrogen atom anti-periplanar to the leaving group, so H migrates.

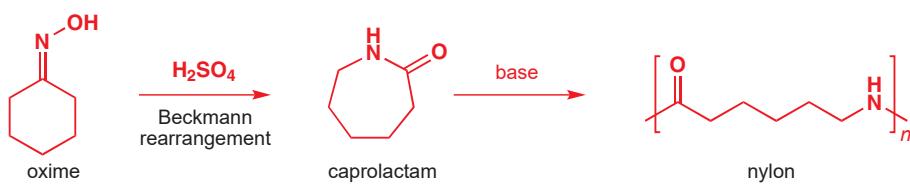


The fourth reaction has, rather than a group that might migrate, the hydroxyl group ideally placed to displace  $\text{N}_2$  and form an epoxide.

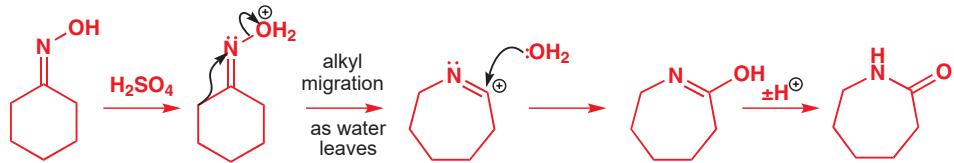
The requirement for the migrating group to be anti-periplanar to the leaving group is quite general in rearrangement reactions. The reason we haven't noticed its effect before is that most of the compounds we have considered have not been conformationally constrained in the way that these are. Free rotation means that the right geometry for rearrangement is always obtainable—stereochemistry is not a factor in the Baeyer–Villiger reaction, for example. We will come back to some more aspects of stereochemical control later in the chapter, when we deal with fragmentation reactions. Before then, we will consider one last rearrangement reaction, in which stereochemistry again plays an important controlling role.

## The Beckmann rearrangement

The industrial manufacture of nylon relies on the alkaline polymerization of a cyclic amide known trivially as caprolactam. Caprolactam can be produced by the action of sulfuric acid on the oxime of cyclohexanone in a rearrangement known as the **Beckmann rearrangement**.

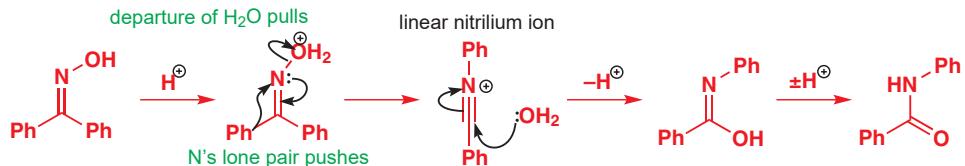


The mechanism of the Beckmann rearrangement follows the same pattern as a pinacol or Baeyer–Villiger reaction: acid converts the oxime OH into a leaving group, and an alkyl group migrates to nitrogen as water departs. The product cation is then trapped by water to give an amide.



Interactive mechanism for the Beckmann rearrangement

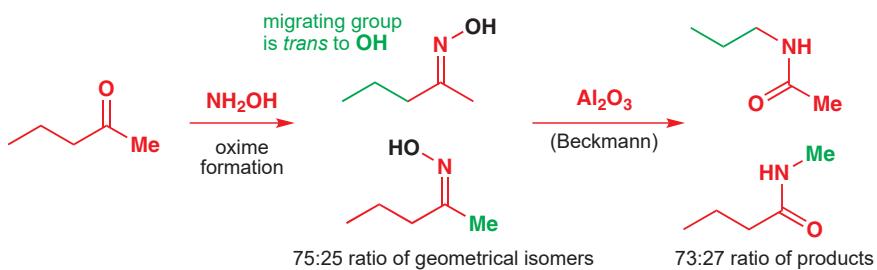
This rearrangement is not confined to cyclic oximes, and other ways of converting OH to a leaving group also work, such as PCl<sub>5</sub>, SOCl<sub>2</sub>, and other acyl or sulfonyl chlorides. In an acyclic Beckmann rearrangement, the product cation is better represented as this nitrilium ion. When we write the mechanism we can then involve the nitrogen's lone pair to 'push' the migrating group back on to N.



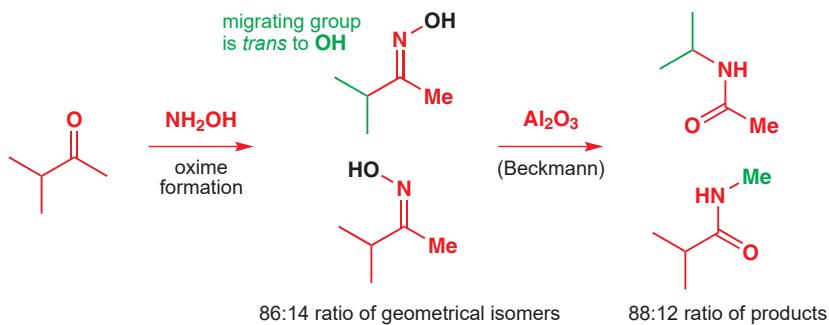
A linear nitrilium ion like this is impossible in a seven-membered ring of the last example.

### Which group migrates in the Beckmann rearrangement?

In the Beckmann rearrangement of unsymmetrical ketones there are two groups that could migrate. There are also two possible geometrical isomers of an unsymmetrical oxime: C=N double bonds can exhibit *cis/trans* isomerism just as C=C double bonds can. When mixtures of geometrical isomers of oximes are rearranged, mixtures of products result, but the ratio of products mirrors exactly the ratio of geometrical isomers in the starting materials—the group that has migrated is in each case the group *trans* to the OH in the starting material.



We have already touched on the idea that, for migration to occur, a migrating group has to be able to interact with the  $\sigma^*$  of the bond to the leaving group, and this is the reason for the specificity here. In the example a couple of pages back the stereospecificity of the reaction was due to the starting material being constrained in a conformationally rigid ring. Here it is the C=N double bond that provides the constraint. If one of the alkyl chains is branched, more of the oxime with the OH group *anti* to that chain will be formed and correspondingly more of the branched group will migrate.



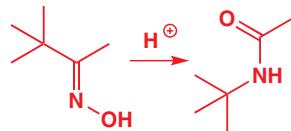
Conditions that allow those double bond isomers to interconvert can allow either group to migrate—which one does so will then be decided, as in the Baeyer–Villiger reaction, by electronic factors. Most protic acids allow the oxime isomers to equilibrate, so, for example, this tosylated oxime rearranges with full stereospecificity in Al<sub>2</sub>O<sub>3</sub> (the *anti* methyl group migrates), but with TsOH, equilibration of the oxime geometrical isomers means that either group could migrate—in the event, the propyl group (which is more able to support a positive charge) migrates faster.

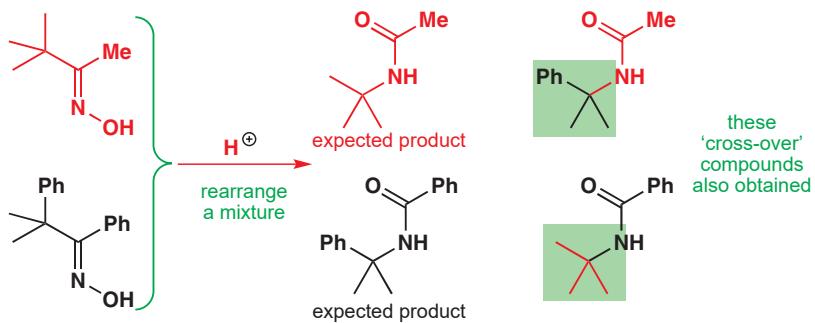


Notice that the effect of the Beckmann rearrangement is to insert a *nitrogen* atom next to the carbonyl group. It forms a useful trio with the Baeyer–Villiger *oxygen* insertion and the diazoalkane *carbon* insertion.

### The Beckmann fragmentation

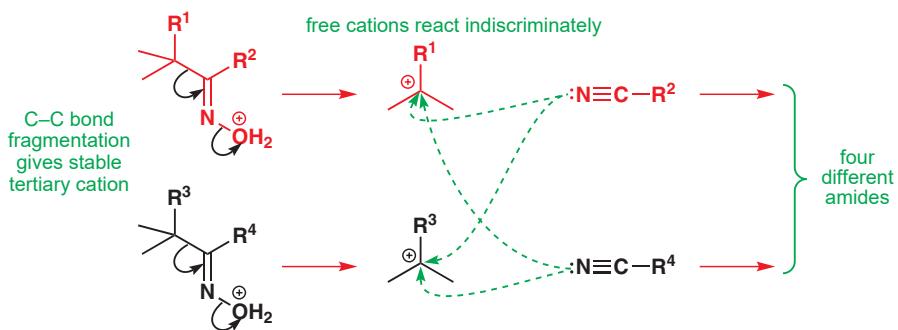
To introduce the theme of the last section of this chapter, a Beckmann rearrangement that is not all that it seems. *t*-Butyl groups migrate well in the Baeyer–Villiger reaction and, indeed, Beckmann rearrangement of the compound in the margin appears to be quite normal too. But, when this compound and another compound with a tertiary centre next to the oxime are mixed together and treated with acid, it becomes apparent that what is happening is not an intramolecular reaction.





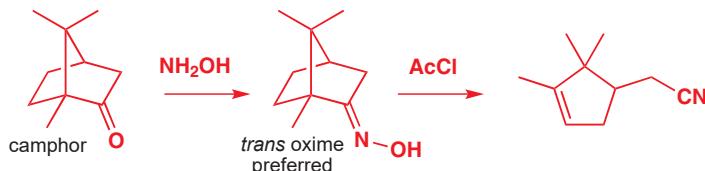
Each migrating tertiary group must have lost contact with the amide fragment it started out with. The molecule must fall apart to give a *t*-alkyl cation and a nitrile: the Beckmann rearrangement now goes via a fragmentation mechanism.

The recombination step of this reaction is really just a Ritter reaction: reaction of a nitrile with a carbocation. You came across the Ritter reaction on p. 353.



Migrating groups have to provide some degree of cation stabilization. But if they stabilize a cation *too well* there is a good chance that fragmentation will occur and the ‘migrating group’ will be lost as a carbocation.

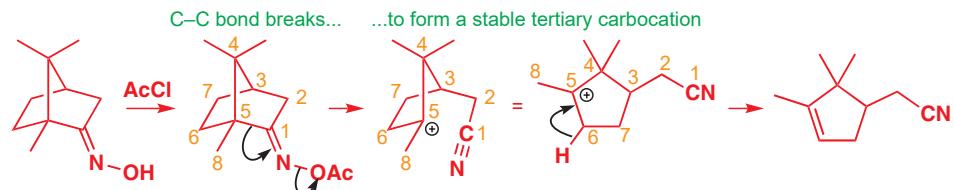
Here is a more convincing example of the same fragmentation reaction: the conditions, but not the results, are those of a Beckmann rearrangement. In this reaction, the ring structure means the cation cannot be trapped by the nitrile, and a fragmentation product is isolated.



Beckmann rearrangements that go with fragmentation are sometimes called ‘anomalous’ or ‘second-order’ Beckmann rearrangements. You should not use the second of these names and, in any case, **Beckmann fragmentation** is much better than either.

Interactive mechanism for Beckmann fragmentation

The mechanism is straightforward once you know what happens to Beckmann rearrangements when the migrating group is tertiary—but hard to follow unless you number the atoms!



## Polarization of C–C bonds helps fragmentation

Up to now, you have met few fragmentation reactions—reactions in which C–C bonds are broken—largely because the C–C bond is so strong. Why then does the Beckmann

fragmentation work? Well, the reason C–C bonds are hard to break is not just because of their strength, as the table of bond energies indicates.

For both carbon and hydrogen, a bond to oxygen is *stronger* than a bond to carbon. Yet we have no hesitation in breaking O–H bonds (of, say, carboxylic acids) with even the weakest of bases and we have spent much of this chapter showing C–O bonds of protonated alcohols rupturing spontaneously! What is going on?

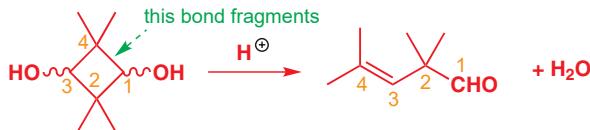
The answer is **polarization**. Oxygen's electronegativity means that C–O and O–H bonds are polarized and are easy to break with hard nucleophiles and bases; C–C and C–H bonds are (usually) not polarized and, although weaker, are harder to break. It follows that to break a C–C bond it helps a lot if it is polarized—there needs to be a source of electrons at one end and an electron ‘sink’ (into which they can flow) at the other.



■ The bond energies listed in the table are the energies required to break the bonds **homolytically** to give two radicals, not **heterolytically** to give two ions. We will look at homolytic fragmentation in much more detail in the next chapter.

### Fragmentations require electron push and electron pull

Fragmentations are reactions in which the molecule breaks open by the cleavage of a C–C single bond, and we start this section with some examples. Both diastereoisomers of this cyclic diol fragment in acid to give an aldehyde.

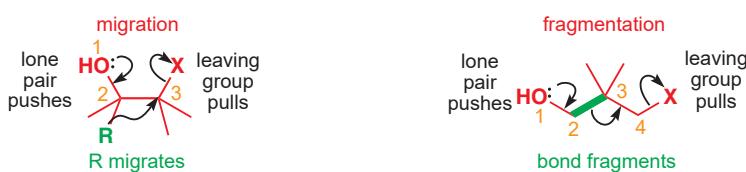


Numbering the atoms shows which bond fragments—now we need to provide a source and a sink for the electrons to polarize the bond. Protonation of a hydroxyl group provides the sink—it can now leave as water. And the lone pair of the other oxygen provides the source. You can think of the electrons in the C–C bond being ‘pushed’ by the oxygen’s lone pair and ‘pulled’ by the departing water—until the bond breaks. A bit of extra impetus comes from release of ring strain: C–C bonds in three- and four-membered rings are weaker than usual (by about 120 kJ mol<sup>-1</sup>).



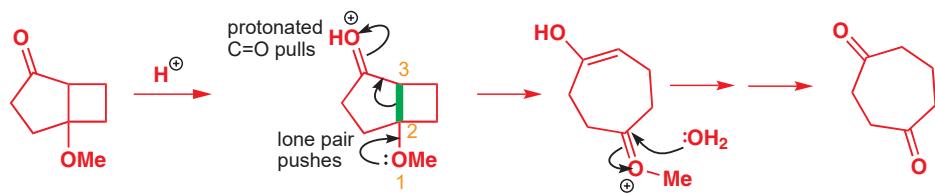
Interactive fragmentation mechanisms relying on bond polarization

We talked about ‘pushing’ and ‘pulling’ electrons when we introduced the pinacol rearrangement, and a very similar thing is happening here *but* the electron source and sink are *separated by one atom* instead of being *adjacent*.

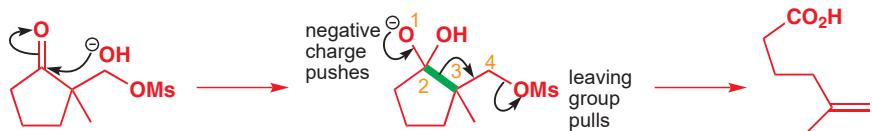


■ Note the numbering in these diagrams: 1, 2, 3, 4 from electron source to electron sink. We shall make use of it in many more fragmentation mechanisms.

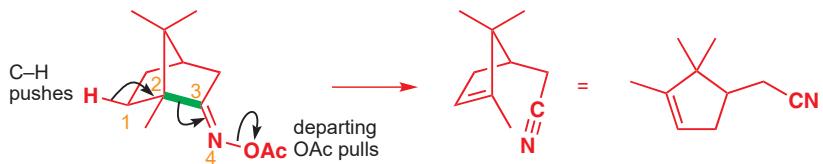
Protonated carbonyl compounds can be electron sinks too (remember the dienone-phenol rearrangement?) and this bicyclic methoxy ketone fragments to a seven-membered ring in acid. Note the same 1, 2, 3, 4 arrangement, with the bond between carbon atoms 2 and 3 fragmenting.



A leaving group such as mesylate can exercise the ‘pull’ and in the next example a carbonyl group provides the ‘push’ after it has been attacked by a nucleophile. This five-membered cyclic ketone fragments on treatment with base—can you detect hints of the benzylic acid rearrangement?

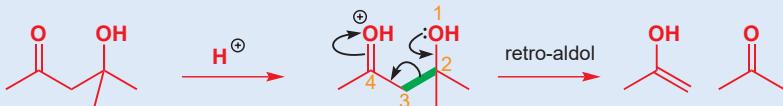


Analysing the Beckmann fragmentation on p. 960 in the same way, we can identify the electron sink (the departing acetate group), although the source in this case is a little more obscure. Saying that the tertiary cation is stable is really saying that the neighbouring C–C and C–H bonds provide electrons (through  $\sigma$  conjugation, see p. 334) to stabilize it, so these are the electron sources (the ‘push’). A good alternative is to write loss of a proton concerted with fragmentation, which gives one particular C–H bond as the source of electrons.



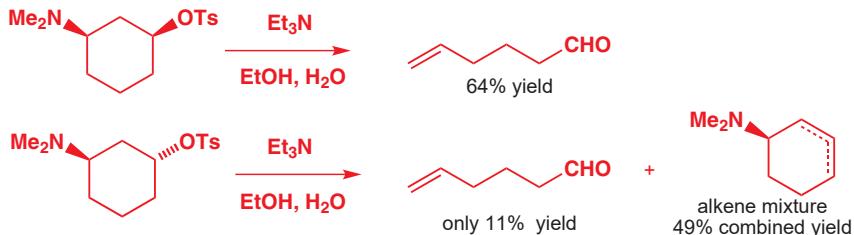
### The retro-aldol is a fragmentation reaction

We should perhaps remind you here of the reversibility of the aldol reaction (Chapter 26): a retro-aldol is a fragmentation reaction with a carbonyl group as electron sink and OH as electron source. The aldol reaction usually goes in the other direction of course, but where steric or ring-strain factors are involved, this may not be the case.

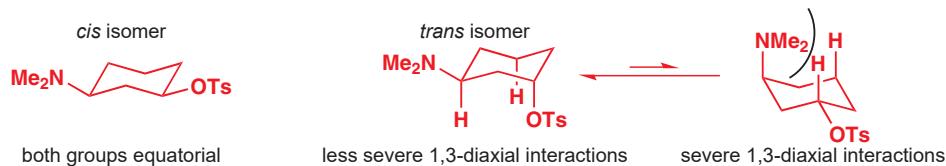


## Fragmentations are controlled by stereochemistry

The control of rearrangements can be stereoelectronic in origin—if a molecule is to rearrange, orbitals have to be able to overlap. This means that, for a Beckmann rearrangement, the migrating group has to be *trans* to the leaving group. Not surprisingly, the same is true for Beckmann fragmentations like the one at the end of the last section, where the green fragmenting bond is *trans* to the leaving group. Before we extend these ideas any further, consider these two quite different reactions of quite similar compounds.



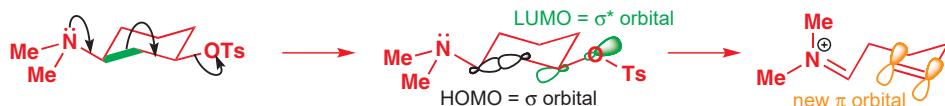
Just as with the rearrangements we looked at on p. 933, we need to draw these compounds in reasonable chair conformations in order to understand what is going on. In the *cis* isomer, both substituents can be equatorial; in the *trans* isomer one has to be axial, and this will be mainly the OTs group, since the two methyl groups of NMe<sub>2</sub> suffer greater 1,3-diaxial interactions.



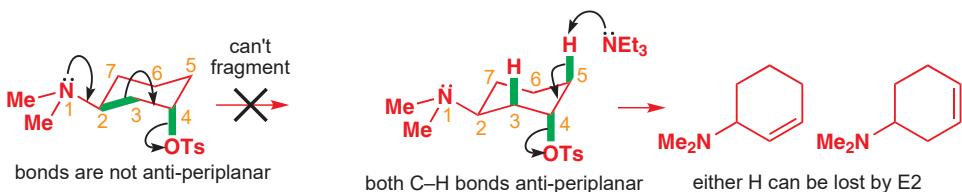
Now, the *cis* isomer has clearly undergone a fragmentation reaction and, as usual, numbering the atoms can help to identify the bond that breaks. The nitrogen lone pair pushes, the departing tosylate pulls, and the resulting iminium ion hydrolyses to the product aldehyde.



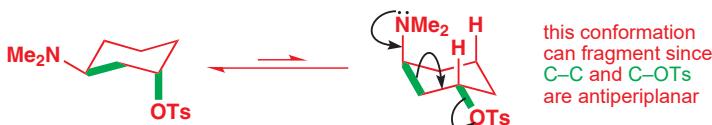
Yet the *trans* isomer does this only in very low yield. Mostly it eliminates TsOH to give a mixture of alkenes. Why? Well, notice that, in the *cis* isomer, the fragmenting bond is *trans* to the leaving group—indeed, it is both parallel and *trans* (in other words anti-periplanar) to the leaving group. Electrons can flow smoothly from the breaking σ bond into the σ\* of the C–OTs bond, forming as they do so a new π bond.



For the *trans* isomer, fragmentation of the most populated conformation is impossible because the leaving group is not anti-periplanar to any C–C bond. The only bonds anti-periplanar to OTs are C–H bonds, making this compound ideally set up for another reaction whose requirement for anti-periplanarity you have already met—E2 elimination.



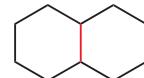
The other conformation can fragment because now the OTs is anti-periplanar to the right C–C bond, and this is probably where the 11% fragmentation product comes from.



## Ring expansion by fragmentation

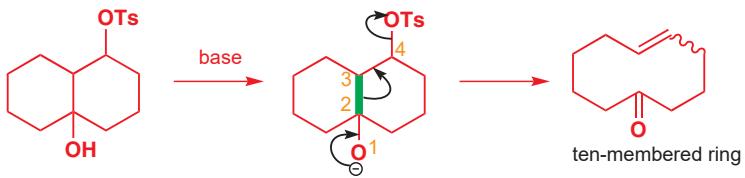
Ring sizes greater than eight are hard to make. Yet five- and six-membered rings are easy to make. Once you realize that a fused pair of six-membered rings is really a ten-membered ring with a bond across the middle, the potential for making medium rings by fragmentation becomes apparent.

6,6-fused decalin



outer ten-membered ring

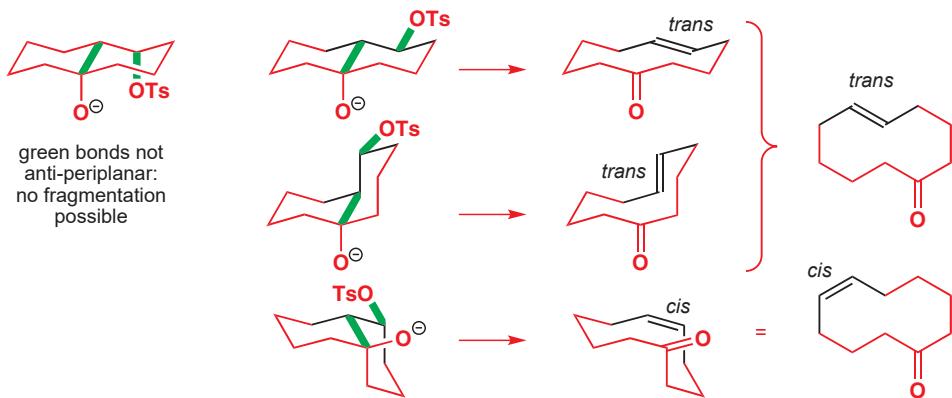
All you need to do is to make the bond to be broken the 2–3 bond in a 1, 2, 3, 4 electron source-sink arrangement and the ten-membered ring should appear out of the wreckage of the fragmentation. Here is an example:



Interactive mechanism for ring expansion by fragmentation

This is the simple overall result, but there is more to explore. The starting hydroxytosylate can exist as four diastereoisomers: two *trans*-decalins and two *cis*-decalins. What is more, the product has a double bond in a ten-membered ring: will it be *cis* or *trans*? (Both are possible in a ring with more than eight members: see Chapter 29.) One of the four diastereoisomers of the starting material cannot place the tosylate anti-periplanar to the ring-fusion bond, so it can't fragment. The other three diastereoisomers all can, but two of them give a *trans* double bond while the third gives *cis*.

► We discussed the conformations of decalins in Chapter 16.

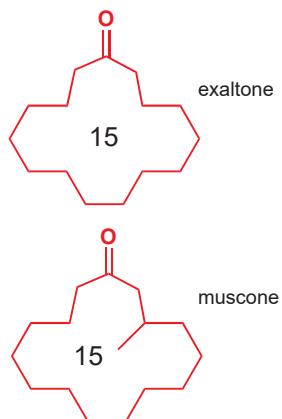
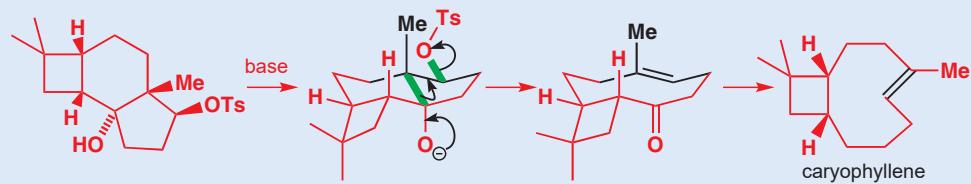


Interactive explanation of the importance of stereochemistry in ring expansions

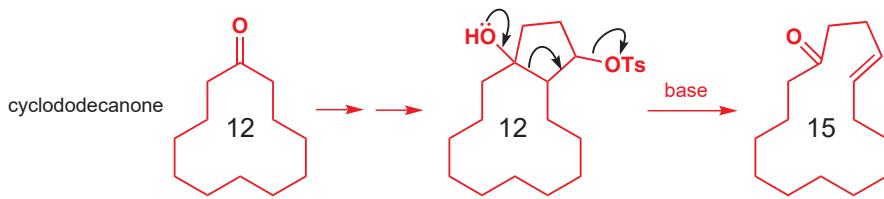
Looking at the alignment of the bonds that end up flanking the double bond in the product shows you where the geometrical isomers come from: these are the black bonds in the starting material, and are *trans* across the forming  $\pi$  system in the first two isomers and *cis* in the third. Fragmentations are stereospecific with regard to double-bond geometry, much as E2 elimination reactions are.

### Caryophyllene by fragmentation

Corey applied this stereospecificity in conjunction with a ring expansion reaction to make the natural product caryophyllene. Caryophyllene is a bicyclic molecule with a nine-membered ring containing an *E* trisubstituted double bond. The right relative stereochemistry in the starting material leads both to fragmentation of the right bond and to formation of the alkene with the right stereochemistry.



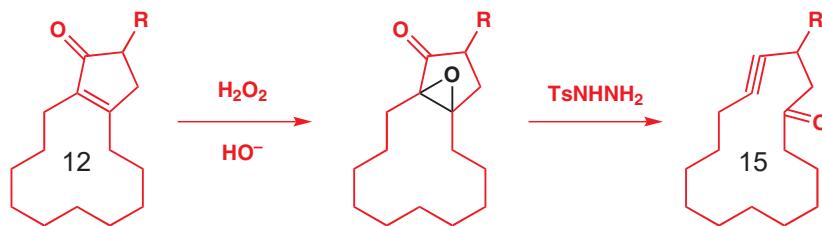
Muscone and exaltone are important perfumery compounds with even-harder-to-make 15-membered ring structures. Cyclododecanone is commercially available: addition of a fused five-membered ring and fragmentation of the 12,5-ring system is a useful route to these 15-membered ring compounds.



### The Eschenmoser fragmentation

In the late 1960s, the Swiss chemist Albert Eschenmoser discovered an important reaction that can be used to achieve similar ring expansions and that now bears his name, the Eschenmoser fragmentation. The starting material for an Eschenmoser fragmentation is the epoxide of an  $\alpha,\beta$ -unsaturated ketone. The fragmentation happens when this epoxyketone is treated with tosylhydrazine, and one of the remarkable things about the product is that it is an alkyne. The fragmentation happens across the epoxide (shown in black), and the product contains both a ketone (in a different place from the ketone in the starting material) and an alkyne. You can see how in this case hydrogenation of the triple bond can give muscone ( $\text{R}=\text{Me}$ ) or exaltone ( $\text{R}=\text{H}$ ).

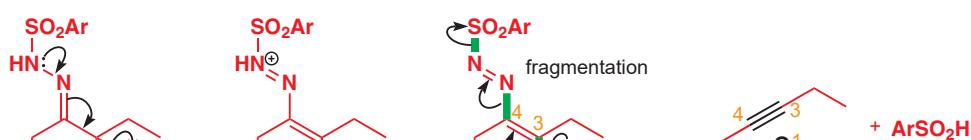
Albert Eschenmoser (1925–), working at the ETH in Zurich, synthesized vitamin  $\text{B}_{12}$ , at the time (1973) the most complicated molecule yet made, in what was for that era an unusual international collaboration with Woodward at Harvard.



The Eschenmoser fragmentation does not have to be a ring expansion, and it is a useful synthetic method for making keto-alkynes. The following reaction, which we will use to discuss the fragmentation's mechanism, was used to make an intermediate in the synthesis of an insect pheromone, *exo*-brevicomin.



■ The epoxyketones are made by epoxidizing the electron-poor enones with basic hydrogen peroxide, see Chapter 22.



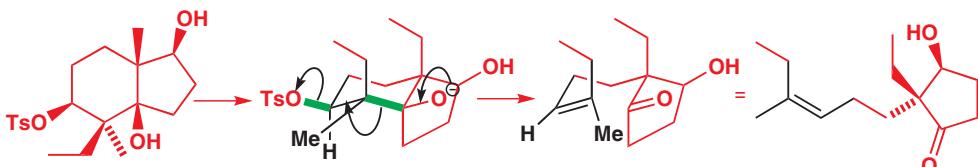
■ The sulfur-containing leaving group here is not toluenesulfonate (tosylate, or  $\text{TsO}^-$ ) but toluenesulfinate (Ar $\text{SO}_2^-$  or  $\text{Ts}^-$ ), giving toluenesulfenic acid ( $\text{TsH}$  or Ar $\text{SO}_2\text{H}$ ), not toluenesulfonic acid ( $\text{TsOH}$  or Ar $\text{SO}_3\text{H}$ ) as a by-product.

### Controlling double bonds using fragmentation

Juvenile hormone (a compound you met in Chapter 27, p. 677) is a compound whose synthesis presents a major challenge: it requires the control of three trisubstituted double bonds (one of which ends up as an epoxide). The key intermediate shown contains two of them.

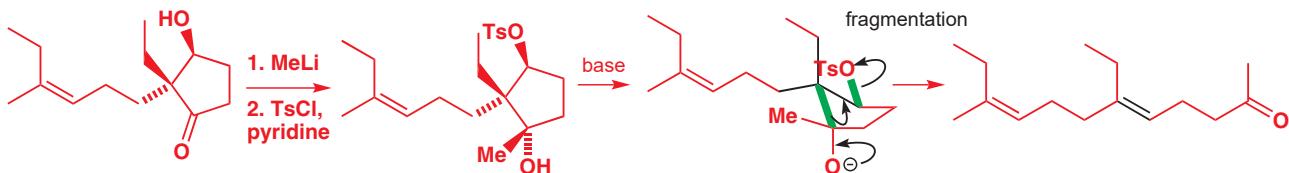


The chemists who succeeded in making this compound reasoned that, if this intermediate could be made stereospecifically by fragmenting a cyclic starting material, the (hard-to-control) double-bond stereochemistry would derive directly from the (easier-to-control) relative stereochemistry of the cyclic compound. The starting material they chose was a 5,6-fused system, which fragments to give one of the double bonds.

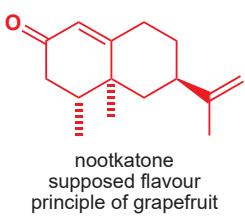


Interactive synthesis of juvenile hormone by fragmentations

The product of this reaction is prepared for another fragmentation by addition of methyl-lithium (you might like to consider why you get this diastereoisomer) and tosylation of the less hindered secondary alcohol. Base promotes the second fragmentation and gives the ketone with the two double bonds in place.



In the next chapter you will meet, among many other reactions, more fragmentations, but they will be radical fragmentations rather than ionic fragmentations, and involve homolytic cleavage of C–C bonds.

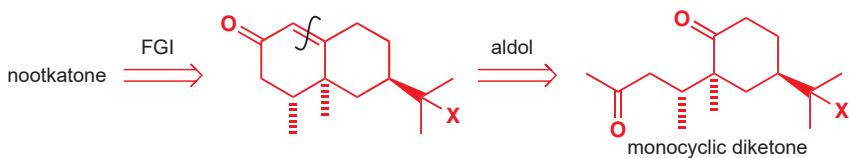


► The terminology ('disconnection', 'FGI') in this paragraph derives from Chapter 28.

## The synthesis of nootkatone: fragmentation showcase

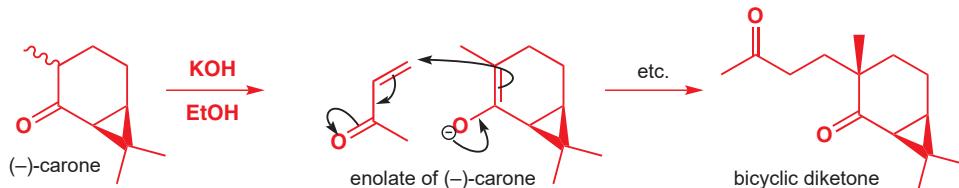
To finish this chapter, we will present three different synthetic routes to the same compound, all of which illustrate the power of fragmentation in the synthesis of cyclic compounds. The story starts with grapefruit, which contains a simple bicyclic enone called nootkatone. It was assumed, wrongly as it happens, that the scent of grapefruit came from this compound, and in the 1970s there was quite a rush to synthesize this compound in various laboratories. A remarkable feature of many successful syntheses was the use of fragmentation reactions. We shall describe parts of three syntheses involving the fragmentation of a six-, a four-, and a three-membered ring.

Most syntheses make the side-chain alkene by an elimination reaction so the first 'disconnection' is an FGI adding HX back into the alkene. The last C–C bond-forming operation in most syntheses is an intramolecular aldol reaction to make the enone so that can be disconnected next. It is the starting material for the aldol, a simple monocyclic diketone, which is usually made by a fragmentation reaction because this is a good way to set up the stereochemistry.

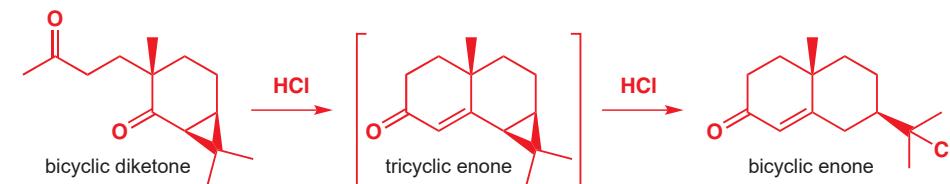


### Fragmentation of a three-membered ring

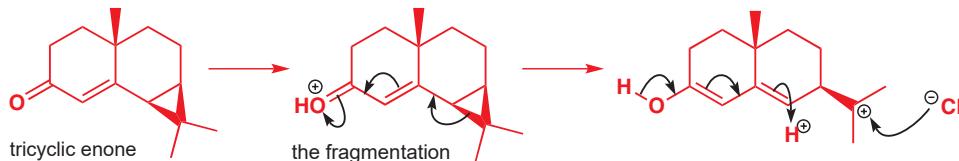
This synthesis does not look as though it will lead to nootkatone because the fragmentation product still requires a great deal of modification. It has the advantage that the stereochemistry is correct at one centre at least. The sequence starts from natural ( $-$ )-carone: conjugate addition of the enolate to butenone without control leads to a bicyclic diketone with one extra stereogenic centre. The enone adds to the bottom face of the enolate opposite the dimethylcyclopropane ring so the methyl group is forced upwards.



Now the diketone is cyclized by a Robinson-style aldol condensation in HCl to give a bicyclic enone. But during the reaction, a new six-membered ring has been formed while the old three-membered ring has disappeared, evidently by fragmentation.



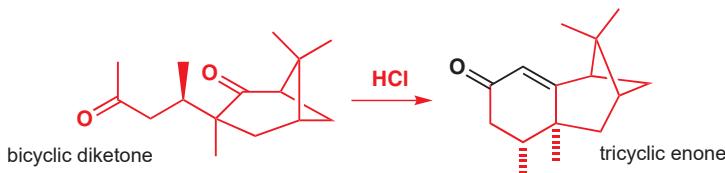
The fragmentation is pulled by the enone (with some help from the acid) and pushed by the stability of a tertiary carbocation as well as the release of strain as the single bond that is fragmented is in a three-membered ring.



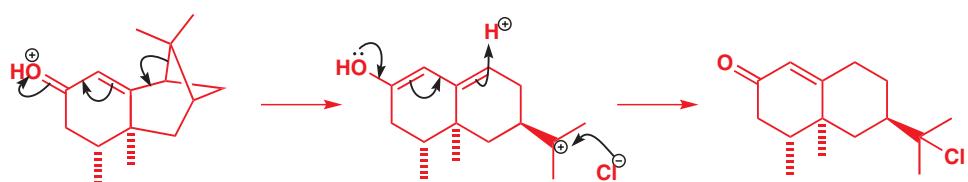
Addition of a proton to the end of the enol and a chloride ion to the cation gives the product. The further development of this compound into nootkatone is beyond the scope of this book.

### Fragmentation of a four-membered ring

This approach leads directly to the enone needed for nootkatone. A diketone prepared from a natural terpene is also treated with HCl and much the same reactions ensue except that the fragmentation now breaks open a four-membered ring. First, the intramolecular aldol reaction to make the second six-membered ring.

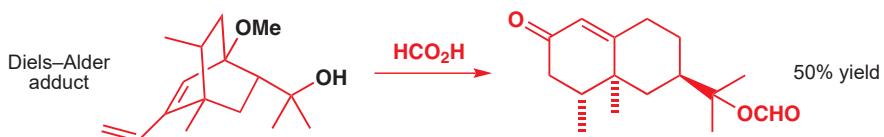


Now the fragmentation, which follows much the same course as the last one: the enone again provides the electron pull while the cleavage of a strained C–C single bond in a four-membered ring to give a tertiary carbocation provides the electron push. A simple elimination is all that is needed to make nootkatone from this bicyclic chloroenone.

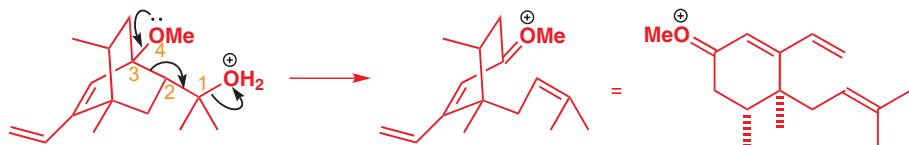


### Fragmentation of a six-membered ring

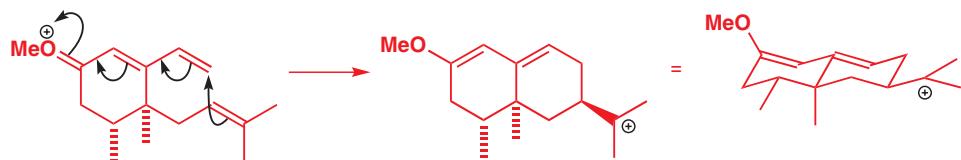
This chemistry is quite different from the examples we have just seen. The starting material has a bridged bicyclic structure and was made by a Diels–Alder reaction. Fragmentation is initiated by formic acid ( $\text{HCO}_2\text{H}$ ), which protonates the tertiary alcohol and creates a tertiary carbocation. The ether provides the push. More serious electronic interactions are needed in this fragmentation as the C–C bond being broken is not in a strained ring.



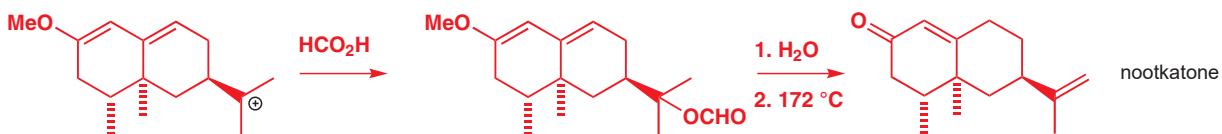
The yield of 50% may not seem wonderful, but there is obviously a lot of chemistry going on here so it is perfectly acceptable when so much is being achieved. The first stage is the fragmentation itself. Drawing the product first of all in the same shape as the starting material and then redrawing, to ensure that we don't make a mistake, we discover that we are well on the way to nootkatone. Note that the stereochemistry of the two methyl groups comes directly from the stereochemistry of the starting materials and no new stereogenic centres are created in the fragmentation. Although one six-membered ring is fragmented, another remains.



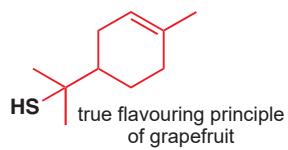
The first-formed product now cyclizes to form the second six-membered ring. This recreates a carbocation at the tertiary centre like the one that set off the fragmentation as the more nucleophilic end of the isolated alkene attacks the end of the conjugate electrophile. This is a thermodynamically controlled reaction with the new stereogenic centre choosing to have an equatorial substituent.



The cation picks up the only nucleophile available—formic acid. This gives the product of the fragmentation, which contains two unstable functional groups—a tertiary formate ester and an enol ether—and this product is not isolated from the reaction mixture. In water it hydrolyses to the enone, which undergoes elimination of formate to give nootkatone on heating.



Yet after all this effort, none of the synthetic samples of nootkatone delivered that intense grapefruit smell—for the simple reason that nootkatone is not the flavour principle of grapefruit! The samples of nootkatone that had been isolated from grapefruit contained minute traces of the true flavour principle—a simple thiol. Humans can detect  $2 \times 10^{-5}$  ppb (parts per billion) of this compound, so even the tiniest trace is very powerful. Nonetheless, the syntheses allowed chemists to correct a misconception.



## Looking forward

Fragmentation reactions cleave C–C single bonds by a combination of electron push and electron pull so that both electrons in the bond move in the same direction as the bond breaks. In the next chapter we shall see reactions that break C–C bonds in a quite different way. No electron push or pull is required because one electron goes one way and one the other. These are radical reactions.

## Further reading

F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry, Part A, Structure and Mechanisms*, Springer, 5th edn, 2007, part A. *Polar Rearrangements*, L. M. Harwood, Oxford Primer, OUP, 1992.

S. Warren and P. Wyatt, *Organic Synthesis: the Disconnection Approach*, 2nd edition, Wiley, Chichester, 2008, chapter 31.  
T.-L. Ho, *Heterolytic Fragmentation of Organic Molecules*, Wiley, 1993.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 37

## 自由基反应

### 联系

#### 基础

- Energy profile diagrams ch12
- Nucleophilic substitution ch15
- Conformational analysis ch16
- Elimination reactions ch17
- Conjugate addition ch22
- Regioselectivity ch24
- Retrosynthetic analysis ch28
- Diastereoselectivity ch32 & ch33
- Main group chemistry ch27

#### 目标

- Radicals are species with unpaired electrons
- Radical reactions follow different rules to those of ionic reactions
- Bond strength is very important
- Radicals can be formed with I, Br, Cl, Sn, and B
- Efficient radical reactions are chain reactions
- There are electrophilic and nucleophilic radicals
- Radicals favour conjugate addition
- Cyclization is easy with radical reactions

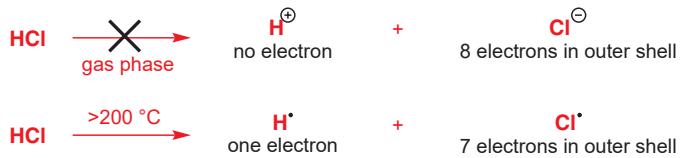
#### 展望

- Carbene chemistry ch38
- Determination of mechanism ch39
- Natural products ch42
- Polymerization web

### Radicals contain unpaired electrons

You may remember that at the beginning of Chapter 8 we said that the cleavage of H–Cl into H<sup>+</sup> and Cl<sup>−</sup> is possible in solution only because the ions that are formed are solvated: in the gas phase, the reaction is endothermic with  $\Delta G = +1347 \text{ kJ mol}^{-1}$ , a value so vast that even if the whole universe were made of gaseous HCl at 273 K, not a single molecule would be dissociated into H<sup>+</sup> and Cl<sup>−</sup> ions. At temperatures above about 200 °C, however, HCl does begin to dissociate, but not into ions. Instead of the chlorine atom taking both bonding electrons with it, leaving a naked proton, the electron pair forming the H–Cl bond is shared out between the two atoms.  $\Delta G$  for this reaction is a much more reasonable +431 kJ mol<sup>−1</sup> and, at high temperatures (above about 200 °C, that is), HCl gas can be dissociated into H and Cl atoms.

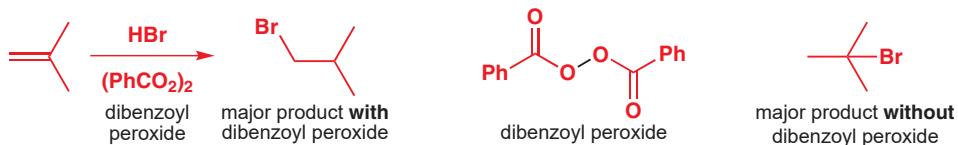
The single, unpaired electron possessed by each atom is represented by a dot. The Cl atom, of course, has another three pairs of electrons that are not shown.



#### ● Heterolysis and homolysis

- When bonds break and one atom gets both bonding electrons, the process is called **heterolysis**. The products of heterolysis are, of course, **ions**.
- When bonds break and the atoms get one bonding electron each, the process is called **homolysis**. The products of homolysis are **radicals**, which may be atoms or molecules, but must contain an unpaired electron.

In Chapter 24 we introduced the fact that bromine radicals react regioselectively with alkenes. Let us remind you of one reaction you met then: radical addition to an alkene. The product is an alkyl bromide, and is a different alkyl bromide from the one formed when HBr adds to an alkene in an ionic manner.

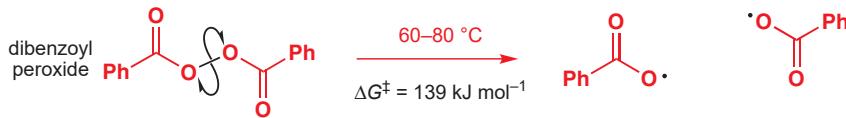


Now would be a good time to revisit the section on radicals in Chapter 24 and to re-read pp. 571–574. Ionic additions to alkenes are covered in Chapter 19.

What does the peroxide do to change the mechanism of the reaction? Peroxides undergo homolysis of the weak O–O bond extremely easily to form two radicals. We said that HCl in the gas phase undergoes homolysis in preference to heterolysis: other types of bond are even more susceptible to homolysis. You can see this for yourself by looking at this table of bond dissociation energies ( $\Delta G$  for  $\text{X–Y} \rightarrow \text{X}^\bullet + \text{Y}^\bullet$ ).

Bond X–Y	$\Delta G$ for $\text{X–Y} \rightarrow \text{X}^\bullet + \text{Y}^\bullet$ , kJ mol <sup>-1</sup>	Bond X–Y	$\Delta G$ for $\text{X–Y} \rightarrow \text{X}^\bullet + \text{Y}^\bullet$ , kJ mol <sup>-1</sup>
H–OH	498	CH <sub>3</sub> –Br	293
H <sub>3</sub> C–H	435	CH <sub>3</sub> –I	234
H <sub>3</sub> C–OH	383	Cl–Cl	243
H <sub>3</sub> C–CH <sub>3</sub>	368	Br–Br	192
H–Cl	431	I–I	151
H–Br	366	HO–OH	213
H–I	298	MeO–OMe	151
CH <sub>3</sub> –Cl	349		

Dialkyl peroxides (dimethyl peroxide is shown in the table) contain the very weak O–O bond. The radicals formed by homolytic cleavage of these bonds, stimulated by a little heat or light, initiate what we call a **radical chain reaction**, which results in the formation of the Br<sup>•</sup> radicals, which add to the alkene's C=C double bond (see Chapter 24).



Try to get a feel for bond strengths: we shall refer to them a lot in this chapter as they're very important to radical reactions. Compare this with the situation for ionic reactions, in which the strengths of the bonds involved are often much less important than polar effects (see the example on p. 207).

## Radicals form by homolysis of weak bonds

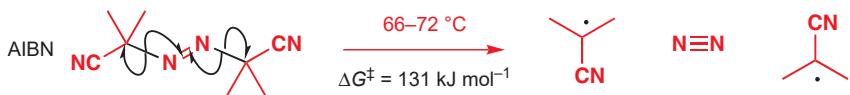
This is the most important way of making radicals: unpairing a pair of electrons by homolysis, making two new radicals. Temperatures of over 200 °C will homolyse most bonds; on the other hand, some weak bonds will undergo homolysis at temperatures little above room temperature. Light is a possible energy source for the homolysis of bonds too. Red light has associated with it 167 kJ mol<sup>-1</sup>; blue light has about 293 kJ mol<sup>-1</sup>. Ultraviolet (200 nm), with an associated energy of 586 kJ mol<sup>-1</sup>, will decompose many organic compounds (including the DNA in skin cells: sunbathers beware!).

There are a number of compounds whose homolysis is particularly important to chemists, and the most important ones are discussed in turn below. They all have weak σ bonds, and generate radicals that can be put to some chemical use. The halogens are quite readily homolysed by light, as you can see from the bond strengths in the table above, a fact that drives the radical halogenation reactions that we shall discuss later.

As you saw in Chapter 24, dibenzoyl peroxide is an important compound because it can act as another initiator of radical reactions. It undergoes homolysis simply on heating.

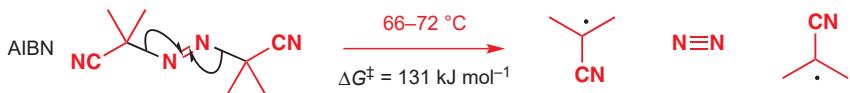
It is not sufficient for light to be energetic enough to promote homolysis; the molecule must have a mechanism for absorbing that energy, and the energy must end up concentrated in the vibrational mode that leads to bond breakage. We shall not consider these points further: if you are interested, you will find detailed explanations in specialized books on photochemistry.

Another compound that is often used in synthetic reactions for the same reason (although it reacts with a different set of compounds) is AIBN (azobisisobutyronitrile).

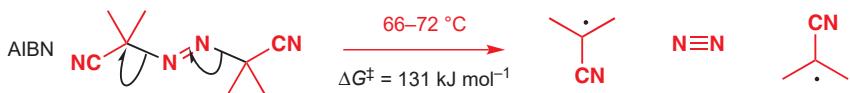


■  $\Delta G^\ddagger$  is the activation energy for the reaction.

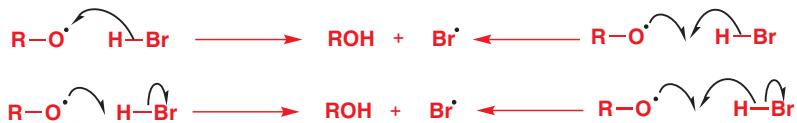
This decomposition mechanism accounts for the separate movements of all the electrons, but we can also draw the mechanism in a slightly different way: we show two radical ('fish hook') arrows forming the molecule of nitrogen but only one arrow to break each of the C–N bonds. It can be assumed that the electrons 'left behind' form radicals as well.



Another way of cutting back on the number of arrows without losing precision in the mechanism is to draw one arrow for each step all in the same (which can be either) direction. The first mechanism has the advantage of complete clarity; the other two make for neater diagrams. Choose which suits you best.

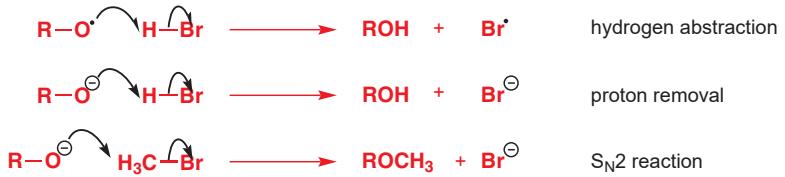


The important thing is to use the right type of arrow and to make it clear whether you are moving one, and not two, electrons. A simpler example is the abstraction of a hydrogen atom by an oxygen-centred radical: any of the mechanisms below is fine.



### Radicals form by abstraction

Notice that we didn't put HBr on the list of molecules that form radicals by homolysis: relative to the weak bonds we have been talking about, the H–Br bond is quite strong (just about as strong as a C–C bond). We described in Chapter 24 how oxygen radicals abstract hydrogen atoms from HBr. You might now like to compare this mechanism with similar ionic reactions.



Hydrogen abstraction is the removal of a hydrogen atom **with its one electron**. It is not the removal of a proton: that would be the removal of a hydrogen atom **with no electrons**, which happens in ionic reactions.

The ability of radicals to propagate by abstraction is a key feature of radical chain reactions, which we shall come to later. There is an important difference between homolysis and abstraction as a way of making radicals: homolysis is a reaction of a spin-paired molecule that produces *two* radicals; abstraction is a reaction of a radical with a spin-paired molecule that produces *one* new radical and a new spin-paired molecule.

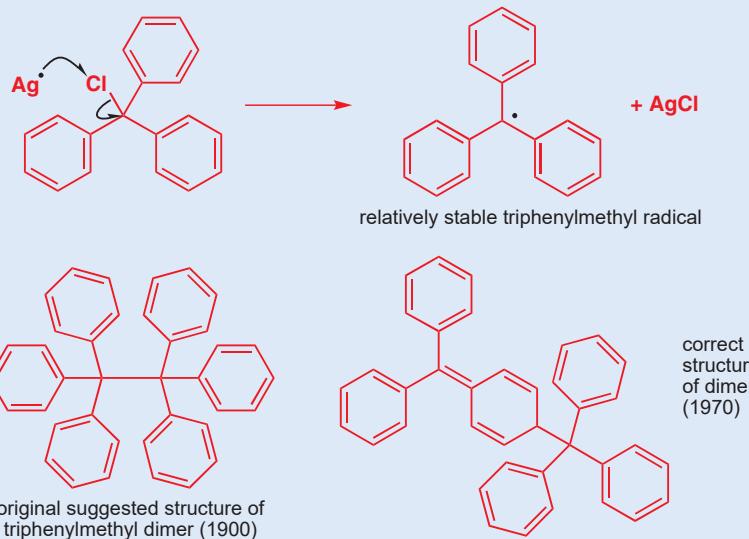
■ We use the term 'spin-paired molecule' to mean a 'normal' molecule, in which all the electrons are paired, in contrast with a radical, which has an unpaired electron.

As the comparison above shows, radical abstractions are in fact substitution reactions (at H in this case). However, radical substitutions differ considerably from S<sub>N</sub>1 or S<sub>N</sub>2 reactions: importantly, *radical substitutions almost never occur at carbon atoms*. We shall come back to radical substitutions, or abstractions (depending on whether you take the point of view of the H atom or the Br atom), and explain why this should be, later in the chapter.

### First radical detected

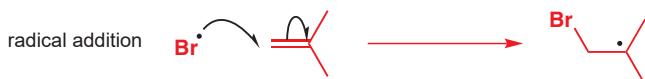
The very first radical to be detected, the triphenylmethyl radical, was made in 1900 by abstraction of Cl<sup>•</sup> from Ph<sub>3</sub>CCl by Ag metal. Many metal atoms such as Ag<sup>•</sup> and Li<sup>•</sup> have single unpaired electrons.

This radical is relatively stable (we shall see why shortly), but reacts with itself reversibly in solution. The product of the dimerization of triphenylmethyl was for 70 years believed to be hexaphenyl ethane but, in 1970, NMR showed that it was, in fact, an unsymmetrical dimer.



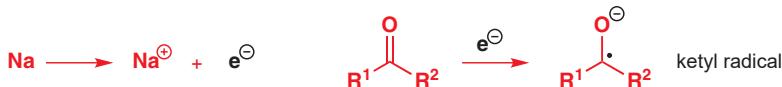
### Radicals form by addition

The key step in the radical addition of HBr to an alkyne in Chapter 24 was the formation of a radical by radical addition. The Br<sup>•</sup> radical (which, you will remember, was formed by abstraction of H<sup>•</sup> from HBr by RO<sup>•</sup>) adds to the alkene to give a new, carbon-centred radical. This is the radical addition mechanism:



Just as charge must be conserved through a chemical reaction, so must the spin of the electrons involved. If a reactant carries an unpaired electron, then so must a product. Addition of a radical to a spin-paired molecule always generates a new radical. Radical addition is therefore a second type of radical-forming reaction.

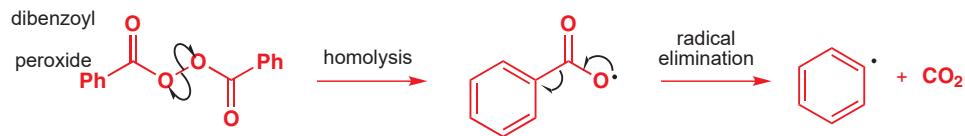
The simplest radical addition reactions occur when a single electron is added to a spin-paired molecule. This process is a reduction. You have already met some examples of single-electron reductions: Birch reductions (Chapter 23) use the single electron formed when a group I metal (sodium, usually) is dissolved in liquid ammonia to reduce organic compounds. Group I metals are common sources of single electrons: by giving up their odd s electron they form a stable M<sup>+</sup> ion. They will donate this electron to several classes of molecules, for example ketones can react with sodium to form ketyl radicals.



→ We shall discuss ketyl radicals and their reactions on p. 980.

### Radicals form by elimination

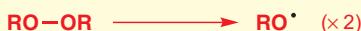
A fourth class of radical-forming reaction is **elimination**. For an example, we can go back to dibenzoyl peroxide, the unstable compound we considered earlier in the chapter. The radicals formed from dibenzoyl peroxide by homolysis are themselves unstable and each can break down by cleavage of a C–C bond, generating CO<sub>2</sub> and a phenyl radical. This is a radical elimination reaction, and is the reverse of a radical addition reaction.



#### ● To summarize methods of radical formation

Radicals form from spin-paired molecules by:

- homolysis of weak σ bonds, e.g.



- electron transfer, that is, reduction (addition of an electron), e.g.



Radicals form from other radicals by:

- substitution (abstraction)



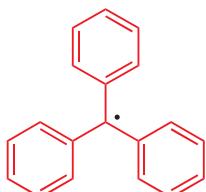
- addition



- elimination (homolysis)



■ *Electron célibataire* is the French term for these bachelor electrons searching earnestly for a partner.



triphenylmethyl radical—  
stable in solution  
in equilibrium with its dimer

### Most radicals are extremely reactive...

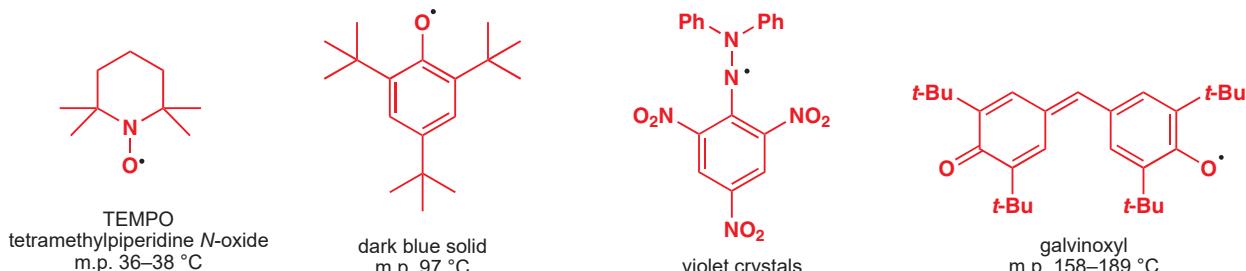
Unpaired electrons are desperate to be paired up again. This means that radicals usually have a very short lifetime; they don't survive long before undergoing a chemical reaction. Chemists are more interested in radicals that are reactive because they can be persuaded to do interesting and useful things. However, before we look at their reactions, we shall consider some radicals that are *unreactive* so that we can analyse the factors that contribute to radical reactivity.

#### ... but a few radicals are very unreactive

Whilst simple alkyl radicals are extremely short-lived, some other radicals survive almost indefinitely. Such radicals are known as *persistent radicals*. We mentioned the triphenylmethyl

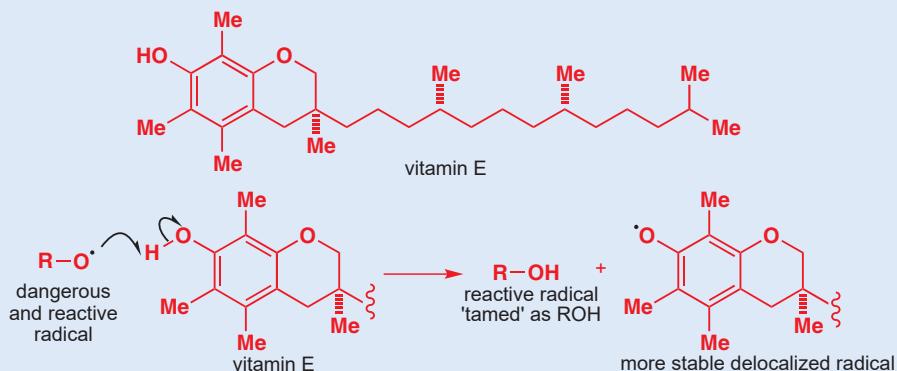
radical on p. 973: this yellow substance exists in solution in equilibrium with its dimer, but it is persistent enough to account for 2–10% of the equilibrium mixture.

Persistent radicals with the single electron carried by an oxygen or a nitrogen atom are also known: these four radicals can all be handled as stable compounds. The first, known as TEMPO, is a commercial product and can even be sublimed.



### Vitamin E tames radicals

Many of the molecules that make up the structure of human tissue are susceptible to homolysis in intense light, and the body makes use of sophisticated chemistry to protect itself from the action of the reactive radical products. Vitamin E plays an important role in the ‘taming’ of these radicals: abstraction of H from the phenolic hydroxyl group produces a relatively stable radical that does no further damage.



There are two reasons why some radicals are more persistent than others: (1) steric hindrance and (2) electronic stabilization. In the four extreme cases above, their exceptional stability is conferred by a mixture of these two effects. Before we can analyse the stability of other radicals, however, we need to look at what is known about the shape and electronic structure of radicals.

## How to analyse the structure of radicals: electron spin resonance

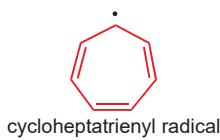
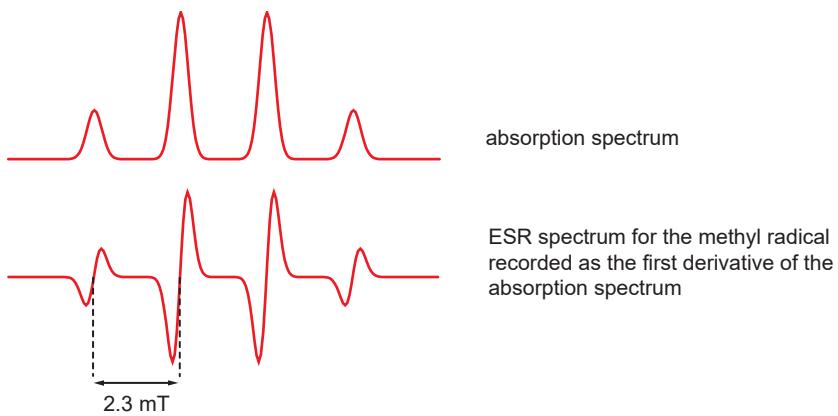
For the last few pages we have been discussing the species we call radicals without offering any evidence that they actually exist. Well, there is evidence, and it comes from a spectroscopic technique known as electron spin resonance, or ESR (also known as EPR, electron paramagnetic resonance). ESR not only confirms that radicals do exist, but it can also tell us quite a lot about their structure.

Unpaired electrons, like the nuclei of certain atoms, have a magnetic moment associated with them. Proton NMR probes the environment of hydrogen atoms by examining the energy difference between the two possible orientations of their magnetic moments in a magnetic field; ESR works in a similar way for unpaired electrons. The magnetic moment of an electron is much bigger than that of a proton, so the difference in energy between the possible quantum

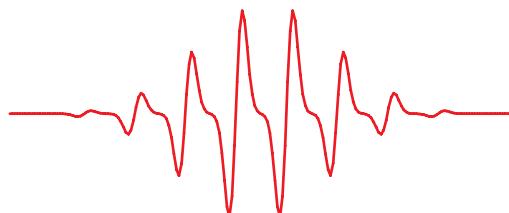
states in an electron field is also much bigger. This means that the magnets used in ESR spectrometers can be weaker than those in NMR spectrometers, usually about 0.3 tesla; even at this low field strength, the resonant frequency of an electron is about 9000 MHz (for comparison, the resonant frequency of a proton at 9.5 tesla is 400 MHz; in other words, a 400 MHz NMR machine has a magnetic field strength of 9.5 tesla).

But there are strong similarities between the techniques. ESR shows us, for example, that unpaired electrons couple with protons in the radical. The spectrum below is that of the methyl radical,  $\text{CH}_3\cdot$ . The 1:3:3:1 quartet pattern is just what you would expect for coupling to three equivalent protons; coupling in ESR is measured in millitesla (or gauss; 1 gauss = 0.1 mT), and for the methyl radical the coupling constant (called  $a_{\text{H}}$ ) is 2.3 mT.

■ Notice that, for historical reasons, ESR spectra are recorded in a different way from NMR spectra: the diagram shows the first derivative of the absorption spectrum (the sort of spectrum you would get from a proton NMR machine).

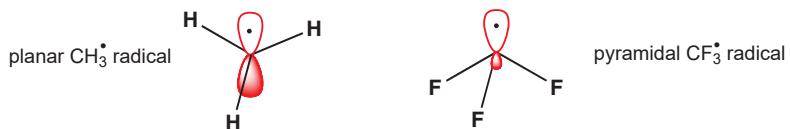


ESR hyperfine splittings (as the coupling patterns are known) can give quite a lot of information about a radical. For example, here is the hyperfine splitting pattern of the cycloheptatrienyl radical. The electron evidently sees all seven protons around the ring as equivalent, and must therefore be fully delocalized. A localized radical would see several different types of proton, resulting in a much more complex splitting pattern.



ESR spectrum of cycloheptatrienyl radical

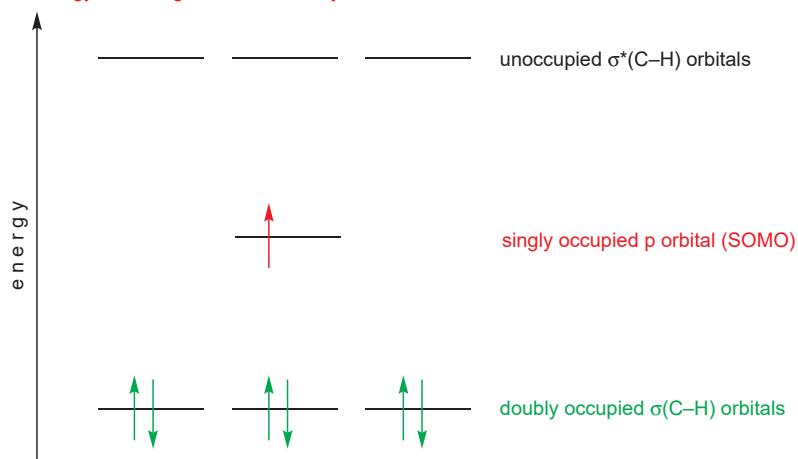
Even the relatively simple spectrum of the methyl radical tells us quite a lot about its structure. For example, the size of the coupling constant  $a_{\text{H}}$  indicates that the methyl radical is planar; the trifluoromethyl radical is, on the other hand, pyramidal. The oxygenated radicals  $\cdot\text{CH}_2\text{OH}$  and  $\cdot\text{CMe}_2\text{OH}$  lie somewhere in between. The calculations that show this lie outside the scope of this book.



### Radicals have singly occupied molecular orbitals

ESR tells us that the methyl radical is planar: the carbon atom must therefore be  $\text{sp}^2$  hybridized, with the unpaired electron in a p orbital. We can represent this in an energy level diagram.

energy level diagram for the methyl radical

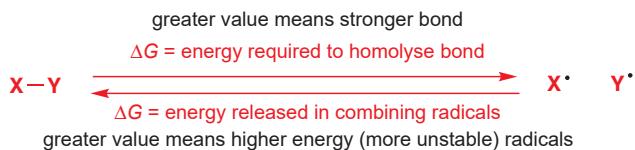


In Chapter 4 we talked about the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) of organic molecules.  $\text{CH}_3$  (like all radicals) has an orbital containing one electron, which we call a **singly occupied molecular orbital (SOMO)**.

As with all molecules, it is the energy of the electrons in the molecular orbitals of the radical that dictate its stability. Any interaction that can decrease the energy levels of the filled molecular orbitals increases the stability of the radical (in other words, decreases its reactivity). Before we use this energy level diagram of the methyl radical to explain the stability of radicals, we need to look at some experimental data that allow us to judge just how stable different radicals are.

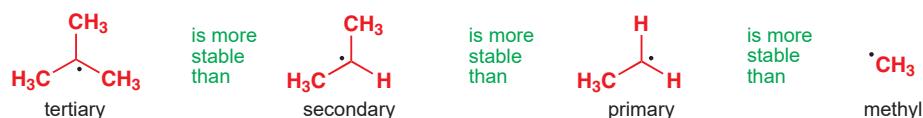
## Radical stability

On p. 971 we used bond strength as a guide to the likelihood that bonds will be homolysed by heat or light. Since bond energies give us an idea of the ease with which radicals can form, they can also give us an idea of the stability of those radicals once they have formed.



This is particularly true if we compare the strengths of bonds between the same atoms, for example carbon and hydrogen, in different molecules; this table does this.

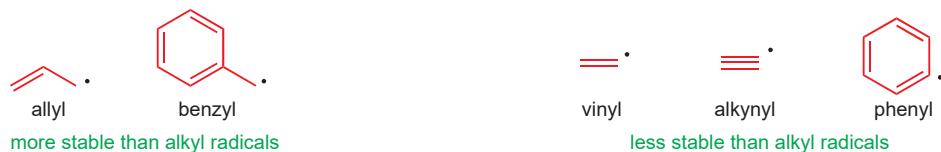
A few simple trends are apparent. For example, C–H bonds decrease in strength in R–H when R goes from primary to secondary to tertiary. Tertiary alkyl radicals are therefore the most stable; methyl radicals the least stable.



C–H bonds next to conjugating groups such as allyl or benzyl are particularly weak, so allyl and benzyl radicals are more stable. But C–H bonds to alkynyl, alkenyl, or aryl groups are strong. We saw the effects of this in Chapter 24.

C–H bond	Dissociation energy, $\text{kJ mol}^{-1}$
$\text{CH}_3\text{---H}$ (methyl)	439
$\text{MeCH}_2\text{---H}$ (primary)	423
$\text{Me}_2\text{CH---H}$ (secondary)	410
$\text{Me}_3\text{C---H}$ (tertiary)	397
$\text{HC}\equiv\text{C---H}$ (alkynyl)	544
$\text{H}_2\text{C}=\text{CH---H}$ (vinyl)	431
$\text{Ph---H}$ (phenyl)	464
$\text{H}_2\text{C}=\text{CHCH}_2\text{---H}$ (allyl)	364
$\text{PhCH}_2\text{---H}$ (benzyl)	372
$\text{RC}(=\text{O})\text{---H}$ (acyl)	364
$\text{EtOCHMe---H}$	385
$\text{N}\equiv\text{CCH}_2\text{---H}$	360
$\text{MeCOCH}_2\text{---H}$	385

The absolute values in this table were determined in the gas phase, but the relative stabilities of the different radicals mirror their relative stabilities in solution.



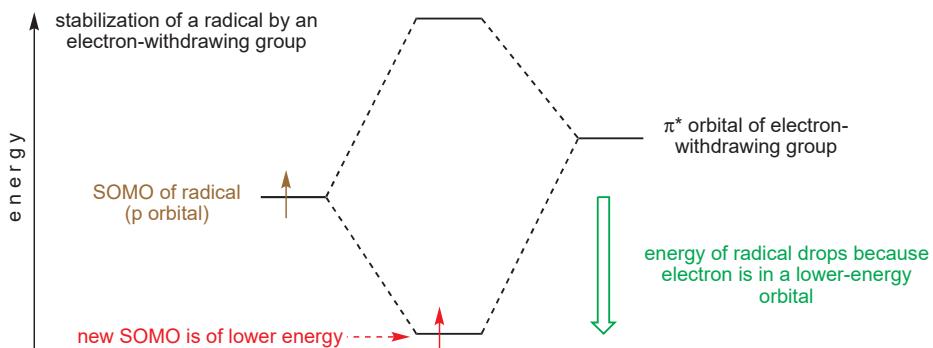
Adjacent functional groups appear to weaken C–H bonds: radicals next to carbonyl, nitrile, or ether functional groups, or centred on a carbonyl carbon atom, are more stable than even tertiary alkyl radicals.



Whether the functional group is electron withdrawing or electron donating is clearly irrelevant here: both types seem to stabilize radicals. We can explain all of this if we look at how the different groups next to the radical centre interact electronically with the radical.

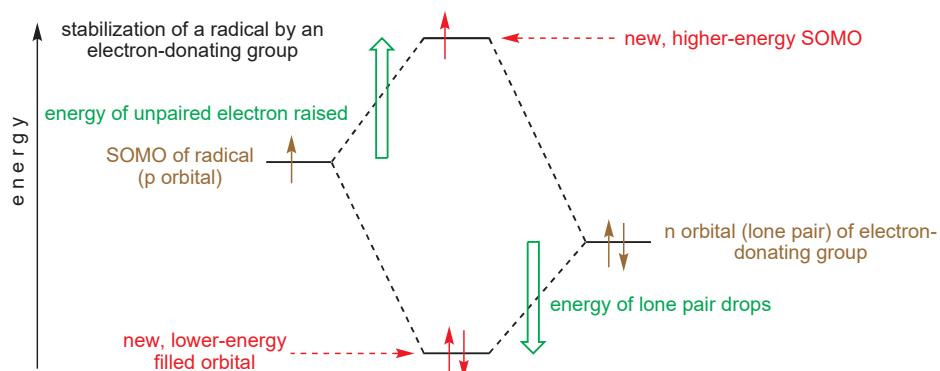
### Radicals are stabilized by conjugating, electron-withdrawing, and electron-donating groups

Let's consider first what happens when a radical centre finds itself next to an electron-withdrawing group. Groups like C=O and C≡N are electron withdrawing because they have a low-lying empty  $\pi^*$  orbital. By overlapping with the (usually p) orbital containing the radical (the SOMO), two new molecular orbitals are generated. One electron (the one in the old SOMO) is available to fill the two new orbitals. It enters the new SOMO, which is of lower energy than the old one, and the radical experiences stabilization because this electron drops in energy.



Radicals that are stabilized by an electron-withdrawing group and an electron-donating group at the same time are sometimes known as **captodative radicals**.

We can analyse what happens with electron-rich groups, such as RO groups, in a similar way. Ether oxygen atoms have relatively high-energy filled  $n$  orbitals, their lone pairs. Interacting this with the SOMO again gives two new molecular orbitals. Three electrons are available to fill them. The SOMO is now higher in energy than it was to start with, but the lone pair is lower. Because two electrons have dropped in energy and only one has risen, there is an overall stabilization of the system, even though the new SOMO is of higher energy than the old one. We shall see later what effect the energy of the SOMO, rather than the overall energy of the radical, has on its reactivity.



In Chapter 15 you saw how the electrons in C–H  $\sigma$  bonds stabilize cations: they stabilize radicals in the same way, which is why tertiary radicals are more stable than primary ones. Conjugation, too, is effective at stabilizing radicals. We know from their ESR spectra (p. 976) that radicals next to double bonds are delocalized; that they are more stable is evident from the bond dissociation energies of allylic and benzylic C–H bonds.

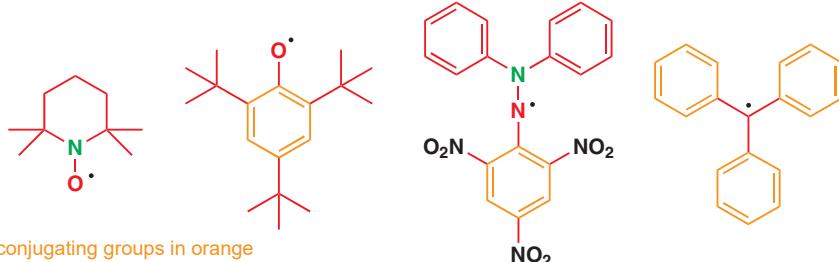
● Anything that would stabilize an anion or a cation will stabilize a radical:

- electron-withdrawing groups
- electron-donating groups (including alkyl groups with C–H  $\sigma$  bonds)
- conjugating groups.

### Steric hindrance makes radicals less reactive

On p. 975 we showed you some radicals that are remarkably stable (persistent): some can even be isolated and purified. You should now be able to see at least part of the reason for their exceptional stability: two of them have adjacent powerful electron-donating groups, one has a powerful electron-withdrawing group as well, and three of the four are conjugated.

these radicals are persistent...



...while these radicals are reactive



But electronic factors alone are not sufficient to explain the exceptional stability of all four radicals, since the two radicals on the right receive just about the same electronic stabilization as the first two above, but are much more reactive.

In fact, the stability of the triphenylmethyl radical we know to be due mainly to steric, rather than electronic, factors. X-ray crystallography shows that the three phenyl rings in this compound are not coplanar but are twisted out of a plane by about 30°, like a propeller. This means that the delocalization in this radical is less than ideal (we know that there is some delocalization from the ESR spectrum) and, in fact, it is little more delocalized than the diphenylmethyl or even the benzyl radical, even though it is much more stable than either. This must be because the central carbon, which bears most of the radical character, is sterically shielded by the twisted phenyl groups, making it very hard for the molecule to react.

■ When it does react, as you saw in the box on p. 973, it does so through one of the less hindered *para* positions.

The rest of this chapter is devoted to the reactions of radicals, and you will see that the two effects we have talked about—electronic stabilization and steric hindrance—are key factors that control these reactions.

## How do radicals react?

A reactive radical has a choice: it can either find another radical and combine to form a spin-paired molecule (or more than one spin-paired molecule), or it can react with a spin-paired molecule to form a new radical. Both are possible, and we shall see examples of each. A third alternative is for a radical to decompose in a unimolecular reaction, giving rise to a new radical and a spin-paired molecule.

- **Three possibilities:**

- radical + radical → spin-paired molecule



- radical + spin-paired molecule → new radical + new spin-paired molecule



- radical → new radical + spin-paired molecule

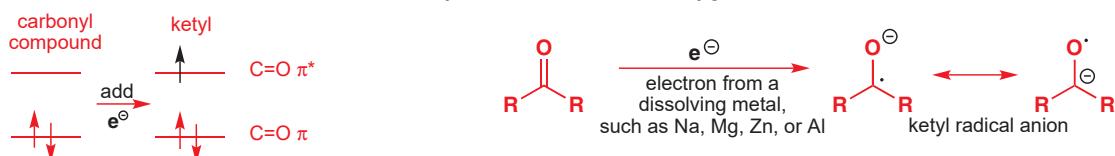


## Radical–radical reactions

In view of the energy released when unpaired electrons pair up, you might expect this type of radical reaction to be more common than reaction with a spin-paired molecule, in which no net pairing of electrons takes place. Radical–radical reactions certainly do take place, but they are not the most important type of reaction involving radicals. We shall see why they are not as common as you might expect shortly, but first we can look at the few examples of radical–radical reactions which do work well.

### The pinacol reaction is a radical dimerization

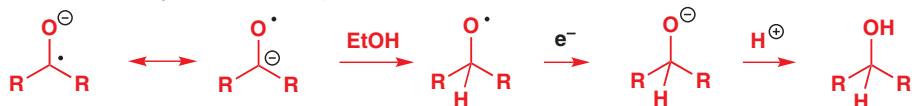
We outlined on p. 973 a way of making radicals by single electron transfer: effectively, the addition reaction of a single electron to a spin-paired molecule. The types of molecules that undergo this reaction are those with low-lying antibonding orbitals for the electron to go into, in particular aromatic systems and carbonyl compounds. The radical anion formed by addition of an electron to a ketone is known as a **ketyl**. The single electron is in the  $\pi^*$  orbital, so we can represent a ketyl with the radical on oxygen or on carbon and the anion on the other atom.



Ketols behave in a manner that depends on the solvent that they are in. In protic solvents (ethanol, for example), the ketyl becomes protonated and then accepts a second electron from the metal (sodium is usually used in these cases). An alkoxide anion results, which, on addi-

tion of acid at the end of the reaction, gives an alcohol. Notice that this is a reaction using sodium metal in ethanol, and not sodium ethoxide, which is the basic product that forms once sodium has dissolved in ethanol. It is important that the sodium is *dissolving* as the reaction takes place, since only then are the free electrons available.

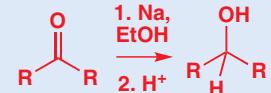
reaction of the ketyl radical anion in protic solvents



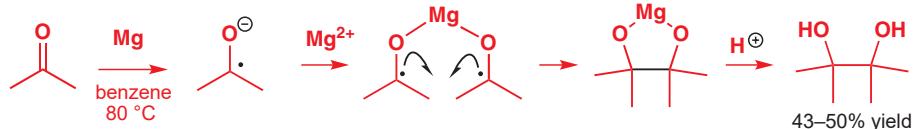
In aprotic solvents, such as benzene or ether, no protons are available so the concentration of ketyl radical builds up significantly and the ketyl radical anions start to dimerize. As well as being a radical–radical process, this dimerization process is an anion–anion reaction, so why doesn't electrostatic repulsion between the anions prevent them from approaching one another? The key to success is to use a metal such as magnesium or aluminium, which forms strong, covalent metal–oxygen bonds and can coordinate to more than one ketyl at once. Once two ketyls are coordinated to the same metal atom, they react rapidly.

This reaction, known as the **Bouveault–Blanc reduction**, was used to reduce carbonyl compounds to alcohols, but now aluminium hydrides and borohydrides are usually more convenient. You met an example of the Bouveault–Blanc reduction in Chapter 32 (p. 832).

overall:



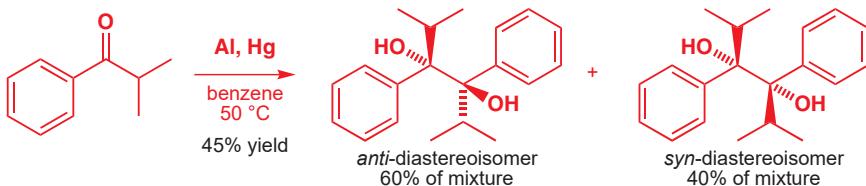
pinacol dimerization of acetone (ketyl radical reaction in hydrocarbon solvent)



Interactive mechanism for pinacol reaction

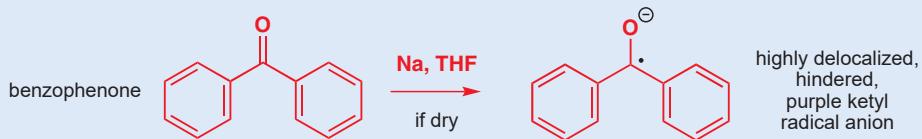
The example shows the dimerization of acetone to give a diol (2,3-dimethylbutane-2,3-diol) whose trivial name, pinacol, is used as a name for this type of reaction using any ketone. Sometimes pinacol reactions create new chiral centres: in this example, the two diastereoisomeric diols are formed in a 60:40 mixture. If you want to make a single diastereoisomer of a diol, a pinacol reaction is not a good choice!

■ You would be better off using one of the methods described in Chapter 33 on diastereoselectivity.



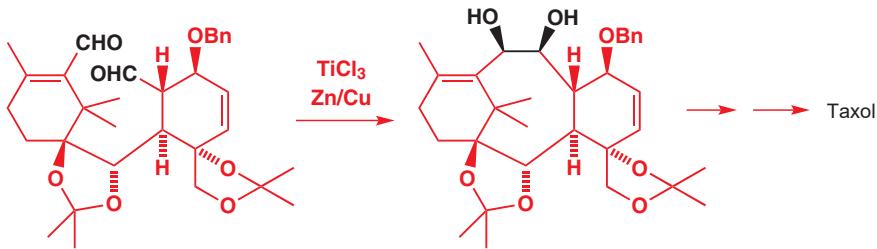
### Benzophenone as an indicator in THF stills

As you should have gathered by now, THF is an important organic solvent in which many low-temperature, inert atmosphere reactions are conducted. It has a drawback, however: it is quite hygroscopic, and often the reactions for which it is used as a solvent must be kept absolutely free of water. It is therefore always distilled immediately before use from sodium metal, which reacts with any traces of water in the THF. However, it is necessary to have an indicator to show that the THF is dry and that the sodium has done its job. The indicator used is a ketone, benzophenone.



When the THF is dry, the distilling liquid containing the benzophenone becomes bright purple. This colour is due to the ketyl of benzophenone, the formation of which under these conditions should not surprise you. It should also come as no surprise that this ketyl, being stabilized by conjugation and quite hindered, is persistent (long-lived)—it does not undergo pinacol dimerization (as we explained above, you would not normally choose sodium to promote pinacols anyway). However, if water is present, the ketyl is rapidly quenched in the manner of the reduction described above to give the (colourless) alkoxide anion: only when all the water is consumed does the colour return.

Pinacol reactions can be carried out intramolecularly, from compounds containing two carbonyl groups. In fact, the key step of one of the very first syntheses of the important anti-cancer compound Taxol was an intramolecular pinacol reaction using titanium as the source of electrons.

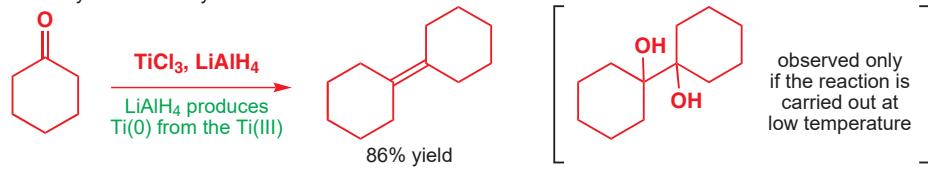


The titanium metal that is the source of electrons is produced during the reaction by reduction of  $\text{TiCl}_3$  using a zinc–copper mixture. This reaction is, in fact, unusual because, as we shall see below, pinacol reactions using titanium do not normally stop at the diol, but give alkenes.

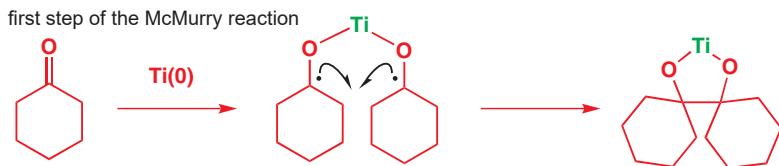
### Titanium promotes the pinacol coupling and then deoxygenates the products: the McMurry reaction

Titanium can be used as the metal source of electrons in the pinacol reaction and, provided the reaction is kept cold and not left for too long, diols can be isolated from the reaction, as in the example above. However, unlike magnesium or aluminium, titanium reacts further with these diol products to give alkenes in a reaction known as the McMurry reaction, after its inventor.

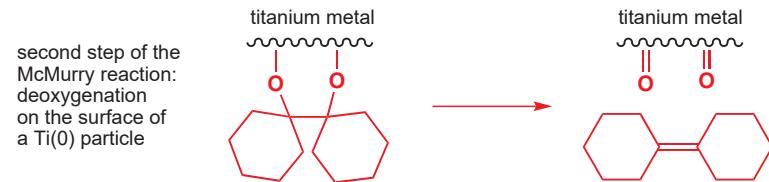
McMurry reaction of cyclohexanone



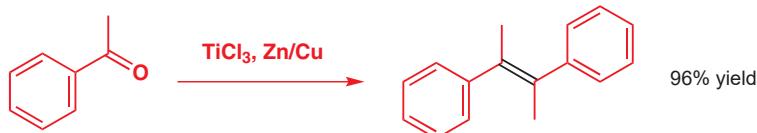
Notice that the titanium(0), which is the source of electrons in the reaction, is produced during the reaction by reacting a  $\text{Ti(III)}$  salt, usually  $\text{TiCl}_3$ , with a reducing agent such as  $\text{LiAlH}_4$  or  $\text{Zn/Cu}$ . The reaction does not work with, say, powdered titanium metal. The McMurry reaction is believed to be a two-stage process involving firstly a pinacol radical–radical coupling.



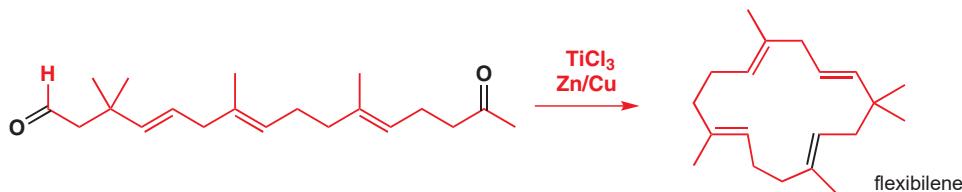
The  $\text{Ti(0)}$  then proceeds to deoxygenate the diol by a mechanism not fully understood, but thought to involve binding of the diol to the surface of the  $\text{Ti(0)}$  particles produced in the reduction of  $\text{TiCl}_3$ .



We expect you to be mildly horrified by the inadequacy of the mechanism above. But, unfortunately, we can't do much better because no-one really knows quite what is happening. The McMurry reaction is very useful for making tetrasubstituted double bonds—there are few other really effective ways of doing this. However, the double bonds really need to be symmetrical (in other words, have the same substituents at each end) because McMurry reactions between two different ketones are rarely successful.

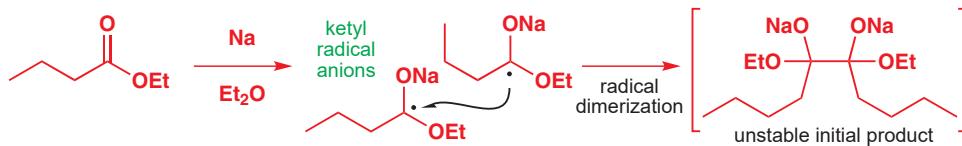


McMurry reactions also work very well intramolecularly, and turn out to be quite a good way of making cyclic alkenes, especially when the ring involved is medium or large (over about eight members). For example, the natural product flexibilene, with a 15-membered ring, can be made by cyclizing a 15-keto-aldehyde.



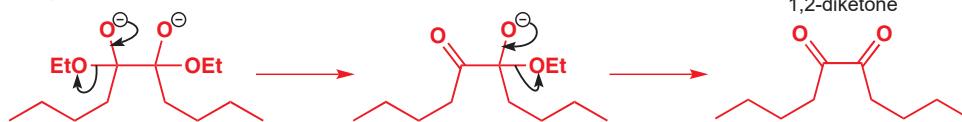
### Esters undergo pinacol-type coupling: the acyloin reaction

You've seen examples of pinacol and McMurry reactions of ketones and aldehydes. What about esters? You would expect the ketyl radical anion to form from an ester in the same way, and then to undergo radical dimerization, and this is indeed what happens.



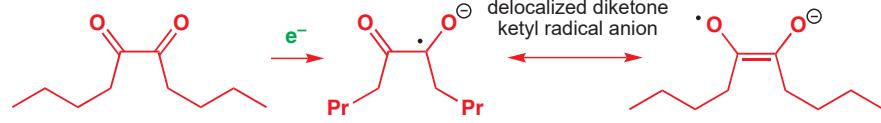
The product of the dimerization looks very much like a tetrahedral intermediate in a carbonyl addition–elimination reaction, and it collapses to give a 1,2-diketone.

collapse of the double 'tetrahedral intermediate'

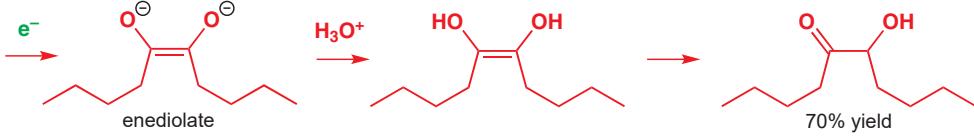


The diketone is, however, still reducible—in fact, 1,2-diketones are more reactive towards electrophiles and reducing agents than ketones because their  $\pi^*$  is lower in energy and straight away two electron transfers take place to form a molecule, which we could term an **enediolate**. On quenching the reaction with acid, this dianion is protonated twice to give the enol of an  $\alpha$ -hydroxy-ketone, and it is this  $\alpha$ -hydroxy-ketone that is the final product of the acyloin reaction. The yield in this example is a quite respectable 70%. However, in many other cases, this usefulness of the acyloin reaction is hampered by the formation of by-products that arise because of the reactivity of the enediolate dianion. It is, of course, quite nucleophilic, and is likely to be formed in the presence of the highly electrophilic diketone. It is also basic, and often catalyses a competing Claisen condensation of the esters being reduced.

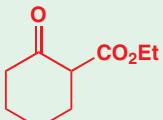
first electron transfer to the diketone:



second electron transfer:

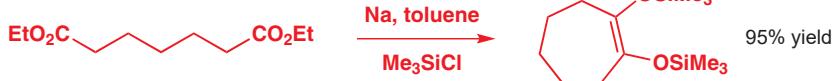


■ In the absence of the  $\text{Me}_3\text{SiCl}$ , the main product from this reaction becomes the cyclic ketoester below, which arises from base-catalysed Dieckmann cyclization (see Chapter 26) of the diester.

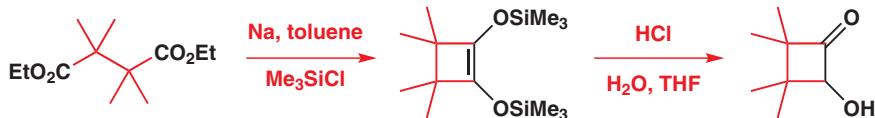


The solution to these problems is to add trimethylsilyl chloride to the reaction mixture. The silyl chloride silylates the enediolate as it is formed, and the product of the acyloin reaction becomes a bis-silyl ether.

an improved version of the acyloin reaction



These silyl ethers are rarely wanted as final products, and they can easily be hydrolysed to  $\alpha$ -hydroxyketones with aqueous acid. This improved version makes four-membered rings efficiently.



It's not by accident that these two examples of the acyloin reaction show the formation of cyclic compounds. It is a particularly powerful method of making carbocyclic rings from four-membered upwards: the energy to be gained by pairing up the two electrons in the radical–radical reaction step more than compensates for the strain that may be generated in forming the ring.

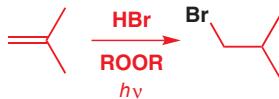
### The pinacol, McMurry, and acyloin reactions are exceptional

■ Think of radicals as smash-and-grab raiders. They pick the first shop that catches their eye, smash the window, and run off with a handful of cheap jewellery from the front of the display. Ions in solution are stealthy burglars. They scan all the houses on the street, choose the most vulnerable, and then carefully gain entry to the room that they know contains the priceless oil painting.

We've already said that this type of reaction, in which two radicals dimerize, is relatively uncommon. Most radicals are simply too reactive to react with one another! This may sound nonsensical, but the reason is simply that highly reactive species are unselective about what they react with. Although it might be energetically favourable for them to find another radical and dimerize, they are much more likely to collide with a solvent molecule, or a molecule of some other compound present in the mixture, than another radical. Reactive radicals are only ever present in solution in very low concentrations, so the chances of a radical–radical collision are very low. Radical attack on spin-paired molecules is much more common and, because the product of such reaction is also a radical, they give rise to the possibility of radical chain reactions.

### Radical chain reactions

In looking at how radicals form, you've already seen examples of how radicals react. In fact, we've already dealt (if only very briefly) with every step of the sequence of reactions that makes up the mechanism of the radical reaction you met at the beginning of the chapter, and shown below.



Let's now consider each step in turn and in more detail.

1. The dialkyl peroxide is homolysed (by heat or light) to give two alkoxy radicals.



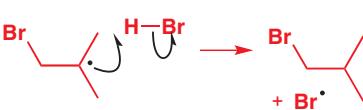
2.  $\text{RO}\cdot$  abstracts H from HBr (radical substitution) to give  $\text{Br}\cdot$ .



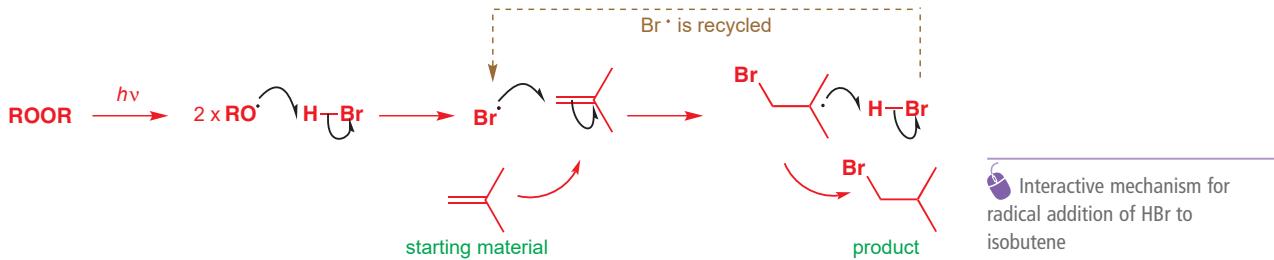
3.  $\text{Br}\cdot$  adds to isobutene to give a carbon-centred radical.



4. The carbon-centred radical abstracts a hydrogen atom from H-Br to form the final addition product and regenerate  $\text{Br}\cdot$ , which can react with another molecule of alkene.



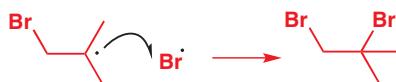
So the whole process is a cycle with the bromine radical regenerated in the last step, the one in which the product is formed.



In each step in the cycle a radical is consumed and a new radical is formed. This type of reaction is therefore known as a **radical chain reaction**, and the two steps that form the cyclic process that keeps the chain running are known as the **chain propagation steps**. Only one molecule of peroxide **initiator** is necessary for a large number of product molecules to be formed and, indeed, the peroxide needs to be added in only catalytic quantities (about 10 mol%) for this reaction to proceed in good yield.

Any less than 10 mol%, however, and the yield drops. The problem is that the chain reaction is not 100% efficient. Because the concentration of radicals in the reaction mixture is low, radical-radical reactions are rare, but nonetheless they happen often enough that more peroxide keeps being needed to start the chain off again.

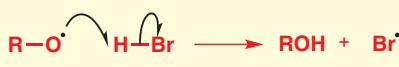
#### possible radical–radical chain termination steps



Reactions like this are known as **termination steps** and are actually an important part of any chain reaction; without termination steps the reaction would be uncontrollable.

#### ● Radical chain reactions consist of:

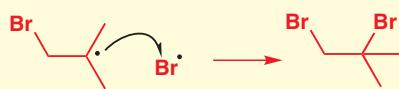
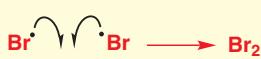
- **initiation steps**



- **propagation steps**



• termination steps



Interactive mechanism for radical termination steps

We have already suggested two reasons why the  $\text{Br}^\bullet$  radical adds to the alkene with this characteristic regioselectivity, giving a primary alkyl bromide when the polar addition of HBr to an alkene would give a tertiary alkyl bromide: (1) attack at the unsubstituted end of the alkene is less sterically hindered and (2) the tertiary radical thus formed is more stable than a primary radical. In fact, of all the hydrogen halides, only HBr will add to alkenes in this fashion: HCl and HI will undergo only polar addition to give the tertiary alkyl halide. Why? We need to be able to answer this type of question too.

## Selectivity in radical chain reactions

In the radical–radical reactions we looked at earlier, there was never any question of what would react with what: only one type of radical was formed and the radicals dimerized in identical pairs. Look at the chain reaction above though—there are three types of radical present,  $\text{Br}^\bullet$ ,  $\text{BrCH}_2\text{Me}_2\text{CH}^\bullet$ , and  $\text{RO}^\bullet$ , and they all react specifically with a chosen spin-paired partner:  $\text{Br}^\bullet$  with the alkene, and  $\text{BrCH}_2\text{Me}_2\text{CH}^\bullet$  and  $\text{RO}^\bullet$  with HBr. We need to understand the factors that govern this chemoselectivity. In order to do so we shall look at another radical reaction with chemoselectivity and regioselectivity that is *measurable*.

## Chlorination of alkanes

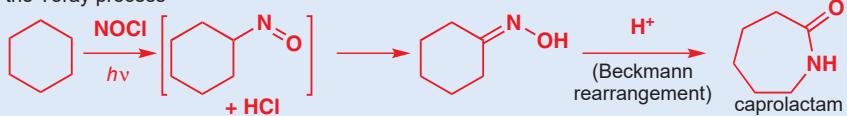
Alkanes will react with chlorine radicals to give alkyl chlorides. For example, cyclohexane plus chlorine gas, in the presence of light, gives cyclohexyl chloride and hydrogen chloride.



### The Toray process

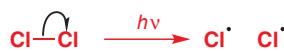
A variant of this reaction, known as the Toray process, is used on an industrial scale to produce caprolactam, a precursor to nylon. Instead of chlorine, nitrosyl chloride is used to form a nitroso compound that rapidly tautomerizes to an oxime. As you saw in Chapter 36, this oxime undergoes a Beckmann rearrangement under acid conditions to form caprolactam.

the Toray process



This type of reaction is important industrially since it is one of the few that allows compounds containing functional groups to be made from alkanes. As you might guess, since it needs light for initiation, the process is another example of a radical chain reaction. As with the radical addition of HBr to alkenes, we can identify initiation, propagation, and termination steps in the mechanism.

initiation



propagation



termination

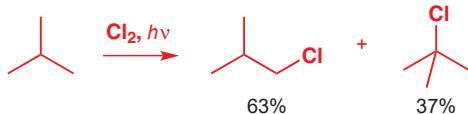
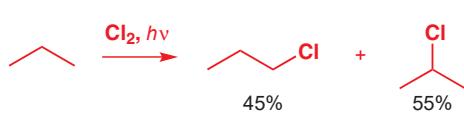


Interactive mechanism for radical addition of  $\text{Cl}_2$  to cyclohexane

In this case, the termination steps are much less important than in the last case we looked at, and typically the chain reaction can continue for  $10^6$  steps for each initiation

event (photolysis of chlorine). Be warned: reactions like this can be explosive in sunlight and are carried out in specialized facilities, not in the open laboratory.

When the chlorine radical abstracts a hydrogen atom from the cyclohexane, only one product can be formed because all 12 hydrogen atoms are equivalent. For other alkanes this may not be the case, and mixtures of alkyl chlorides can result. For example, propane is chlorinated to give a mixture of alkyl chlorides containing 45% 1-chloropropane and 55% 2-chloropropane, and isobutane is chlorinated to give 63% iso-butyl chloride and 37% *tert*-butyl chloride.



These bond energies were given in the tables on p. 971.

How can we explain the ratios of products that are formed? The key is to look at the relative stabilities of the radicals involved in the reaction and the strengths of the bonds that are formed and broken. First, the chlorination of propane. A chlorine radical, produced by photolysis, can abstract either a primary hydrogen atom, from the end of the molecule, or a secondary hydrogen atom, from the middle. For the two processes, we have these energy gains and losses:

		abstraction of primary hydrogen
		$\Delta H, \text{ kJ mol}^{-1}$
one H–Cl bond formed	– 431	
one primary C–H bond broken	+ 423	
total	– 8	

		abstraction of secondary hydrogen
		$\Delta H, \text{ kJ mol}^{-1}$
one H–Cl bond formed	– 431	
one secondary C–H bond broken	+ 410	
total	– 21	

Abstraction of the secondary hydrogen atom is more exothermic than abstraction of the primary hydrogen atom for the related reasons that: (1) secondary C–H bonds are weaker than primary ones and (2) secondary radicals are more stable than primary ones. So, we get more 2-chloropropane than 1-chloropropane. But in this case, that isn't the only factor involved: remember that there are six primary hydrogen atoms and only two secondary ones, so the relative reactivity of the primary and secondary positions is even more different than the simple ratio of products from the reaction suggests. This statistical factor is more evident in the second example we gave above, the chlorination of isobutane. Now the choice is between formation of a tertiary radical and formation of a primary one.

		abstraction of primary hydrogen
		$\Delta H, \text{ kJ mol}^{-1}$
one H–Cl bond formed	– 431	
one primary C–H bond broken	+ 423	
total	– 8	

		abstraction of tertiary hydrogen
		$\Delta H, \text{ kJ mol}^{-1}$
one H–Cl bond formed	– 431	
one tertiary C–H bond broken	+ 397	
total	– 34	

Tertiary radical formation is more exothermic, yet more primary alkyl chloride is formed than tertiary alkyl chloride. However, once the 9:1 ratio of primary to tertiary hydrogen atoms is taken into account, the relative reactivities, as determined experimentally, turn out to be as shown in the table below.

ratio of products formed (tertiary:primary)	37:63
number of hydrogen atoms (tertiary:primary)	1:9
relative reactivity of each C—H bond (tertiary:primary)	$37/1:63/9 = 37:7 = \text{ca. } 5:1$

● Bond strength is important in radical reactions

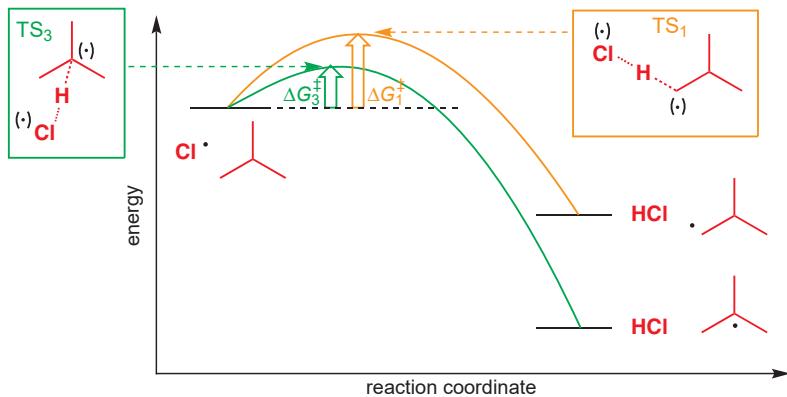
These reactions illustrate a key point about radical reactions—an important factor affecting selectivity is the strength of the bonds being formed and broken.

■ Bond strength is only a *guide* to selectivity in radical reactions. As we shall see shortly, it's not the only factor involved. Indeed, you've already seen *steric effects* in action when the  $\text{Br}^\bullet$  radical is added to the less hindered end of the alkene in the first radical reaction of this chapter, and you will later see how *frontier orbital effects* can operate too.

■ We use the symbol ( $\bullet$ ) to mean a partial radical; a radical that is partially centred on this atom. The symbols ( $-$ ) and ( $+$ ) are used to mean a similar thing when a charge is shared by more than one atom.

■ Of course our calculations involving bond energies only gave us values for  $\Delta H$ , not  $\Delta G$ , which is what this diagram represents. However, we can assume that the  $T\Delta S$  term in the relationship  $\Delta G = \Delta H - T\Delta S$  is relatively insignificant.

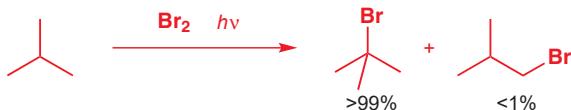
The rate of attack by  $\text{Cl}^\bullet$  on a tertiary C—H bond, then, is about five times the rate of attack by  $\text{Cl}^\bullet$  on a primary C—H bond. We said that this is because the formation of the tertiary radical is more exothermic than the formation of the primary radical. But the rate of a reaction depends not on  $\Delta H$  for that reaction but on the activation energy of the reaction; in other words, the energy needed to reach the transition state for the reaction. But we can still use the stability of the product radicals as a guide to the stability of the transition state because the transition state must have significant radical character.



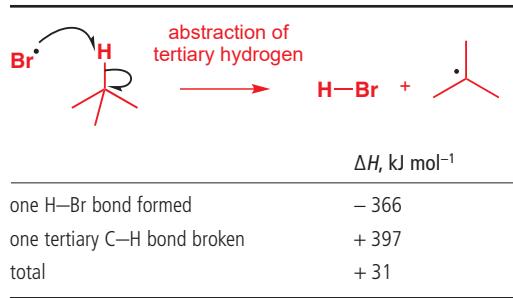
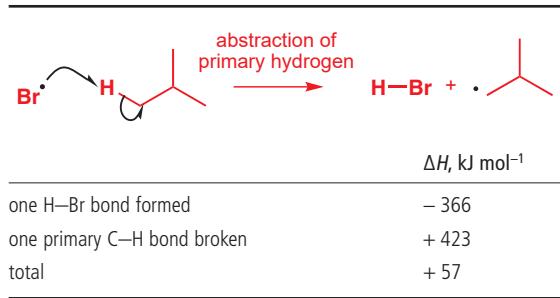
The energy diagram above illustrates this point. As the reactants ( $\text{Cl}^\bullet$  plus isobutane) move towards the products, they pass through a transition state ( $\text{TS}_1$  for formation of the primary radical,  $\text{TS}_3$  for formation of the tertiary) in which the radical character of the  $\text{Cl}^\bullet$  starting material is spread over both the Cl and the C centres. The greater stability of a tertiary radical compared with a primary one must be reflected to a lesser degree in these transition states: a radical shared between Cl and a tertiary centre will be more stable than a radical shared between Cl and a primary centre. The transition state  $\text{TS}_3$  for the reaction at the tertiary C—H bond is therefore of lower energy than the transition state  $\text{TS}_1$  for reaction at the primary C—H bond. In other words, the activation energy  $\Delta G_3^\ddagger$  is smaller than  $\Delta G_1^\ddagger$ , so reaction at the tertiary C—H bond is faster.

### Bromination of alkanes is more selective

Bromine will also halogenate alkanes, and it does so much more selectively than chlorine. For example, the following reaction yields *tert*-butyl bromide with less than 1% of the primary isomer.



In this case, the first step of the radical chain reaction, the abstraction of H by  $\text{Br}^\bullet$ , is endothermic for both the primary and tertiary hydrogen atoms, but more so for primary radical formation, so the tertiary radical is preferred.



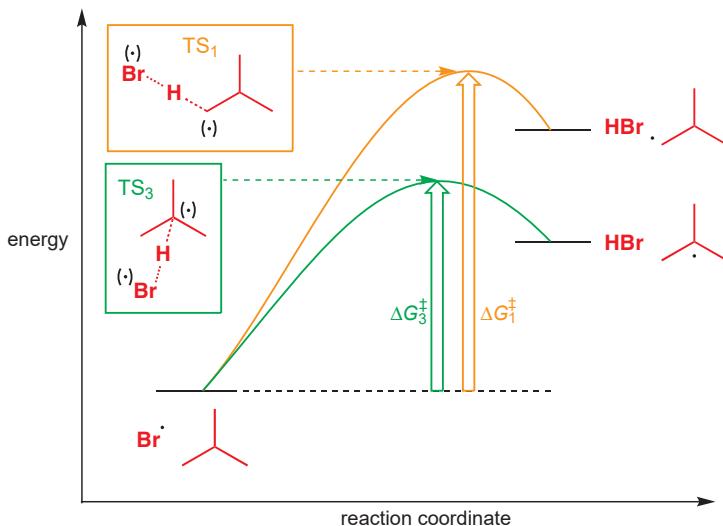
Of course, in both brominations and chlorinations the *overall* reaction is favourable because the second step—the halogenation of the alkyl radical—is significantly exothermic, by about 106  $\text{kJ mol}^{-1}$  for chlorination and about 83  $\text{kJ mol}^{-1}$  for bromination. The same is true for fluorination, but with fluorine this step is so exothermic that fluorination becomes dangerously explosive. Conversely, radical iodination is impossible because the final step is insufficiently exothermic to make up for the endothermic formation of an alkyl radical.

Why is bromination so much more selective than the chlorination of alkanes? This is a good example of the **Hammond postulate**, applied to real chemistry. Because the products of the first step of the bromination ( $\text{R}\cdot$  plus HBr) are higher in energy than the starting materials, the transition state must be similar in structure and energy to the radical being formed; the difference in energies of the primary and tertiary product radicals should therefore be markedly reflected in the different energies of the transition states  $\text{TS}_1$  and  $\text{TS}_3$ , and  $\Delta G_1^\ddagger$  will be significantly larger than  $\Delta G_3^\ddagger$ . For the chlorination reaction, the products were just slightly lower in energy than the starting materials, so the transition states for the two possible reactions both resembled the starting materials rather more and the products rather less. These are the same for both tertiary and primary hydrogen abstractions, of course, so the difference in energy of the product radicals exerts a less pronounced effect on the difference in energy of the transition states.

second step of a halogenation:  
always exothermic



The **Hammond postulate** gives information about the structure of transition states. It says that two states that interconvert directly (are directly linked in a reaction profile diagram) and that are close in energy are also similar in structure. So a transition state will be most like the starting material, an intermediate, or the product if it is close in energy to one of these observable structures.



## Allylic bromination

Because radical brominations are so selective, they can be used successfully in the laboratory to make alkyl bromides. There are relatively few ways of functionalizing an unfunctionalized centre, and radical allylic bromination is one of the most effective. We introduced this reaction in Chapter 24, where we contrasted the radical reactivity of  $\text{Br}_2$  towards alkenes (leading to an allyl bromide by hydrogen abstraction) with its ionic reactivity (leading to addition of bromine across the alkene). We can now look in a little more detail at the selectivities involved.

► We introduced radical bromination on p. 571.

► The way that NBS does this is explained on p. 573.

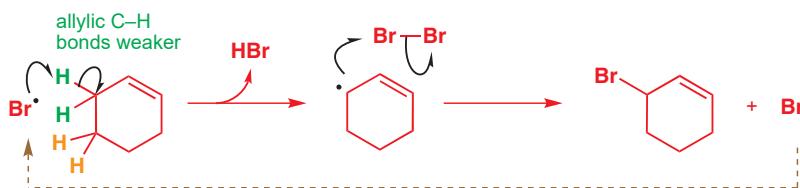
 Interactive mechanism for allylic bromination

■ These figures were determined in the gas phase, and here our reactions are in solution. Nonetheless, because solvation effects are more or less the same for all radicals, we expect the order of the bond strengths to remain the same in both phases.

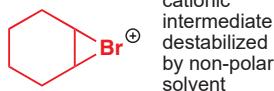
Here is a typical allylic bromination. NBS (*N*-bromosuccinimide) is used to form a small amount of Br<sub>2</sub> and to keep the Br<sub>2</sub> concentration low.



Photolysis of Br<sub>2</sub> initiates the reaction, which then propagates as shown below. The mechanism also illustrates the first aspect of selectivity: only a (green) allylic H atom is abstracted because an allylic C–H bond is considerably weaker than a secondary C–H bond (364 vs. 410 kJ mol<sup>-1</sup> from the table on p. 977).

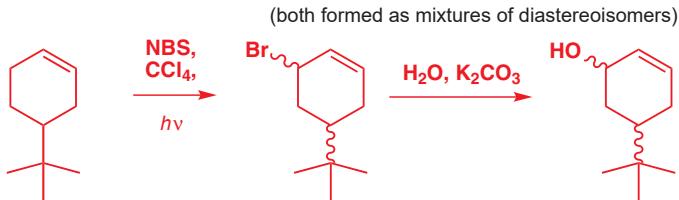


There is a problem with this reaction if bromine itself is used because an alternative radical addition reaction can compete with radical abstraction.



The first step of this competing addition reaction is reversible; the reaction is driven forward by the participation of a second molecule of bromine that traps the product alkyl radical. This side reaction can be prevented if the concentration of Br<sub>2</sub> in the reaction is kept very low, which is the role of NBS. The alternative competing polar addition of Br<sub>2</sub> to the alkene is likewise prevented with the low bromine concentration provided by NBS, although the non-polar solvent CCl<sub>4</sub> also disfavours the formation of the cationic bromonium ion intermediate.

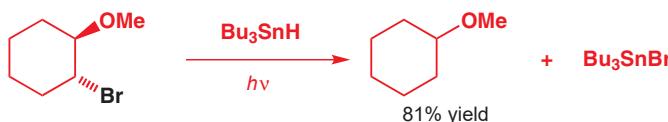
While radical halogenation of alkanes is used only rarely in the laboratory, radical allylic bromination of alkenes is a versatile and commonly used way of making allylic bromides. Nucleophilic substitution reactions can then be used to convert the bromide to other functional groups. For example, some chemists in Manchester needed to make the two diastereoisomers of 5-*tert*-butyl-cyclohex-2-en-1-ol to study their reactions with osmium tetroxide. *tert*-Butyl cyclohexene is readily available, so they used a radical allylic bromination to introduce the functional group in the allylic position, which they converted to a hydroxyl group using aqueous base. Steric effects also play a role here in the regioselectivity of the reaction: only the less hindered allylic hydrogen atoms further from the *tert*-butyl group are removed.



## Reversing the selectivity: radical substitution of Br by H

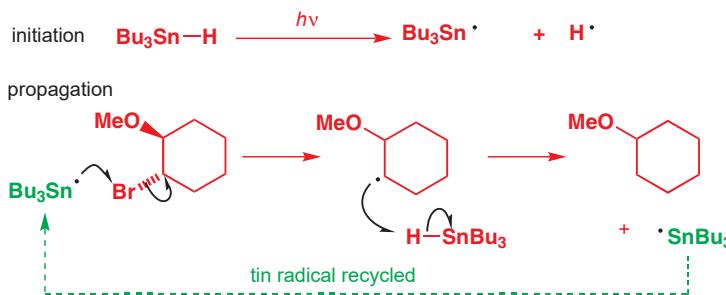
Radical substitution reactions can also be used to *remove* functional groups from molecules. A useful reagent for this (and, as you will see, for other radical reactions too) is tributyltin

hydride,  $\text{Bu}_3\text{SnH}$ . The Sn–H bond is weak and  $\text{Bu}_3\text{SnH}$  will react with alkyl halides to replace the halogen atom with H, producing  $\text{Bu}_3\text{SnHal}$  as a by-product.



→ We discussed the removal of functional groups, and why you might want to do it, in Chapter 23.

Clearly, for this reaction to be energetically favourable, the new bonds formed (Sn–Br and C–H) must be stronger than the old bonds broken (Sn–H and C–halogen). Look at this table of average bond energies and you will see that this is indeed so. The use of a tin hydride is crucial to this reaction: Sn–H bonds are weaker than Sn–Br bonds, while, for carbon, C–H bonds are stronger.  $\text{Bu}_3\text{SnH}$  is therefore an effective source of  $\text{Bu}_3\text{Sn}^\bullet$  radicals, and the  $\text{Bu}_3\text{Sn}^\bullet$  radical will abstract halogens, particularly I or Br, but also Cl, from organic halides, breaking a weak C–halogen (C–Hal) bond and forming a strong Sn–Hal bond. The complete mechanism of the reaction reveals a chain reaction.

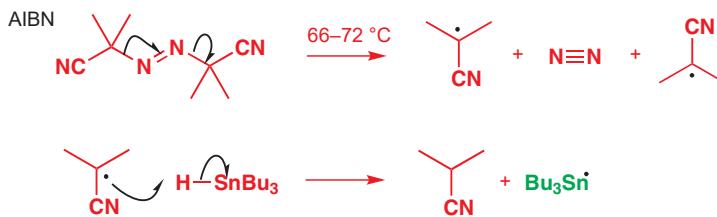


Bond	Representative bond energy, $\text{kJ mol}^{-1}$
C–Br	280
Sn–H	308
C–H	418
Sn–Br	552

Interactive mechanism for tin hydride reduction of alkyl halides

### Homolysis of $\text{Bu}_3\text{SnH}$ is promoted by the initiator AIBN

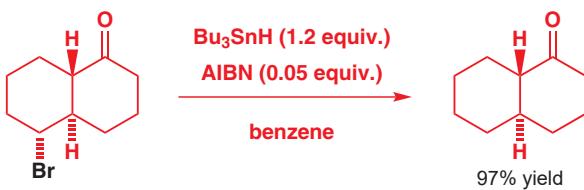
As you would imagine, the weakest C–Hal bonds are the easiest to cleave, so alkyl bromides are reduced more rapidly than alkyl chlorides, and alkyl fluorides are unreactive. With alkyl iodides and bromides, daylight can be sufficient to initiate the reaction, but with alkyl chlorides, and often with alkyl bromides as well, it is generally necessary to produce a higher concentration of  $\text{Bu}_3\text{Sn}^\bullet$  radicals by adding an initiator to the reaction. The best choice is usually AIBN, which you met earlier in the chapter (p. 972). This compound undergoes thermal homolysis above  $60^\circ\text{C}$  to give nitrile-stabilized radicals that abstract the hydrogen atom from  $\text{Bu}_3\text{SnH}$ .



→ We used peroxides as initiators of the addition of H–Br to alkenes on p. 971.

Why use AIBN as an initiator; why not a peroxide? Since we want to cleave only a weak Sn–H bond, we can get away with using a relatively unreactive nitrile-stabilized radical. Peroxides, on the other hand, generate  $\text{RO}^\bullet$  radicals. These are highly reactive and will abstract hydrogen from almost any organic molecule, not just the weakly bonded hydrogen atom of  $\text{Bu}_3\text{SnH}$ , and this would lead to side reactions and lack of selectivity. AIBN is needed only in sufficient quantities to be an initiator of the reaction; it is the  $\text{Bu}_3\text{SnH}$  that provides the hydrogen atoms that end up in the product, so usually you need only 0.02 to 0.05 equivalents of AIBN and a slight excess (1.2 equivalents) of  $\text{Bu}_3\text{SnH}$ .

The bond energy of  $\text{H}-\text{CH}_2\text{CN}$  is only  $360 \text{ kJ mol}^{-1}$ ; a tertiary C–H bond next to a CN group should be even weaker.  
Bond energy of O–H =  $460 \text{ kJ mol}^{-1}$ ; few C–H bonds are stronger than  $440 \text{ kJ mol}^{-1}$ .



## Carbon–carbon bond formation with radicals

You have now met these examples of radical chain reactions:

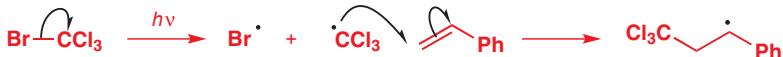
1. radical addition of halogens to double bonds
2. radical substitution of hydrogen by halogens, or of halogens by hydrogen.

You have seen how the selectivity of these reactions depends upon the bond strengths of the bond being formed or broken. Until about 1975, these reactions, with a few exceptions, were all that were expected of radicals. Since that date, however, the use of radicals in synthetic chemistry has increased tremendously, to the point where complex ring structures such as those of the natural product hirsutene or the steroids can be made from simple acyclic precursors in one radical-promoted step.

What has made this all possible is that chemists have learned how to understand the selectivity of radical reactions to such a degree that they can design starting materials and reagents to define precisely the bonds that will break and form during the reactions. We shall now go on to look at the most important consequence of this ability to control radical reactions: they can be used to make carbon–carbon bonds.

The radical reaction in the margin forms a new carbon–carbon bond. The mechanism is quite similar to that of the very first radical reaction we showed you, right at the beginning of the chapter. Now, with your additional appreciation of the role of bond strength in the selectivity of radical reactions, you should be able to understand why each step proceeds in the way that it does.

First the weakest bond, C–Br, is broken by the light being shone on to the reaction. Two radicals form,  $\text{CCl}_3^\cdot$  and  $\text{Br}^\cdot$ , and it is the  $\text{CCl}_3^\cdot$  that adds to the (less hindered) unsubstituted end of the alkene to produce a (more stable) secondary benzylic radical.



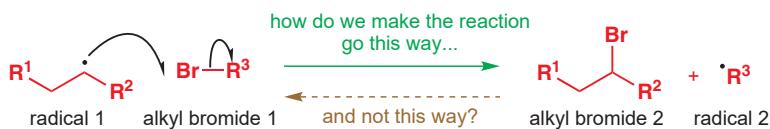
This radical abstracts a Br atom from the  $\text{BrCCl}_3$ , breaking the (weakest) C–Br bond, forming the product, and regenerating  $\cdot\text{CCl}_3$ , which adds to another molecule of alkene. Notice that the carbon-centred radical abstracts  $\text{Br}^\cdot$  and not  $\cdot\text{CCl}_3$  from  $\text{BrCCl}_3$ —to abstract  $\cdot\text{CCl}_3$  would require a radical substitution at carbon—remember, radicals want the easy pickings from the front of the display; they don't go nosing round the back to see if there's anything better to be had.



This reaction works quite well, giving 78% of the product, but it relies on the fact that the starting material,  $\text{BrCCl}_3$ , has an unusually weak C–Br bond (the  $\cdot\text{CCl}_3$  radical is highly stabilized by those three chlorine atoms). You can't use most other alkyl bromides for a number of reasons, not least of them being that the product is also an alkyl bromide and, without the selectivity provided by the  $\text{CCl}_3$  group, the result would be a mixture of polymers. The problem is that we want the product radical to abstract Br from the starting alkyl bromide to make

It is mainly this step that produces the  $\cdot\text{CCl}_3$  that undergoes addition to the alkene—the initial photolysis, of course, produces both  $\text{Br}^\cdot$  and  $\cdot\text{CCl}_3$ , either of which could add, but, once the radical chain has been initiated, only  $\cdot\text{CCl}_3$  is reproduced.

a new alkyl bromide and a new starting radical, and there is no energetic driving force behind this transformation.



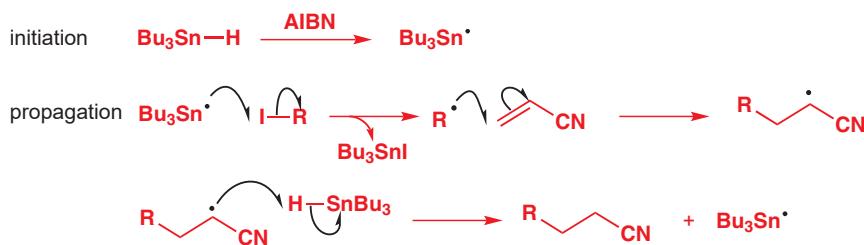
For a way of overcoming this problem, let's go back to the reaction we looked at a few pages ago, the dehalogenation of alkyl halides by  $\text{Bu}_3\text{SnH}$ . The mechanism involves formation of an alkyl (carbon-centred) radical by abstraction of Br by  $\text{Bu}_3\text{Sn}^\bullet$ . This alkyl radical then just abstracted H $^\bullet$  from  $\text{Bu}_3\text{SnH}$ .



Is it not possible to use this alkyl radical more constructively, and encourage it to react with another molecule (an alkene, say, as  $^\bullet\text{CCl}_3$  did)? The answer is a qualified yes: look at this reaction:



We have added a carbon-centred radical to an alkene in a radical chain reaction! Here is the mechanism:



Interactive mechanism for radical addition of an alkyl group to acrylonitrile

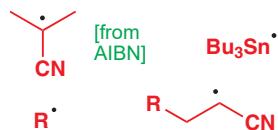
Something important has happened here: the product radical no longer has to abstract the halogen from the starting material, but instead has to abstract H from  $\text{Bu}_3\text{SnH}$ ; it is the  $\text{Bu}_3\text{Sn}^\bullet$  thus formed that then regenerates the starting radical. The driving force is provided by formation of C–H at the expense of Sn–H and then Sn–Br at the expense of C–Br.

The use of tin hydrides increases the power of radical reactions in organic synthesis tremendously, and all of the steps in these radical chain processes have been studied in great detail because of the importance of the reactions. We won't dwell excessively on these details, but we need to go back and re-examine some points about this reaction because there are some further subtleties that you need to understand. Bear in mind that we have four radicals all in the reaction mixture at the same time. Yet each reacts with its chosen partner, forsaking all others.

Let's take each type of radical in turn, and look at its selectivity. Clearly bond strength has something to do with this, but how do you explain the opposing selectivities of R $^\bullet$  and the nitrile-stabilized radicals? We shall see that the origins of the selectivities impose some restrictions on the type of starting material that can be used for these C–C bond-forming reactions.

► We explained on p. 991 how these same favourable thermodynamics drove the  $\text{Bu}_3\text{SnH}$ -promoted reduction of alkyl halides.

four radicals in the mixture:



Radical	Reacts like this	Does not react like this
$\text{Bu}_3\text{Sn}^\bullet$		
$\text{R}^\bullet$		
$\text{R}-\text{CH}_2-\cdot-\text{CN}$		
$\text{NC}-\dot{\text{C}}(\text{H})-\text{CH}_2-$		

For the **tin radical**,  $\text{Bu}_3\text{Sn}^\bullet$ , there is a choice of reaction partners: we need it to abstract the halide from the starting material, but it could alternatively add to the alkene. The Sn–C bond is relatively weak, so addition to the alkene becomes a significant reaction only if:

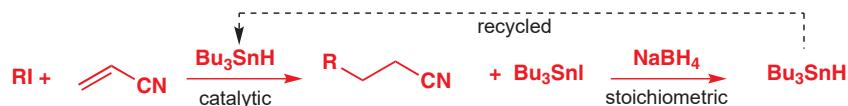
- there is a large excess of alkene present, and
- the starting alkyl halide is relatively unreactive. This means that only alkyl bromides and iodides can be used effectively to form carbon–carbon bonds; alkyl chlorides are just too unreactive.

The contrasting reactivity of the **alkyl radical  $\text{R}^\bullet$**  and the **nitrile-containing radicals** needs a little more analysis, and we will look at how both concentration and electronics affect their selectivities.

### Concentration effects

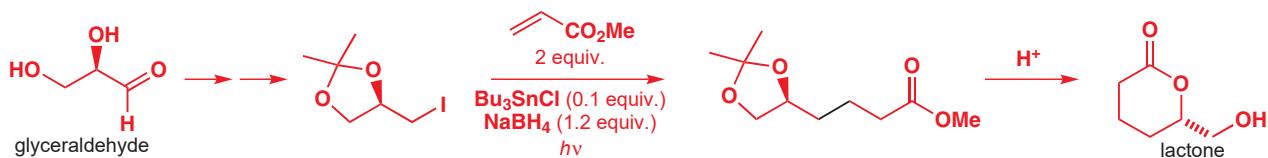
You know that  $\text{R}^\bullet$  is perfectly capable of abstracting H from  $\text{Bu}_3\text{SnH}$  because that is what happened in the dehalogenation reaction on p. 991, but here a different reaction happens: addition to the alkene. In fact, the rate *constant* for reaction of  $\text{R}^\bullet$  with  $\text{Bu}_3\text{SnH}$  is about the same as that for reaction with acrylonitrile ( $\text{CH}_2=\text{CHCN}$ ), so the only way in which good yields can be obtained is by ensuring that the concentration of acrylonitrile is always at least 10 times that of the tin hydride. The difference in rates will then be sufficient to give 10 times as much addition to the alkene as reduction by the tin hydride. Too much acrylonitrile in the reaction mixture causes problems with side reactions, so a good way of achieving this is to add the tin hydride very slowly during the reaction—often a device known as a syringe pump is used for this. Of course, for complete reaction, a whole equivalent of hydride is necessary, but this can be added over a period of hours.

An elegant alternative is to use a technique conceptually similar to the use of NBS to provide a low concentration of  $\text{Br}_2$  for radical allylic substitution. Instead of adding one equivalent of  $\text{Bu}_3\text{SnH}$ , a catalytic amount (usually 0.1–0.2 equivalents) of  $\text{Bu}_3\text{SnCl}$  is added at the beginning of the reaction, with 1 equivalent of  $\text{NaBH}_4$ .  $\text{NaBH}_4$  will reduce  $\text{Bu}_3\text{SnHal}$  to  $\text{Bu}_3\text{SnH}$ , so about 0.1 equivalent of  $\text{Bu}_3\text{SnH}$  is formed immediately. With each cycle of the chain reaction, a molecule of this  $\text{Bu}_3\text{SnH}$  is converted to  $\text{Bu}_3\text{SnBr}$ , which  $\text{NaBH}_4$  can reduce back to  $\text{Bu}_3\text{SnH}$ . Only as much  $\text{Bu}_3\text{SnH}$  is produced as is needed because the rate of production is limited by the rate of reaction.



This method was used in the following example, in which an enantiomerically pure lactone, a useful synthetic building block, was made from naturally occurring glyceraldehyde.

■ A useful alternative to  $\text{NaBH}_4$  as a reducing agent, particularly when there are reactive carbonyl groups in the molecule, is  $\text{NaCnBH}_3$ , which still reduces  $\text{Bu}_3\text{SnHal}$  but will not touch aldehydes or ketones (see Chapter 23).



### Frontier orbital effects

The second key to success in making sure that the alkyl radical behaves well is to use a reactive radical trap. In fact, this is a major limitation of intermolecular radical carbon–carbon bond-forming reactions: for the trapping of alkyl radicals only electrophilic alkenes (attached to electron-withdrawing groups such as  $-\text{CN}$ ,  $-\text{CO}_2\text{Me}$ , and  $-\text{COMe}$ ) will do. This is a limitation, but nonetheless cyclohexyl iodide adds to all these alkenes with the yields shown and the rate of addition to most of these alkenes is  $10^3$  to  $10^4$  times that of addition to 1-hexene.



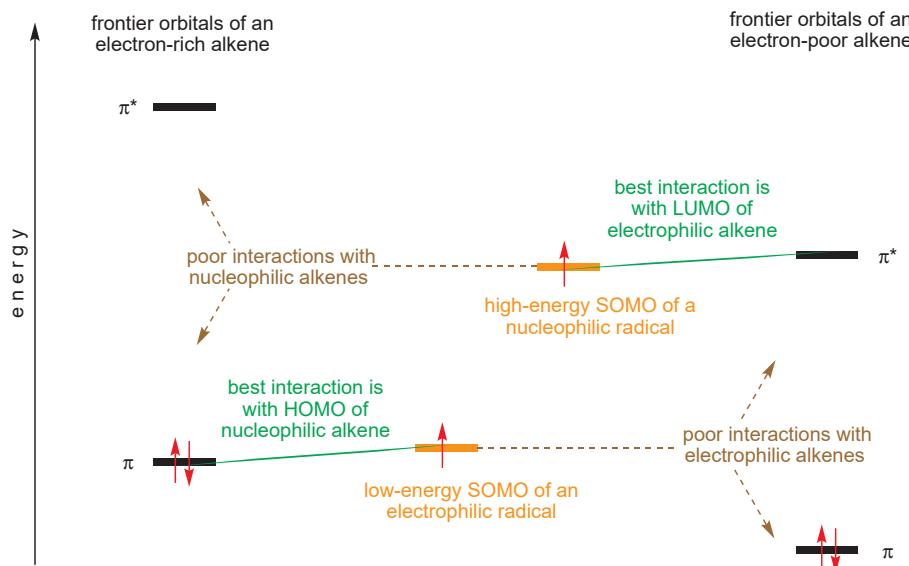
Alkene	% yield	Alkene	% yield
$\text{CH}_2=\text{CN}$	95	$\text{CH}_2=\text{C}(=\text{O})\text{CH}_3$	85
$\text{CH}_2=\text{CHCN}$	86	$\text{CH}_2=\text{C}(=\text{O})\text{OMe}$	85
$\text{CH}_2=\text{CH}-\text{CH}_2\text{CN}$	72	$\text{CH}_2=\text{CHPh}$	83
$\text{CH}_2=\text{C}(=\text{O})\text{H}$	90	$\text{CH}_2=\text{CCl}_3$	87

To explain why, we have to go back to our analysis (on p. 978) of the electronic structure of radicals and the energy of SOMOs. We said there that, while both electron-withdrawing groups and electron-donating groups will stabilize radicals, electron-withdrawing groups tend to lower the energy of the SOMO, while electron-donating groups tend to raise the energy of the SOMO.

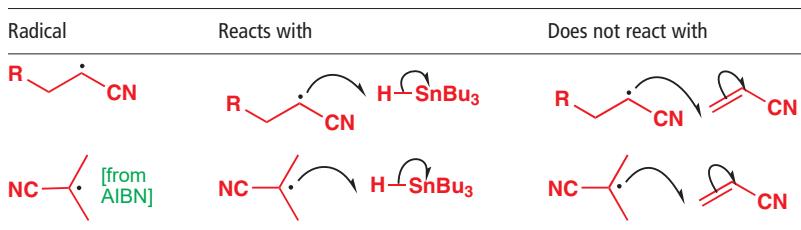
#### ● Electrophilic and nucleophilic radicals

- Low-energy SOMOs are more willing to accept an electron than to give one up; radicals adjacent to electron-withdrawing groups are therefore *electrophilic*.
- High-energy SOMOs are more willing to give up an electron than to accept an electron; radicals adjacent to electron-donating groups are therefore *nucleophilic*.

Hence the preferred reactivity of these alkyl radicals: they are relatively nucleophilic and therefore prefer to react with electrophilic alkenes. Reaction between a nucleophilic alkyl radical and an unfunctionalized (and therefore nucleophilic) alkene is much slower. Similarly, radicals adjacent to electron-withdrawing groups do not react well with electrophilic alkenes. We can represent all this on an energy level diagram.



We can now consider the third type of radical in the reaction mixture highlighted on p. 993—the **nitrile-stabilized alkyl radicals**. The diagram above explains the third aspect of radical chemoselectivity in the reaction: why both the product radical and the radicals produced by AIBN choose to react with  $\text{Bu}_3\text{SnH}$  and not with acrylonitrile. These radicals are electrophilic—they have an electron-withdrawing nitrile group attached to the radical centre, so reaction with an electron-poor alkene is slow.

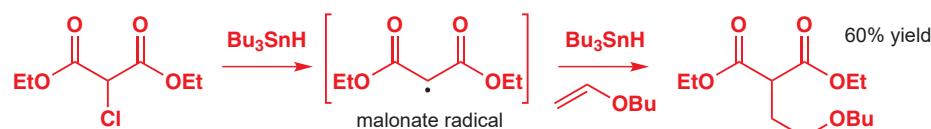


#### ● Summary of requirements for the successful use of the tin method

$\text{Bu}_3\text{SnH}$	must be added or generated slowly
R-X starting material	must contain a weak C-X bond (C-I or C-Br)
radical trap	must be an electrophilic alkene must be present in a concentration at least 10 times that of $\text{Bu}_3\text{SnH}$

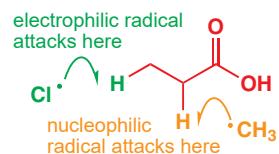
### Electrophilic radicals

Having seen the energy diagram above, you will not be surprised to learn that the malonate radical adds readily not to electrophilic alkenes, but to nucleophilic alkenes, such as this vinyl ether, which carries an electron-donating oxygen substituent. The malonate radical is electron deficient; it has a low-energy SOMO which interacts best with the relatively high-energy HOMO of the electron-rich, nucleophilic alkene.



■ Notice that this reaction works even though a C-Cl bond needs to be broken to generate the radical. Usually only C-I and C-Br bonds can be used. However, this is a very weak C-Cl bond because the radical produced is so stable. This electrophilic radical can also be formed by H abstraction and by oxidation.

This difference in reactivity applies to non-carbon-centred radicals too. For example, the methyl radical  $\cdot\text{CH}_3$  and the chlorine radical  $\text{Cl}\cdot$  will both abstract a hydrogen atom from propionic acid. As you would expect, the methyl radical abstracts the hydrogen atom from next to the carbonyl group to form a carbonyl-stabilized radical. Perhaps surprisingly (in view of what we said earlier about the selectivity of radical chlorinations), the chlorine radical abstracts a hydrogen atom from the terminal methyl group of the acid, despite the fact that this C–H bond is stronger. The reason has to be to do with HOMO–LUMO interactions. The methyl radical is nucleophilic, with a high-energy SOMO. It therefore attacks the C–H bond with the lowest LUMO, in other words,  $\alpha$  to the carbonyl group. The chlorine atom, on the other hand, is electrophilic: it has a low-energy SOMO (because it is an electronegative element) and attacks the C–H bonds of the terminal methyl group because they have the highest-energy HOMO. Chlorination of functionalized compounds is not as straightforward as that of simple alkanes!

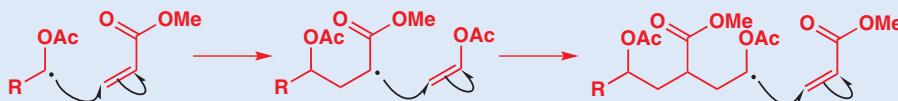


### Copolymerization

Radical chain reactions are particularly suited to the synthesis of polymers, and there is one example of a polymerization that is worth including here since it demonstrates very nicely the effect of electron-withdrawing or -donating substituents on radical reactivity. When a mixture of vinyl acetate and methyl acrylate is treated with a radical initiator, a rather remarkable polymerization takes place. The polymer produced contains *alternating* vinyl acetate and methyl acrylate monomers along the length of its chain.



The mechanism of the reaction shows you why. The nucleophilic radical from vinyl acetate (adjacent to filled  $n$  orbital of OAc; high-energy SOMO) prefers to add to the electrophilic alkene (the acrylate). The new radical (adjacent to the empty  $\pi^*$  orbital of CO<sub>2</sub>Me; low-energy SOMO) is electrophilic and prefers to add to nucleophilic alkene (the vinyl acetate). This produces a new nucleophilic radical, which again prefers to add to the electrophilic alkene, and the whole cycle occurs repeatedly.



The radical produced by addition to vinyl acetate is nucleophilic, so it adds to methyl acrylate; the radical produced by addition to methyl acrylate is electrophilic, so it adds to vinyl acetate. This reaction is a clear demonstration of the power of frontier orbital theory to explain the reactivity of organic molecules—it would be hard to come up with any other convincing explanation.

Interactive displays of common polymer structures

There is more on polymerization in the online chapter of that name

## The reactivity pattern of radicals is quite different from that of polar reagents

The first reaction that you met in this book, in Chapter 6, was nucleophilic addition to a carbonyl group. Yet we have shown you no examples of radicals adding to carbonyl groups. This typical reaction of polar reagents is really quite rare with radicals.

In Chapter 8 we introduced the concept of  $pK_a$  in which we saw acids and bases exchanging protons. Among the strongest organic acids are those containing O–H bonds. Yet you have seen no radical reactions in which an O–H bond is broken. Carbon acids tend to be much weaker—yet you've seen plenty of examples of C–H bonds being broken by radical attack.

In Chapter 15 we introduced nucleophilic substitution at saturated carbon, using as an example some alkyl bromides. Now, radicals do react with alkyl halides—but not at carbon! Instead they abstract the halogen, leaving an alkyl radical.

The difference in reactivity between, say, organolithiums and radicals, both of them highly reactive, is nicely illustrated by the way in which they react with enones.



► For the earlier discussions on hard and soft see p. 357 and 506.

► There is a striking illustration of the mismatch between the reactivity of bonds in a simple molecule and the strength of those bonds on p. 207.

We used the terms *hard* and *soft* in Chapters 15 and 22. From all these reactions it's evident that radicals are very soft species: their reactions are driven not at all by the charge density on an atom but by the strength of the bonds being attacked and by the coefficients and energies of the frontier orbitals. O–H bonds are easily broken by strong bases and C=O bonds attacked by strong nucleophiles because of the polarization in the O–H and C=O bond. O–H and C=O bonds are strong, and radicals care nothing for polarization, so radicals prefer to attack the much weaker C–H bonds which (because they are unpolarized) are often inert towards ionic reagents.

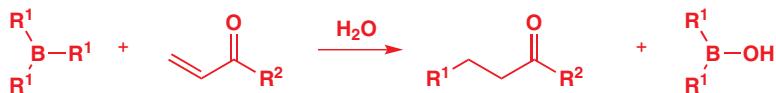
### ● Summary of typical reactivity patterns

With	Polar nucleophiles typically react like this	Radicals typically react like this
unsaturated C=O compounds		
X–H bonds		
alkyl halides		

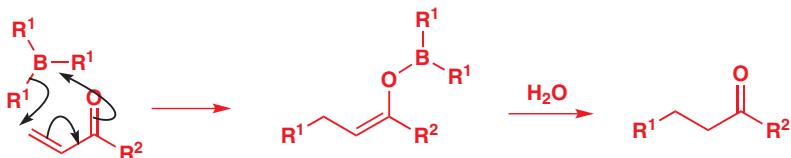
## Alkyl radicals from boranes and oxygen

Although the tin hydride + alkyl halide method is very efficient, tin compounds are falling out of favour because of their toxicity. The reaction between boranes and oxygen provides a simple alternative, and many of the reactions carried out formerly using the tin hydride radical chemistry of pp. 993–997 can now be done using the method we are about to describe.

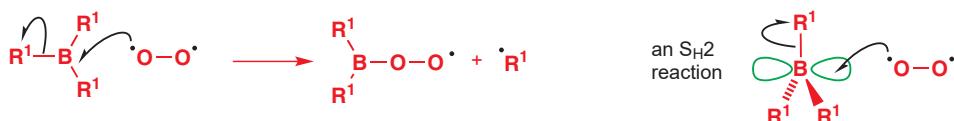
Mixing trialkylboranes with  $\alpha,\beta$ -unsaturated carbonyl compounds in the presence of water gives conjugate addition of one of the alkyl groups from the boron. The carbonyl compound can be an aldehyde ( $R^2 = H$ ) or a ketone ( $R^2 = \text{alkyl}$ ).



There was a dispute at first as to whether this was a radical reaction or an ionic reaction. The ionic reaction might have been a kind of pericyclic reaction with the intermediate boron enolate being hydrolysed by the water.

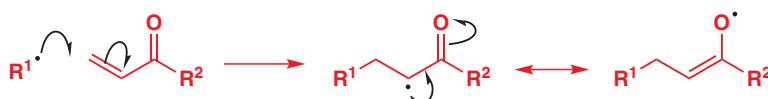


However, H. C. Brown discovered that the reaction was completely inhibited by just 5% of the stable radical galvinoxyl (shown on p. 975), known to be an efficient scavenger for radicals. But where were the radicals coming from? Further experiments showed that small amounts of oxygen were needed to make the reaction work. As you saw in Chapter 3, oxygen is a triplet diradical and displaces alkyl radicals from the trialkyl borane. This reaction looks at first like an  $S_N2$  and is called an  $S_H2$  (second order homolytic displacement), but in reality the oxygen adds to the empty p orbital of planar trigonal boron to release an alkyl radical and start the chain reaction.

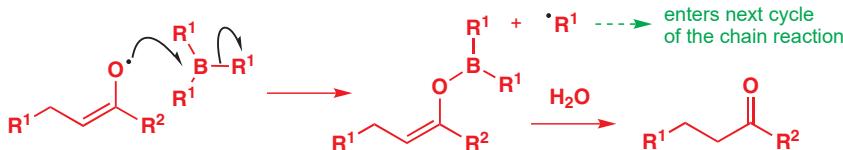


Explanation of the term 'triplet' in this context will be found in Chapter 38, p. 1010.

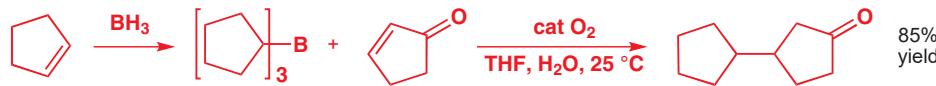
The alkyl radical now adds to the enone to give a delocalized intermediate that can be represented as a carbon- or oxygen-centred radical.



The chain is completed by displacement of another alkyl radical from a trialkylborane at oxygen by the delocalized radical and the formation of the same boron enolate proposed in the ionic reaction. This alkyl radical adds in its turn to the enone, and the boron enolate which forms is hydrolysed to the ketone product. Only small amounts of oxygen are needed to initiate the chain and it is not surprising that the air around the reaction mixture is enough to start a typical reaction. The water (which is inert to radicals, so can be present in the reaction mixture) again hydrolyses the boron enolate.



By combining a hydroboration step, which forms the borane, with the radical addition it is possible to carry out transformations such as the one below.



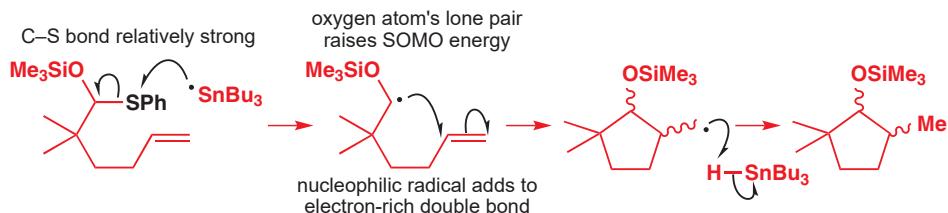
## Intramolecular radical reactions are more efficient than intermolecular ones

All of the reactions you have met so far involve radical attack of one molecule on another. We've pointed out some of the drawbacks when C–C bonds are made in this way: the radical trap has to be activated (that is, electrophilic to capture nucleophilic radicals) and must often be present in excess, and the radical starting material must contain very weak C–X bonds (such as C–Br, C–I). The requirements are much less stringent, however, if the radical reaction is intramolecular. For example, this reaction works:



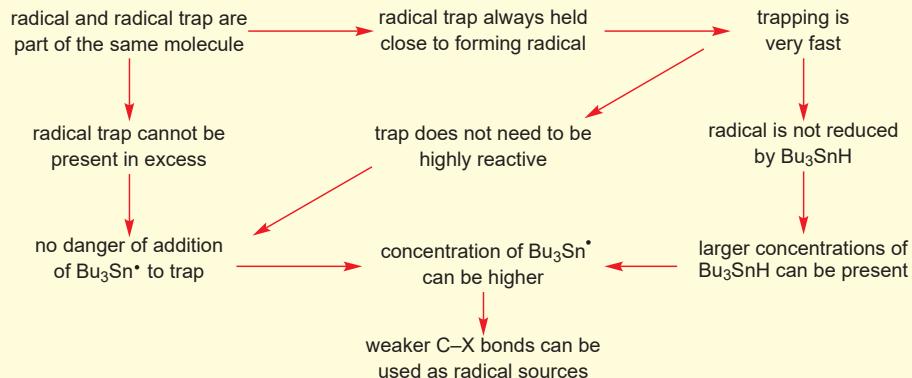
Notice that the double bond is not activated: in fact, it is nucleophilic, and the reaction still works even though the radical is also substituted with an electron-donating group. The C–S bond that is broken is also relatively strong, yet nonetheless a high yield of product is obtained. Why should this be so? What difference does it make that the reactions are intramolecular?

 Interactive mechanism for intramolecular radical cyclization

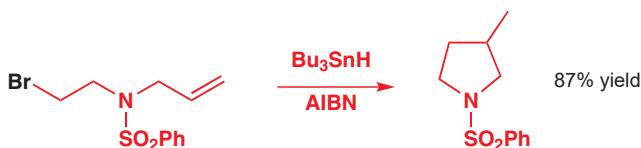


The key is that the intramolecular cyclization of the radical is now enormously favoured over other possible courses of action for the radical. Remember that when we were carrying out radical reactions *intermolecularly*, addition to the radical trap was encouraged by increasing the concentration of radical trap and decreasing the concentration of  $\text{Bu}_3\text{SnH}$  to avoid radical reduction. For *intramolecular* reactions, the double bond that acts as the radical trap is always held close to the radical, and cyclization takes place extremely rapidly, even on to unactivated double bonds. The hydride donor ( $\text{Bu}_3\text{SnH}$ ) doesn't get a look in, and can be present in higher concentrations than would otherwise be possible. Moreover, as there is only one equivalent of radical trap, and the trap need not be highly reactive, there is little danger of high concentrations of  $\text{Bu}_3\text{Sn}^\bullet$  reacting with it, so the concentration of  $\text{Bu}_3\text{Sn}^\bullet$  can build up to levels where the rate of abstraction of groups like Cl, SPh, and SePh is acceptable, despite their stronger C–X bonds.

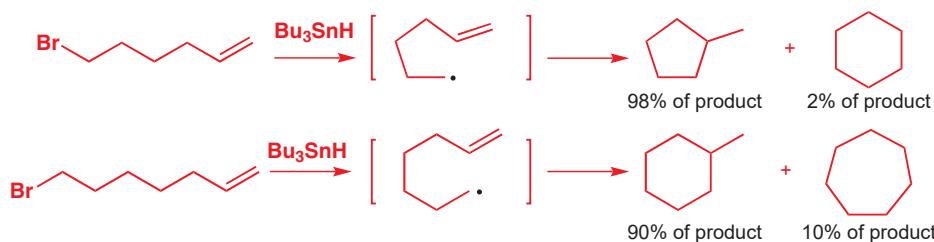
### ● Why are intramolecular radical reactions so good?



For all these reasons, intramolecular radical reactions are very powerful, and are often used to make five-membered rings.



It is possible to make other ring sizes also, but the range is rather limited. Because of ring strain, three- and four-membered rings cannot be formed by radical reactions. Otherwise, smaller rings form faster than larger ones: look at these selectivities.



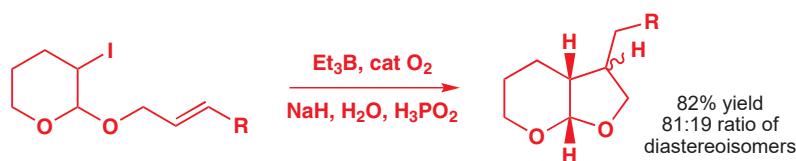
Interactive mechanism for radical ring closures

The preference for formation of a smaller ring is a very powerful one: in this reaction, the five-membered ring forms and not the six-membered one, even though cyclization to give a six-membered ring would also give a more stabilized radical.

► Baldwin's rules, describing the formation of different ring sizes, were described in Chapter 31, p. 810. They apply to radical reactions and ionic reactions equally well.

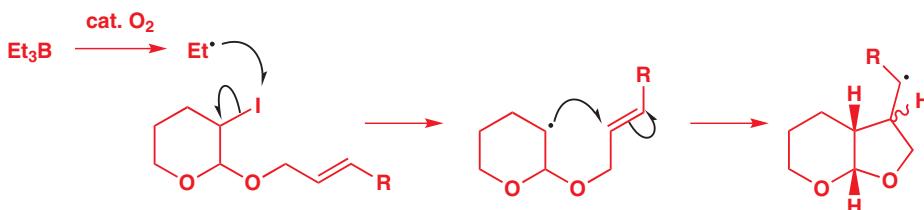


We said earlier that the toxicity of tin poses some problems, so it is useful that the borane–oxygen method (p. 998) works well for initiating radical cyclizations too. It is not necessary to incorporate boron into the starting material, since a combination of Et<sub>3</sub>B, O<sub>2</sub>, and hypophosphorous acid, H<sub>3</sub>PO<sub>2</sub>, can generate a radical from a halide which will cyclize in the same way as the tin-promoted examples you have just seen. Once again, a five-membered ring is preferred to the alternative six-membered ring.

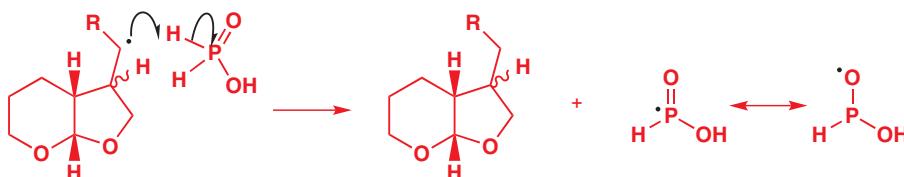


Notice that the ethyl groups from Et<sub>3</sub>B are not incorporated into the product. The displacement of Et<sup>•</sup> from Et<sub>3</sub>B initiates the chain reaction by abstracting the iodine atom from the starting material. The radical cyclizes to give a five-membered ring, as expected. A *cis* ring junction is inevitable because of the acetal ‘tether’.

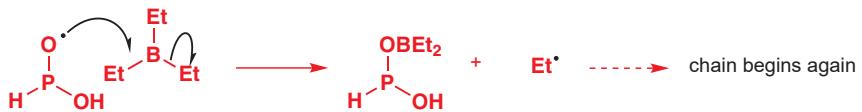
► This type of stereochemical control is discussed in Chapter 32.



The product radical has to collect a hydrogen from somewhere, and this is the role of the hypophosphorous acid. Abstraction of H gives a radical that can be drawn either as P-centred or O-centred.



The chain is finally completed by a hydrogen abstraction from  $\text{H}_3\text{PO}_2$ , which gives a radical that attacks the borane, just like oxygen did in the initiation step. A new ethyl radical is generated, which starts the cycle again.



## Looking forward

Radicals are important because they react in ways difficult to achieve with anions and cations, and show usefully different selectivity. Although radical reactions are generally less important than ionic reactions, environmental and biological radical reactions are remarkably common in an atmosphere that is 20% oxygen diradical. Diradicals will feature to a greater extent in the next chapter, in which we move on from carbon atoms carrying seven valence electrons to carbon atoms carrying only six valence electrons, called *carbenes*.

## Further reading

A basic introduction is *Radical Chemistry: The Fundamentals*, J. Perkins, Oxford Primer, OUP, Oxford, 2000. *Reactive Intermediates*, C. J. Moody and G. H. Whitham, Oxford Primer, OUP, Oxford, 2001, has a section on radicals.

The evidence that the McMurry reaction happens on a metal surface is quite nice, though, and if you're interested you can read McMurry's own account of it in *Accounts of Chemical Research*, 1983, **16**, 405 and J. E. McMurry, *Chem. Rev.*, 1989, **89**, 1513.

There are a couple of recipes in B. S. Furniss, A. J. Hannaford, P. W. G. Smith, and A. T. Tatchell, *Vogel's Textbook of Practical*

*Organic Chemistry*, Longman, 5th edn, 1989, pp. 576–579 that give examples of the use of NBS and dibenzoyl peroxide.

The borane-oxygen method of making radicals is reviewed by C. Ollivier and P. Renaud in *Chemical Reviews*, 2001, **101**, 3415. In common with most *Chemical Reviews*, this is a long scholarly article but reviews like this are essential to chemists wanting to know about a new reagent, method, or synthesis.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 卡宾的合成与反应

## 联系

### 基础

- Energy profile diagrams ch12
- Elimination reactions ch17
- Main group chemistry ch27
- Controlling stereochemistry ch14 & ch31–ch33
- Diastereoselectivity ch33
- Heterocycles ch29 & ch30
- Pericyclic reactions ch34 & ch35
- Rearrangements ch36
- Radicals ch37

### 目标

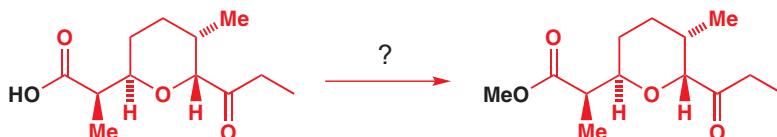
- Carbenes are neutral species with only six electrons
- Carbenes can have paired or unpaired electrons
- Carbenes are normally electrophilic
- Typical reactions include insertion into C=C bonds
- Insertion into C–H and O–H bonds is possible
- Intramolecular insertion is stereospecific
- Carbenes rearrange easily
- Carbenes are useful in synthesis
- Ruthenium–carbene complexes undergo metathesis reactions

### 展望

- Determination of mechanism ch39
- Organometallic chemistry ch40

## Diazomethane makes methyl esters from carboxylic acids

In 1981, some chemists in Pennsylvania needed to convert this carboxylic acid into its methyl ester as part of the synthesis of an antibiotic compound. What reagent did they choose to do the reaction?



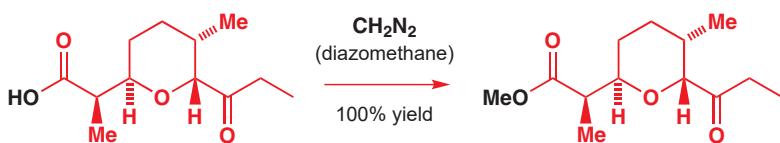
You remember, of course, that esters can be made from carboxylic acids and alcohols under acid catalysis, so you might expect them to use this type of method. On a small scale, it's usually better to convert the acid to an acyl chloride before coupling with an alcohol, using pyridine (or DMAP) as a base; this type of reaction might have been a reasonable choice too.



But, in fact, they chose neither of these methods. Instead, they simply treated the carboxylic acid with a compound called diazomethane,  $\text{CH}_2\text{N}_2$ , and isolated the methyl ester.

Acyl chlorides are made from carboxylic acids with either thionyl chloride or oxalyl chloride. Look back at Chapter 10 if you need reminding of any of these reactions.

■ You might like to think about why the alternatives would not be so suitable in this case.



Diazomethane,  $\text{CH}_2\text{N}_2$ , is a rather curious compound that has to be drawn as a dipole. There are several different ways of expressing its structure.

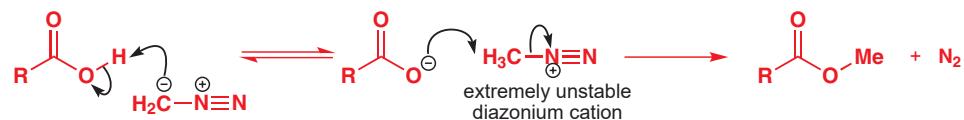
■ You've met other molecules like this—neutral compounds where we have to write charges to account for electrons correctly: carbon monoxide is one, and so are nitro compounds and the 1,3-dipoles you met in Chapter 34.

Interactive mechanism for methylation of carboxylic acid with diazomethane

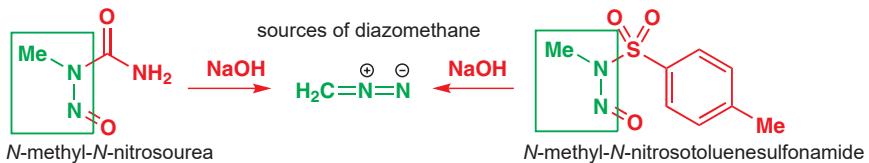
Conveniently, solutions containing diazomethane are yellow, so the reaction is **self-titrating**—as the carboxylic acid reacts, the yellow diazomethane is removed, but as long as excess diazomethane remains the yellow colour persists.



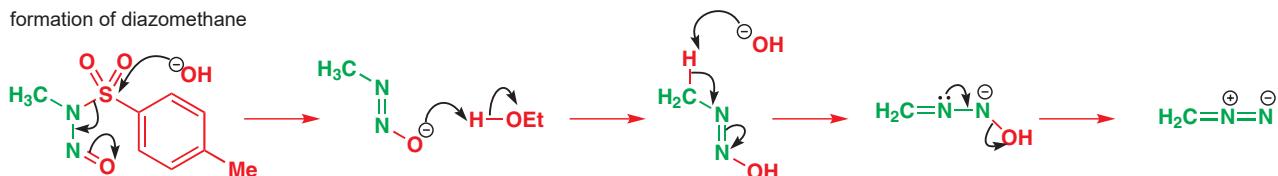
Diazomethane methylates carboxylic acids because carboxylic acids readily protonate it, giving an extremely unstable diazonium cation. This compound is desperate to lose  $\text{N}_2$ , the world's best leaving group, and so it does, with the  $\text{N}_2$  being substituted by the carboxylate anion. The carboxylate anion is in exactly the right position to carry out the  $\text{S}_{\text{N}}2$  reaction shown below.



Diazomethane methylation is a good way of making methyl esters from carboxylic acids on a small scale because yields are excellent and the only by-product is nitrogen. However, there is a drawback: diazomethane has a boiling point of  $-24^\circ\text{C}$ , and it is a toxic and highly explosive gas. It therefore has to be used in solution, usually in ether; the solution must be dilute, because concentrated solutions of diazomethane are also explosive. It is usually produced by reaction of *N*-methyl-*N*-nitrosourea or *N*-methyl-*N*-nitrosotoluenesulfonamide with base, and distilled out of that reaction mixture as an azeotrope with ether, straight into a solution of the carboxylic acid.



The mechanism of the reaction that forms diazomethane is shown below. The key step is base-catalysed elimination, although the curly arrows we have to draw to represent this are rather tortuous!



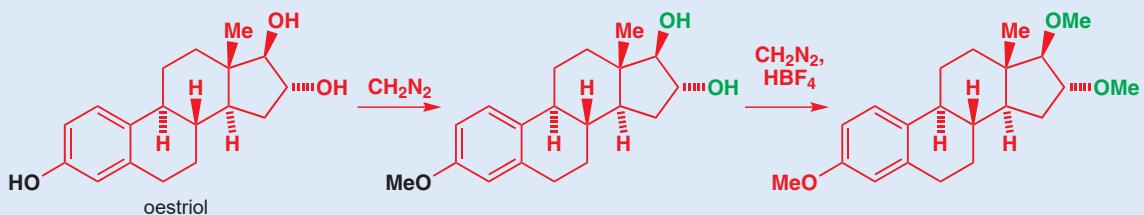
Diazomethane will also methylate phenols because they too are acidic enough to protonate it. Ordinary alcohols, though, are not methylated because they are not strong enough acids to protonate diazomethane.



### Selective methylation

Chemists studying the hormone degradation products present in the urine of pregnant women needed to methylate the phenolic hydroxyl group of the steroid oestriol. By using diazomethane, they avoided reaction at the two other

hydroxylic groups. When, subsequently, they did want to methylate the other two hydroxyl groups, they had to add acid ( $\text{HBF}_4$ ) to the reaction to protonate the diazomethane.

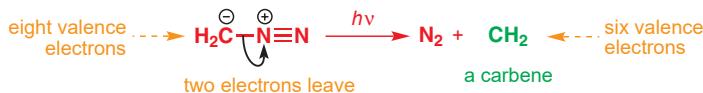


## Photolysis of diazomethane produces a carbene

Alcohols *can* be methylated by diazomethane if the mixture is irradiated with light.



The mechanism is now totally different because the light energy promotes loss of nitrogen ( $\text{N}_2$ ) from the molecule *without protonation*. This means that what is left behind is a carbon atom carrying just two hydrogen atoms ( $\text{CH}_2$ ), and having only six electrons. Species like this are called *carbenes*, and they are the subject of this chapter.



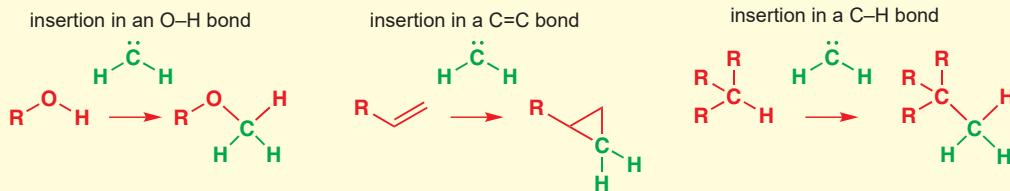
- Carbenes are neutral species containing a carbon atom with only six valence electrons.

The six electrons of a carbene are located two in each bond, plus two non-bonding electrons often represented as :CR<sub>2</sub> (as though they were a lone pair). As you will see later, this can be misleading, but :CR<sub>2</sub> is a widely used symbol for a carbene. In the case of :CH<sub>2</sub> generated from diazomethane, the carbene is trapped by the alcohol to make an ether.

Like the radicals in Chapter 37, carbenes are extremely reactive species. More important than their reaction with alcohols to make ethers are their reactions with alkenes to make cyclopropanes and their insertion into C–H bonds.

### Typical carbene reactions

The carbene inserts itself into a σ bond or a π bond.

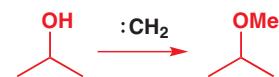


We will discuss the mechanisms of these three important reactions shortly, but we have introduced them to you now because they demonstrate that the reactions of carbenes are dominated by *insertion* (here, insertion into O–H, C=C, and C–H) driven by their extreme

■ Although this reaction illustrates an important point, the yield is too low, there are too many by-products, and the potential for serious explosions is too great for it ever to be useful as a way of making methyl ethers.

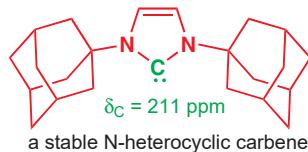
■ Carbenium ions such as  $^+\text{CH}_3$  also have only six valence electrons, but, of course, unlike carbenes they are charged.

Interactive mechanism for carbene formation by photolysis



electrophilicity. A carbon atom with only six electrons will do almost anything to get another two!

## How do we know that carbenes exist?



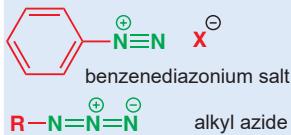
You may be somewhat surprised that the structure of carbenes can be investigated by ESR—after all, we explained in Chapter 37 that ESR observes unpaired electrons, and you might expect the six valence electrons of a carbene all to be paired. Indeed, in some carbenes they are, but in many they are not. This is an important point, and we will discuss it further later in the chapter.

### Naming azo compounds

Don't confuse *diaz*o compounds with *azo* compounds. Diazomethane has twice as many nitrogen atoms per carbon atom as azomethane.



You met *diazonium* salts in Chapter 22. Arene diazonium salts are stable compounds, but alkyl diazonium salts, which are formed by protonation of diazo compounds, are not. They decompose rapidly with loss of  $\text{N}_2$ —this was how the carboxylic acid got methylated at the beginning of the chapter. Other relatives of the *azo* and *diazo* compounds are alkyl azides. Alkyl azides have three nitrogen atoms and are usually stable but azides of low molecular weight may explode on impact or heating.



The best evidence for the existence of carbenes comes from a group of structures which contain a carbene but are stable compounds. The most important of these are known as the 'N-heterocyclic carbenes'—the carbene is incorporated into a five-membered ring and stabilized by the presence of two adjacent electron-donating nitrogen atoms and the bulky N-substituents. The example below was first made in 1991: it is crystalline, and its X-ray crystal shows the bond angle at the carbene carbon to be  $102^\circ$ , and  $^{13}\text{C}$  NMR confirms that the carbene C atom is electron deficient. We will come back to the significance of this later.

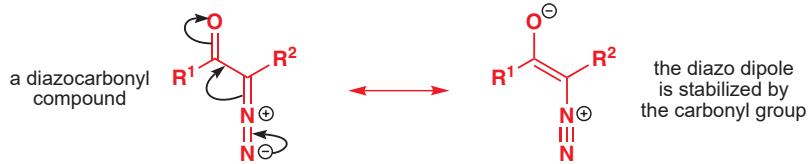
These stable carbenes are very much the exception: most carbenes are too reactive to be isolated. Reactive carbenes can, however, be observed by irradiating precursors (often diazo compounds like diazomethane, which we have just been discussing) trapped in frozen argon at very low temperatures (less than 77 K). IR and ESR spectroscopy (see p. 975) can then be used to determine their structure.

## Ways to make carbenes

Carbenes are usually formed from precursors by the loss of small, stable molecules. We will discuss some of the most important methods in turn, but you have already seen one in action: the loss of nitrogen from a diazo compound.

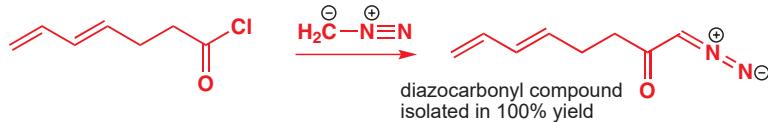
### Carbenes from diazo compounds

We showed you the formation of a carbene from diazomethane to illustrate how this reaction was different from the (ionic) methylation of carboxylic acids. But this is not a very practical way of generating carbenes, not least because of the explosive nature of diazoalkanes. However, diazocarbonyl compounds are a different matter.

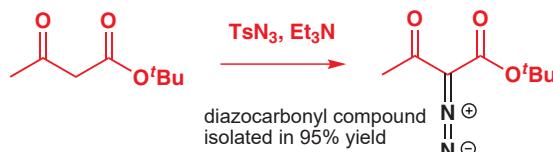


They are much more stable, because the electron-withdrawing carbonyl group stabilizes the diazo dipole, and are very useful sources of carbenes carrying a carbonyl substituent. There are two main ways of making diazocarbonyl compounds:

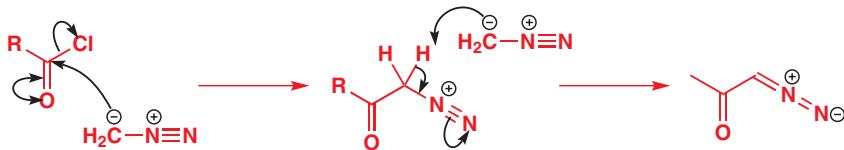
1. by reacting an acyl chloride with diazomethane



2. by reacting the parent carbonyl compound with tosyl azide,  $\text{TsN}_3$ , in the presence of base.

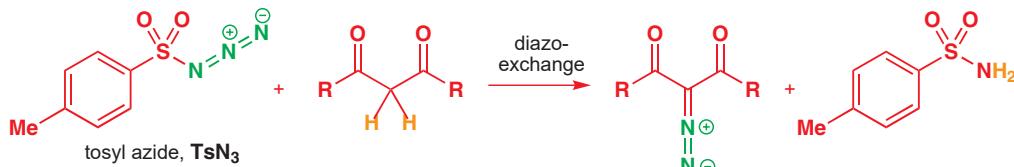


The reaction of diazomethane with acyl chlorides starts as a simple acylation to give a diazonium compound. If there is an excess of diazomethane, a second molecule acts as a base to remove a rather acidic proton between the carbonyl and the diazonium groups to give the diazocarbonyl compound.

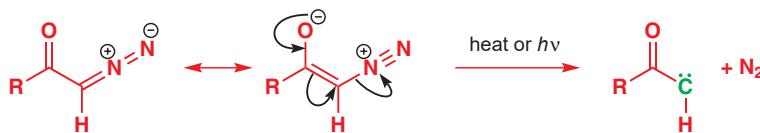


Interactive mechanism for carbene formation from acyl chlorides with diazomethane

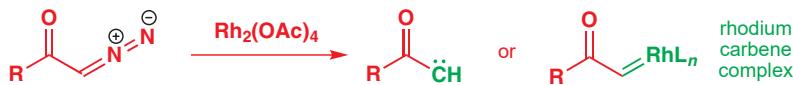
What happens to that second molecule of diazomethane? By collecting a proton it turns into the very reactive diazonium salt, which collects a chloride ion, and  $\text{MeCl}$  is given off as a gas. The second method uses tosyl azide, which is just  $\text{N}_2$  attached to a good leaving group.



Diazocarbonyl compounds can be decomposed to carbenes by heat or light. The loss of gaseous nitrogen compensates energetically for the formation of the unstable carbene.



It is much more common in modern chemistry to use a transition metal, such as copper or rhodium, to promote formation of the carbene.



Carbenes formed in this way are, in fact, not true carbenes because they remain complexed with the metal used to form them. They are known as *carbenoids*, and their reactions are discussed later in the chapter.

■  $\text{RhL}_n$  means rhodium with an unspecified number of unspecified ligands. This notation is common in organometallic chemistry when the nature of the carbon–metal bonding is important, but the precise structure of the metal complex is not.

### Fischer carbenes

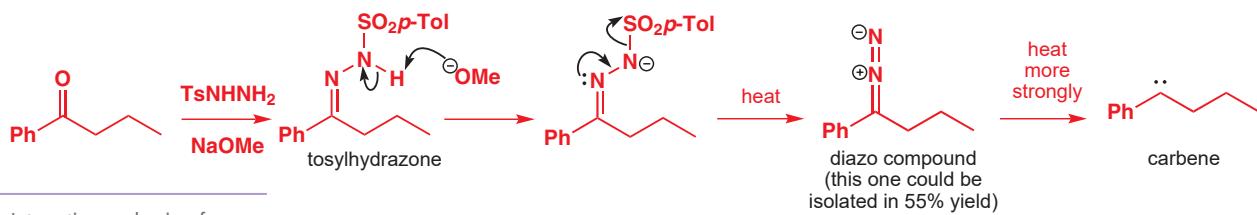
While these rhodium and copper carbenoids are unstable, some transition metals such as tungsten and chromium form stable, isolable carbenoids, called **metallocarbenes** or **Fischer carbenes**.



### Carbenes from tosylhydrazones

Many more carbenes can be made safely from diazoalkanes if the diazoalkane is just an intermediate in the reaction and not the starting material. Good starting materials for these reactions are tosylhydrazones, which produce transient diazo compounds by base-catalysed elimination of toluenesulfinate. The diazo compound is not normally isolated, and decomposes to the carbene on heating.

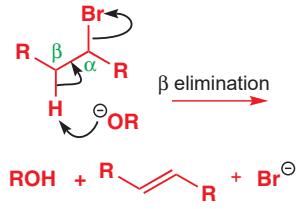
■ This reaction is sometimes called the **Bamford–Stevens reaction**. Notice that the leaving group from nitrogen is not the familiar tosylate (toluene-*p*-sulfonate  $\text{TsO}^-$  or  $\text{TolSO}_3^-$ ) but the less familiar toluene-*p*-sulfinate ( $\text{Ts}^-$  or  $\text{TolSO}_2^-$ ).



Interactive mechanism for carbene formation from tosylhydrazone

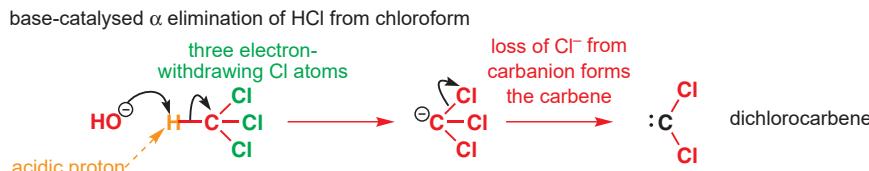
Carbenes are formed in a number of other similar reactions—for example, loss of carbon monoxide from ketenes or elimination of nitrogen from azirines—but these are rarely used as a way of deliberately making carbenes.

### Carbene formation by $\alpha$ elimination



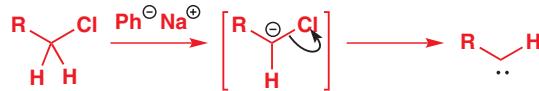
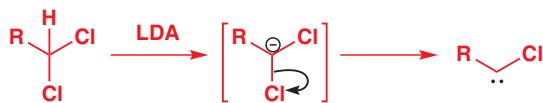
Interactive mechanism for carbene formation by  $\alpha$  elimination

In Chapter 17 we discussed  $\beta$  elimination in detail—reactions in which a hydrogen atom is removed from the carbon atom  $\beta$  to the leaving group.  $\alpha$  Eliminations (eliminations in which both the proton and the leaving group are located on the same atom) are also possible—in fact, the reaction we've just been talking about (elimination of toluenesulfonate from tosylhydrazones) is an  $\alpha$  elimination.  $\alpha$  Eliminations follow a mechanism akin to an E1cB  $\beta$  elimination—a strong base removes an acidic proton adjacent to an electron-withdrawing group to give a carbanion. Loss of a leaving group from the carbanion creates a carbene.



One of the best known  $\alpha$  elimination reactions occurs when chloroform is treated with base. This is the most important way of making dichlorocarbene,  $:CCl_2$ , and other dihalocarbenes too, although it must be said that the widespread use of dichlorocarbene in chemistry is due mainly to the ease with which it can be made using this method!

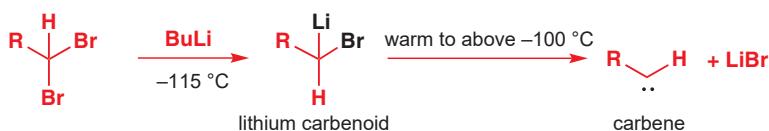
Hydroxide and alkoxide anions are strong enough bases to promote  $\alpha$  elimination from chloroform, and from other trihalomethanes. Carbenes can be formed from dihaloalkanes by deprotonation with stronger bases such as LDA, and even from primary alkyl chlorides using the extremely powerful bases phenyllithium or  $t\text{-BuLi}/t\text{-BuOK}$  (weaker bases just cause  $\beta$  elimination).



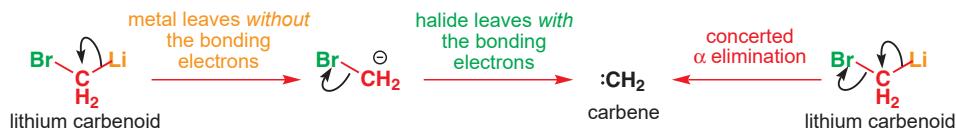
■ It is unfortunate that the term carbenoid is used for two distinct classes of molecule—usually it refers to the transition-metal bound carbene formed by metal-catalysed decomposition of diazo compounds (see p. 1018)—and for this reason the carbenoids that we are discussing here are best referred to as 'lithium carbenoids', with the metal specified.

The mixture  $t\text{-BuLi}/t\text{-BuOK}$  is known as **Schlosser's base**, and is one of the most powerful bases known. It will abstract protons from allylic or benzylic positions, and will even deprotonate benzene. Similar, very powerful, bases can be made from other combinations of alkylolithiums and group I metal alkoxides.

When geminal dibromoalkanes are treated with  $BuLi$ , a halogen–metal exchange reaction produces a lithium carbenoid, with a metal atom and a halogen attached to the same carbon atom. Lithium carbenoids are stable at very low temperatures—they can be observed by NMR, but they decompose to carbenes at about  $-100^\circ\text{C}$ .



The essence of this type of carbenoid is that it should have a leaving group, such as a halogen, that can accept a pair of electrons and another, usually a metal, that can donate a pair of electrons. If the metal leaves first, a carbanion is created that can lose the halogen to make a carbene. They might also leave together. Both mechanisms are  $\alpha$  eliminations.

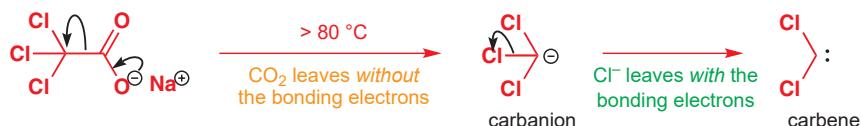


While lithium carbenoids have limited applicability, an analogous zinc carbenoid, which can be formed by insertion of zinc into diiodomethane, is a reagent in one of the most widely used carbenoid reactions in chemistry—the Simmons–Smith reaction.



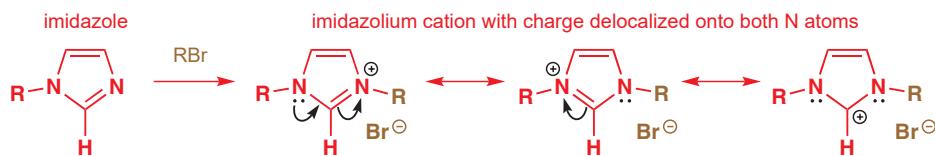
► The Simmons–Smith reaction, one of the best ways of making cyclopropanes, is discussed later in the chapter.

The problem with many of these reactions is that they require strong bases—either the organometallic compound itself is basic or a base must be used to create the carbanion. Carbenes are so unstable that they must be formed in the presence of the compound they are intended to react with, and this can be a problem if that compound is base-sensitive. For dichlorocarbene, a way round the problem is to make the carbanion by losing  $\text{CO}_2$  instead of a metal or a proton. Decarboxylation of sodium trichloroacetate is ideal as it happens at about 80 °C in solution.



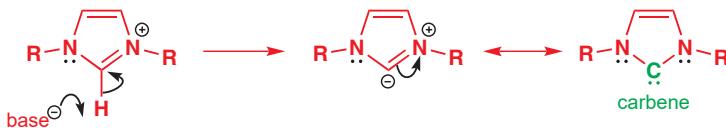
### Carbene formation by deprotonation of a cation

Our final method is in some ways the most straightforward in terms of mechanism: simple removal of a proton from a stable cation. This is the method used to make very stable carbenes, and it works because both the cation used as the starting material and the carbene product are stabilized by one or more adjacent lone pairs. Here is an example. Imidazoles are nucleophilic, and can be alkylated to give relatively stable imidazolium cations, which we can represent with the charge delocalized between the two nitrogen atoms, although there is another possible representation with the charge on carbon.



When the imidazolium cation is treated with a strong base, for example sodium hydride, the proton of this central, partially positively charged carbon is removed, to give a compound which initially looks like a carbanion.

deprotonation of the imidazolium cation to form a carbene





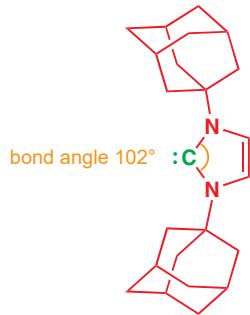
But we can use a curly arrow to move the negative charge towards the positively charged nitrogen, leaving a neutral species with a lone pair at carbon. A close look at the central carbon shows, however, that it has only two substituents—it is a carbene. Carbenes with adjacent lone pairs can often be thought of in this way, the lone pair partially delocalized onto the C atom to help stabilize the electron-deficient carbene.

### ● Summary: the most important ways of making carbenes

Carbenes are neutral species containing a carbon atom with only six valence electrons.

Type of carbene	Method of formation
	metal (rhodium or copper)-catalysed decomposition of diazocarbonyl compound
	thermal decomposition of diazo compound, often derived from tosylhydrazone
	$\alpha$ elimination of chloroform with base or decarboxylation of trichloroacetate
	Deprotonation of RCH=X <sup>+</sup> cation

## Carbenes can be divided into two types

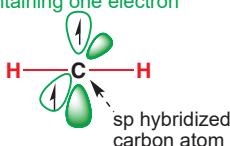
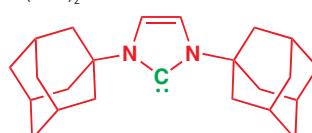


► ESR (electron spin resonance), also known as EPR (electron paramagnetic resonance), was discussed in the context of radicals on p. 975.

We made two important observations in the box on p. 1016 regarding the structure of carbenes that we will now return to and seek an explanation for. Firstly, we said that the X-ray crystal structure of the stable, crystalline carbene on the left shows that the bond angle at the carbene C is 102° and, secondly, we said that many carbenes can be observed by ESR—in other words, they have unpaired electrons.

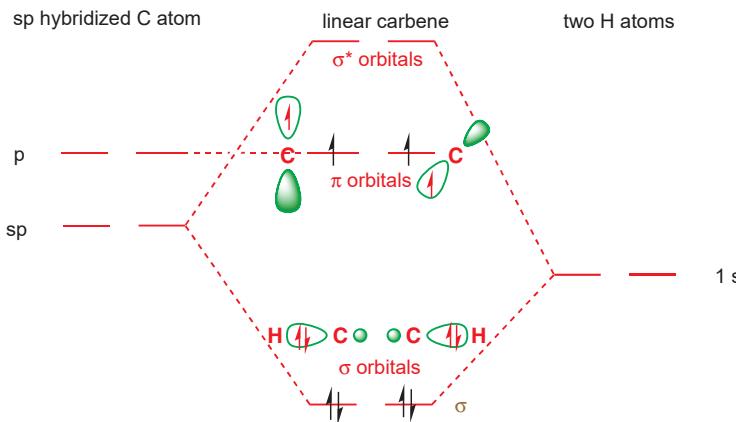
Spectroscopic investigations of a number of carbenes of differing structures have shown that they fall broadly into two groups: (1) those (which you will learn to call ‘triplets’) that ESR spectroscopy demonstrates have unpaired electrons and whose bond angles are 130–150° and (2) those (like the stable crystalline carbene above, and which you will learn to call ‘singlets’) that have bond angles of 100–110° but cannot be observed by ESR. Many carbenes, like CH<sub>2</sub> itself, can be found in either group, although one may be more common.

Type 1: triplet carbenes	Type 2: singlet carbenes
bond angle 130–150°	bond angle 100–110°
observable by ESR	all electrons paired
:CH <sub>2</sub>	:CCl <sub>2</sub>
:CHPh	:CHCl
:CHR	:C(OMe) <sub>2</sub>
:CPh <sub>2</sub>	



All these observations can be accounted for by considering the electronic structure of a carbene. Carbenes have two-coordinate carbon atoms: you might therefore expect them to have a linear (diagonal) structure—like that of an alkyne—with an sp hybridized carbon atom.

Such a linear carbene would have six electrons to distribute amongst two  $\sigma$  orbitals and two (higher-energy) p orbitals. The two electrons in the degenerate p orbitals would remain unpaired because of electron repulsion in the same way as in molecular oxygen  $\bullet\text{O}-\text{O}\bullet$ .



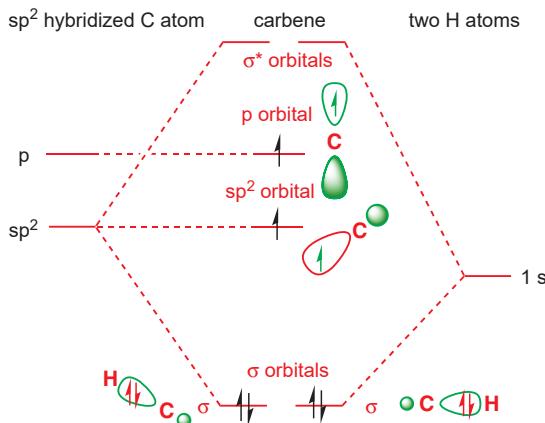
Yet few carbenes are linear: most are bent, with bond angles between  $100^\circ$  and  $150^\circ$ , suggesting a trigonal ( $\text{sp}^2$ ) hybridization state. An  $\text{sp}^2$  hybridized carbene would have three (lower-energy)  $\text{sp}^2$  orbitals and one (high-energy) p orbital in which to distribute its six electrons. There are two ways of doing this. Either all of the electrons can be paired, with each pair occupying one of the  $\text{sp}^2$  orbitals, or two of the electrons can remain unpaired, with one electron in each of the p orbitals and one of the  $\text{sp}^2$  orbitals.

two ways of arranging the electrons in a bent ( $\text{sp}^2$ ) carbene:

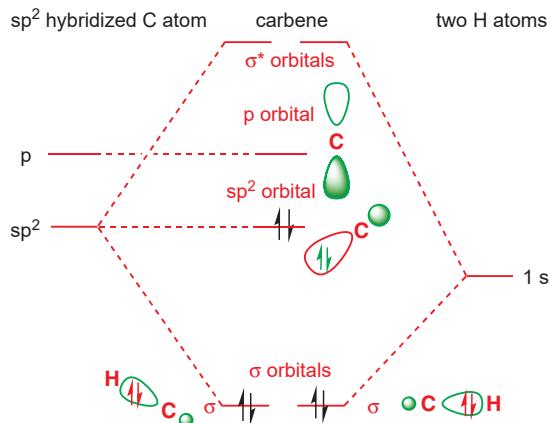


These two possibilities explain our two observed classes of carbene, and the two possible arrangements of electrons (spin states) are termed triplet and singlet. The orbitals are the same in both cases but in triplet carbenes we have one electron in each of two molecular orbitals and in singlet carbenes both electrons go into the  $\text{sp}^2$  orbital.

electronic structure of a bent ( $\text{sp}^2$ ) triplet carbene with two unpaired electrons

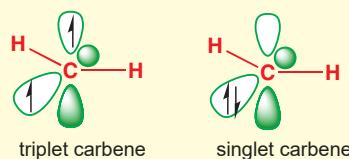


electronic structure of a bent ( $\text{sp}^2$ ) singlet carbene with two paired electrons



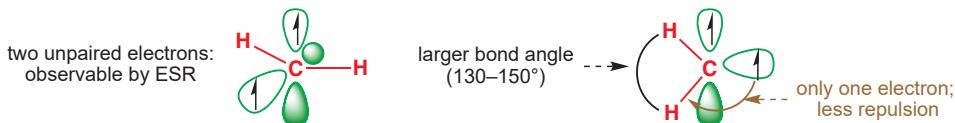
### ● Singlet and triplet carbenes

Triplet carbenes have two unpaired electrons, one in each of an  $\text{sp}$  and a  $\text{p}$  orbital, while singlet carbenes have a pair of electrons in a non-bonding  $\text{sp}^2$  orbital and have an empty  $\text{p}$  orbital.

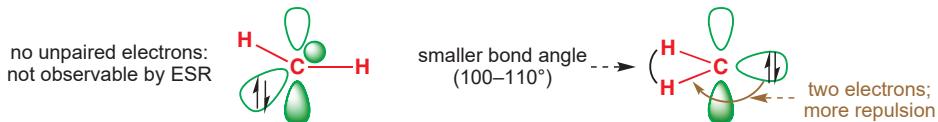


The existence of the two spin states explains the different behaviour of triplet and singlet carbenes towards ESR spectroscopy; the orbital occupancy also explains the smaller bond angle in singlet carbenes, which have an electron-repelling lone pair in an  $sp^2$  orbital.

#### Triplet carbenes



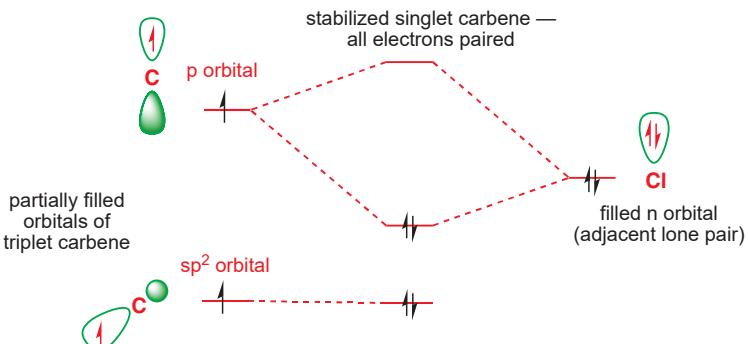
#### Singlet carbenes



In the table on p. 1010 we saw that the substituents on the carbene affect which of the two classes (which we now call singlet and triplet) it falls into. Why? All carbenes have the potential to exist in either the singlet or the triplet state, so what we mean when we say that a carbene such as :CH<sub>2</sub> is a ‘triplet carbene’ is that the triplet state for this carbene is lower in energy than the singlet state. The opposite is true for :CCl<sub>2</sub>. Most type of carbenes are more stable as triplets because the energy to be gained by bringing the electron in the p orbital down into the  $sp^2$  orbital is insufficient to overcome the repulsion that exists between two electrons in a single orbital.

For most triplet carbenes the singlet spin state that would arise by pairing up the two electrons lies only about 40 kJ mol<sup>-1</sup> above the ground (triplet) state: in other words, 40 kJ mol<sup>-1</sup> is required to pair up the two electrons.

Carbenes that have singlet ground states (such as :CCl<sub>2</sub>) all have electron-rich substituents carrying lone pairs adjacent to the carbene centre. These lone pairs can interact with the p orbital of the carbene to produce a new, lower-energy orbital which the two electrons occupy. This stabilization of the lone pair provides the incentive that the electron in the p orbital needs to pair up in the  $sp^2$  orbital.



► This is a manifestation of Hund’s rule—see Chapter 4.

■ When a carbene is actually formed in a chemical reaction, it may not be formed in its most stable state, as we shall see.

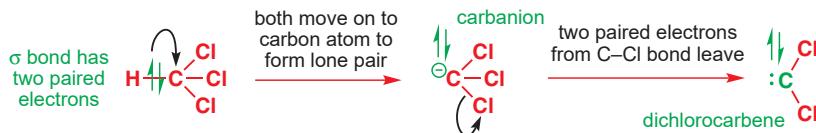


This interaction corresponds to the point we made above about adjacent lone pairs stabilizing carbenes via the delocalization shown in the margin. As these arrows suggest, carbenes that have heavily electron-donating substituents are less electrophilic than other carbenes: indeed, diamino carbenes can be quite nucleophilic. The division of carbenes into two types explains

their structure. It also helps to explain some of their reactions, especially those that have a stereochemical implication. We will spend the rest of this chapter discussing how carbenes react.

### The structure of carbenes depends on how they are made

So far we have considered only the most stable possible structure, singlet or triplet, of a given carbene. In reality, a carbene will be formed in a chemical reaction and may well be formed as the less stable of the alternatives. If a reaction occurs by an ionic mechanism on a molecule with all electrons paired (as most molecules are!) then it must be formed as a singlet. Follow the  $\alpha$  elimination mechanism, for example.



The starting material, a molecule of chloroform  $\text{CHCl}_3$ , has all paired electrons. The C–H  $\sigma$  bond breaks and the two paired electrons from it form the lone pair of the carbanion. The carbanion also has all paired electrons. The two paired electrons of one of the C–Cl bonds leaves the carbanion and the carbene is formed. It has two paired electrons in each of the two remaining C–Cl bonds and the lone pair, also paired. It is formed as a singlet. As it happens, the singlet version of  $\text{CCl}_2$  is also the more stable. But if the carbene were instead  $\text{CH}_2$  and if it reacted rapidly, it might not have a chance to change into the more stable triplet state. Since carbenes are very reactive, this question can be important. In explaining their reactions in the next section we shall need to consider:

- how the carbene was formed
- how rapidly it reacts
- whether it can change into the other state (singlet or triplet).

## How do carbenes react?

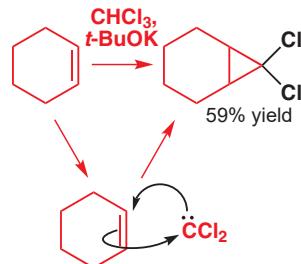
Carbenes are desperate to find another pair of electrons with which to complete their valence shell of electrons. In this respect they are like carbocations. Like carbocations, they are electrophilic but, unlike carbocations, they are uncharged. This has consequences for the type of nucleophiles carbenes choose to react with. Carbocations attack nucleophiles with high charge density—those carrying a negative or partial negative charge (think of the type of nucleophiles that will take part in  $\text{S}_{\text{N}}1$  or Friedel–Crafts reactions). Carbenes, on the other hand, attack compounds we'd normally never consider as nucleophiles—even simple alkanes—by taking electrons from their HOMO. Of course, a carbocation will usually react with the HOMO of a molecule, but it will be much more selective about which HOMOs will do—usually these have to be lone pairs or electron-rich alkenes. For carbenes, any HOMO will do—a lone pair, a C=C double bond (electron-rich or -poor), or even a C–H bond.

As you will see (and as we generalized at the beginning of the chapter), many of these reactions can be considered as insertion reactions—overall the carbene appears to have found a bond and inserted itself in the middle of it. It's important to remember that the term 'insertion' describes the overall consequence of the reaction, but isn't always an accurate description of the reaction's mechanism.

In this respect, a carbene is like an electrophilic radical—very reactive and very soft.

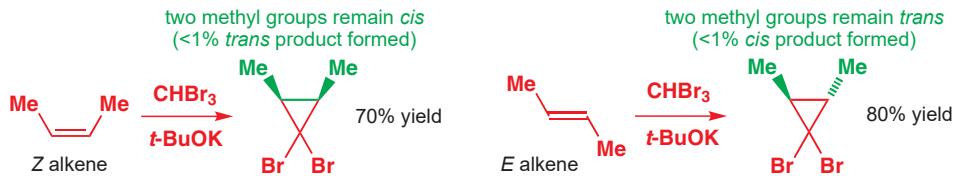
### Carbenes react with alkenes to give cyclopropanes

This reaction is the most important way of making cyclopropanes, and is probably the most important reaction of carbenes. The mechanism of this type of reaction (an example is shown in the margin) depends on whether the carbene is a singlet or a triplet, and the outcome of the reaction can provide our first chemical test of the conclusions we came to in the



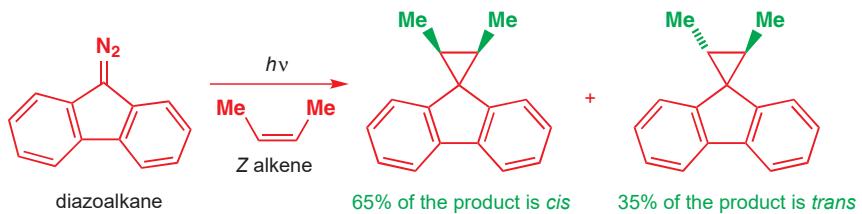
previous section. Singlet carbenes, like this one here (remember that substituents with lone pairs stabilize the singlet spin state) can add to alkenes in an entirely concerted manner: the curly arrows for the process can be written as shown in the margin.

Because the process is concerted, we expect that the geometry of the alkene should be preserved in the product—the reaction ought to be *stereospecific*. The two examples below show that this is indeed the case. It is more impressive that the *Z* alkene gives the *cis*-cyclopropane as this is less stable than the *trans*-cyclopropane and would change to *E* if it could.

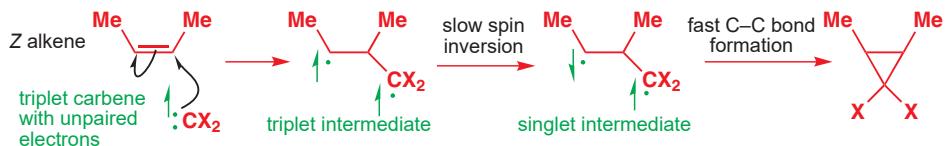


The alkene insertion reaction is stereospecific only for singlet carbenes. For triplet carbenes, the reaction is non-stereospecific. In the example below, a triplet carbene gives a mixture of cyclopropane diastereoisomers from a pure *Z* alkene.

■ Although carbenes formed thermally from diazoalkenes must initially be singlets, photochemical irradiation allows them to convert to the more stable triplet.

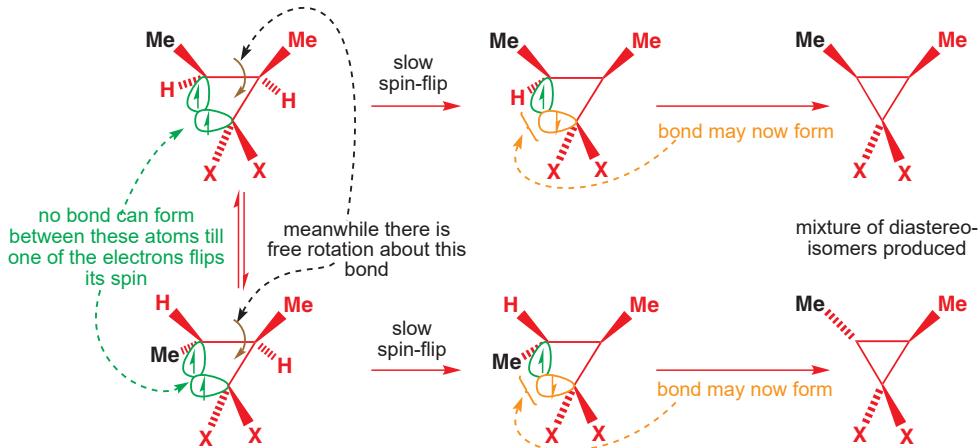


The mechanism of the reaction must be different with a triplet carbene. In fact, a concerted reaction is impossible for triplet carbenes because of the spins of the electrons involved. The spins of a triplet carbene aren't paired, so once the carbene has added to the alkene in a radical reaction, the diradical (triplet) intermediate must wait until one of the spins inverts ('flips') before the second C–C bond can be formed with paired electrons.



Interactive mechanism for triplet carbenes in cyclopropane formation

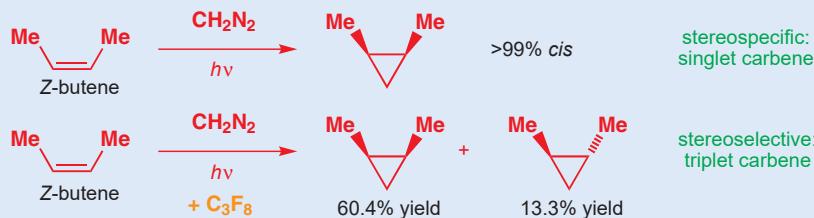
Spin-flipping, which can occur only through collision with another molecule (of solvent usually), is relatively slow on the time-scale of molecular rotations and, by the time the electrons are in a fit state to pair up, the stereochemistry of the starting material has been scrambled by free rotation in the intermediate.



The same constraints arising from the need for conservation of electron spin apply to the formation as well as to the reaction of carbenes. When a carbene forms by  $\alpha$  elimination, say, from a molecule with all electrons paired, it must be formed as the singlet, whether or not the triplet state is lower in energy. Only later may the carbene undergo spin-flipping to the triplet state. Since most carbene reactions are very rapid, this means that carbenes that are known to have triplet ground states may, in fact, react in their first-formed singlet state because they don't have time to spin-flip to the triplet. This is true for :CH<sub>2</sub> produced from CH<sub>2</sub>N<sub>2</sub>, which adds stereospecifically to double bonds because it is formed as a singlet and because the singlet state is more reactive than the triplet.

### Some evidence for triplet carbenes in cyclopropane formation

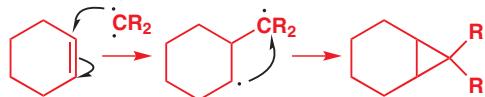
If the reaction is diluted with a large amount of an inert solvent such as C<sub>3</sub>F<sub>8</sub> (perfluoropropane) then :CH<sub>2</sub> undergoes more collisions before it reacts and so the chances of spin-flipping of singlet :CH<sub>2</sub> to triplet :CH<sub>2</sub> is increased. Addition to alkenes is then less stereospecific.



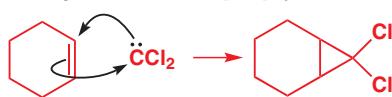
Stereospecificity (or lack of it) in the addition of a carbene to an alkene can be a good test of whether the carbene reacts as a singlet or triplet: lack of stereospecificity in a carbene addition almost certainly indicates that a triplet carbene is involved, but the fact that an addition *is* stereospecific doesn't mean that the carbene must be a singlet. In some cases, bond rotation may be quite slow, and spin-flipping rapid, leading to stereospecific addition. Notice that in this example the less stable *cis* (*Z*) alkene was used: the reaction will give the less encumbered *trans*-cyclopropane if it can.

The addition of a triplet carbene to an alkene can be considered to be rather like a radical addition to a double bond. The concerted addition of a singlet carbene, on the other hand, is a pericyclic reaction, and from Chapter 34 you should be able to classify it as a [1 + 2] cycloaddition.

addition of triplet carbenes is a radical reaction

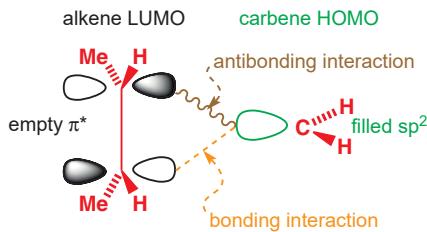
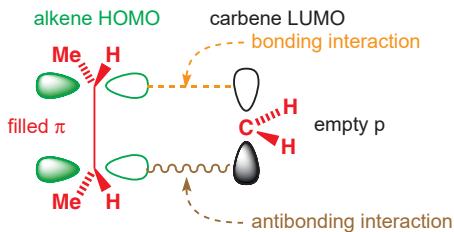


addition of singlet carbenes is a [1+2] cycloaddition



As a cycloaddition, singlet carbene addition to an alkene must obey the rules of orbital symmetry discussed in Chapters 34 and 35. We might consider the empty p orbital of the carbene (LUMO) interacting with the  $\pi$  bond (HOMO) of the alkene or the lone pair of the carbene in its filled  $sp^2$  orbital (HOMO) interacting with the  $\pi^*$  antibonding orbital of the alkene (LUMO).

#### direct approach of carbene

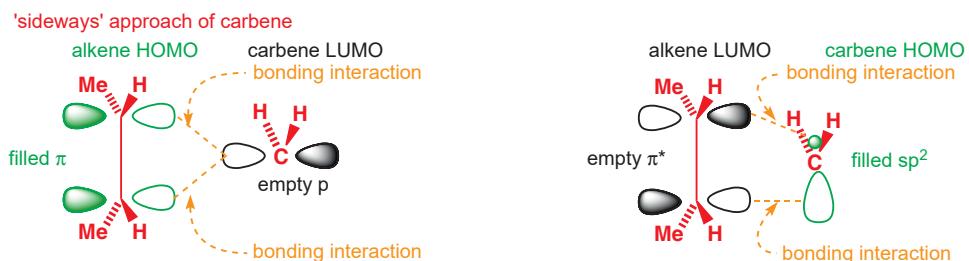


You can immediately see that there is a problem when we try to interact these orbitals constructively to build two new bonds—direct approach of the carbene to the alkene is impossible because there is always an antibonding interaction. Two new bonds can be formed, however, if the carbene approaches the alkene in a 'sideways-on' manner.

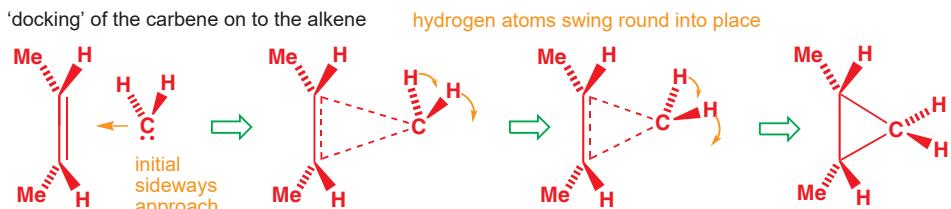
Interactive comparison of singlet and triplet carbenes in cyclopropane formation

■ Cycloadditions in which one of the components is a single atom (in other words, [1 + *n*] cycloadditions) are sometimes called **cheletropic reactions**.

Interactive examples of other cheletropic reactions with SO<sub>2</sub>



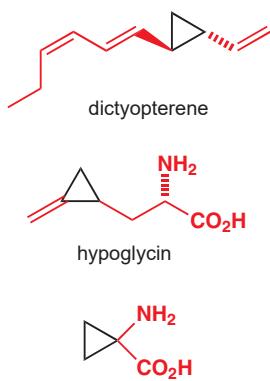
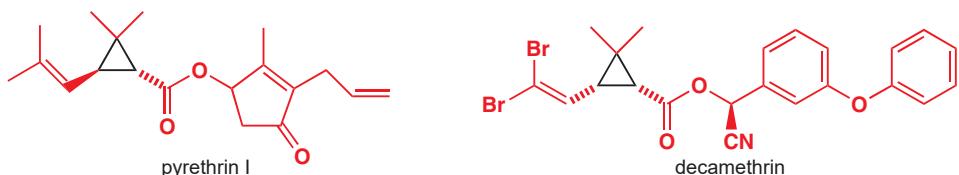
The cyclopropane product must, of course, have a more or less tetrahedral arrangement about the carbon atom that was the carbene so that, even if the carbene approaches in a sideways-on manner, it must then swing round through  $90^\circ$  as the bonds form.



 Interactive mechanism for singlet carbenes in cyclopropane formation

## Making cyclopropanes

Many natural products and biologically active compounds contain cyclopropane rings: we shall feature just a few. First, a most important natural insecticide, a pyrethrin from the East African pyrethrum daisy, and its synthetic analogue decamethrin, one of the most important insecticides in agriculture. Very low doses of this highly active and non-persistent insecticide are needed.

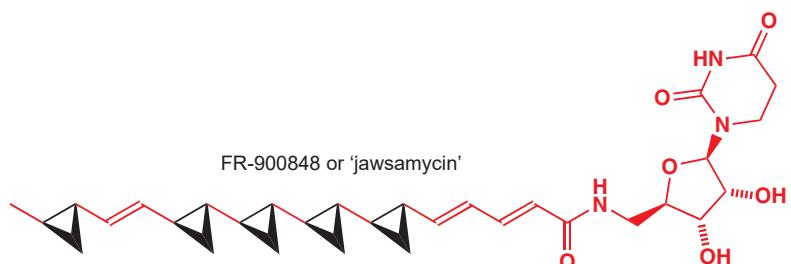


The ‘ozone’ or ‘iodine’ smell of the sea has nothing to do with O<sub>3</sub> or I<sub>2</sub>. It’s more likely a dictyopterene, a family of volatile cyclopropanes used by female brown algae to attract male gametes.

Other cyclopropanes include two natural but highly unusual amino acids. Hypoglycin is a blood sugar level lowering agent from the unripe fruit of the ackee tree. It's the causative agent of Jamaican vomiting sickness. Don't eat the green ackee.

The second and simpler amino acid is found in apples, pears, and grapefruit, and encourages fruit ripening by degradation to ethylene.

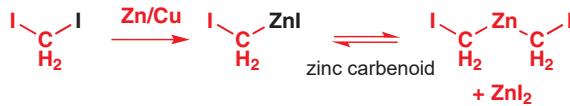
Our last and most extraordinary example is an antifungal antibiotic first synthesized in 1996 and containing no fewer than five cyclopropanes. It has the prosaic name FR-900848 but is known unofficially as ‘jawsamycin’.



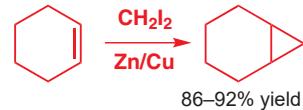
Most chemical syntheses of compounds containing cyclopropyl groups make use of the addition of a carbene, or carbene equivalent, to an alkene. What do we mean by carbene equivalent? Usually, this is a molecule that has the potential to form a carbene, although it may not actually react via a carbene intermediate. One such example is the zinc carbenoid formed when diiodomethane reacts with zinc metal (most conveniently as a mixture with copper—a ‘zinc–copper couple’). It reacts with alkenes just as a carbene would—it undergoes addition to the  $\pi$  bond and produces a cyclopropane.

the Simmons–Smith reaction

formation of the zinc carbenoid

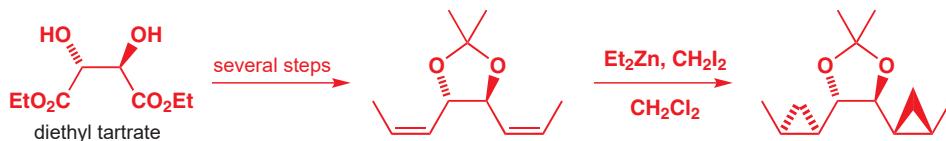


reaction of the zinc carbenoid

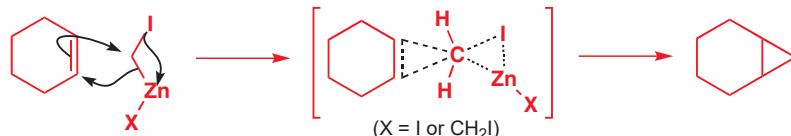


You met this zinc carbenoid on p. 1009.  $\text{Zn}/\text{Cu}$  couple is a type of alloy but without a precise composition or structure; typically it contains >90% zinc.

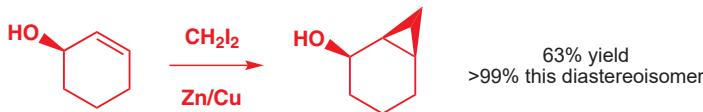
The reaction is known as the Simmons–Smith reaction, after the two chemists at the DuPont chemical factory who discovered it in 1958. Even after several decades, it is the most important way of making cyclopropane compounds, although nowadays a variant that uses more easily handled starting materials is often used. Diethyl zinc replaces the  $\text{Zn}/\text{Cu}$  couple of the traditional Simmons–Smith reaction. In this example, a double cyclopropanation on a  $C_2$  symmetric diene derived from tartaric acid gives very good stereoselectivity for reasons we will soon discuss.



The mechanism of the Simmons–Smith reaction appears to be a carbene transfer from the metal to the alkene without any free carbene being released. It may look something like this.



Some of the evidence for this comes from a reaction that not only throws light on to the mechanism of Simmons–Smith cyclopropanations, but makes them of even greater value in synthesis. When an allylic alcohol is cyclopropanated, the new methylene group adds stereoselectively to the same face of the double bond as the hydroxyl group.



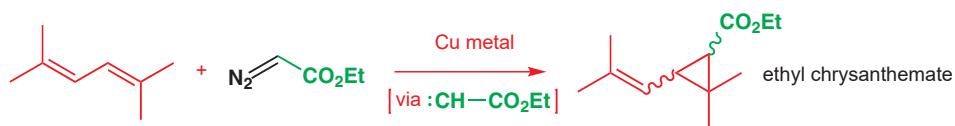
► You might notice the similarity to the epoxidation of allylic alcohols with *m*-CPBA mentioned in Chapter 32.

Interactive mechanism for chelation-directed cyclopropanation

Allylic alcohols are also cyclopropanated over 100 times faster than their unfunctionalized alkene equivalents. Coordination between the zinc atom and the hydroxyl group in the transition state explains both the stereoselectivity and the rate increase. Unfortunately, while the Simmons–Smith reaction works well when a methylene ( $\text{CH}_2$ ) group is being transferred, it is less good with substituted methylene groups ( $\text{RCH}_2$  or  $\text{R}_2\text{C}\cdot$ ).

The carbene derived by metal-catalysed decomposition of ethyl diazoacetate attacks alkenes to introduce a two-carbon fragment into a cyclopropane—an industrial synthesis of ethyl chrysanthemate, a precursor to the pyrethrin insecticides (see p. 1016), uses this reaction. The diene in the starting material is more nucleophilic (has a higher energy HOMO; see Chapter 19) than the single alkene in the product, so the reaction can be stopped after one carbene addition.

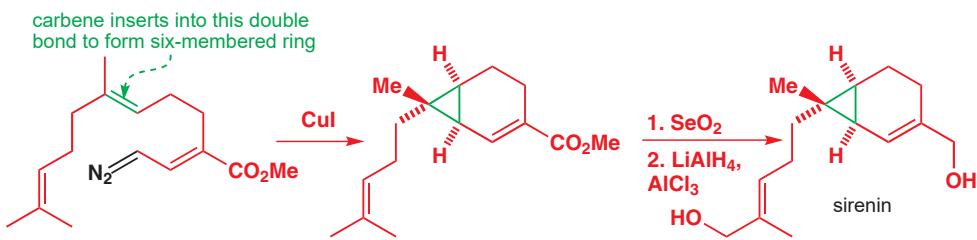
► On the subject of stereochemistry, note that the Simmons–Smith zinc carbenoid behaves like a singlet carbene—its additions to alkenes are stereospecific (the product cyclopropane retains the geometry of the alkene) as well as stereoselective (the carbenoid adds to the same face as the hydroxyl group).



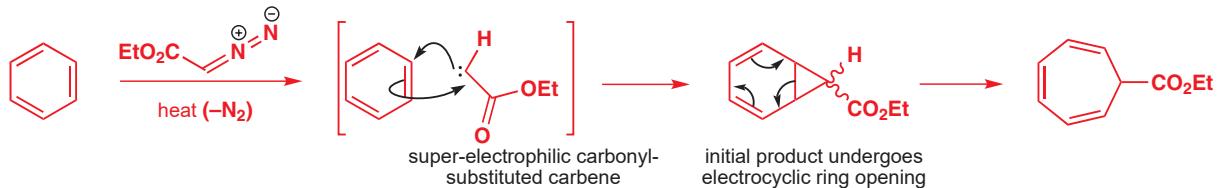
The intramolecular version of this reaction is more reliable, and has often been used to make compounds containing multiply substituted cyclopropanes. Corey made use of it in a synthesis of sirenin, the sperm-attractant of a female water mould.

► The selenium dioxide oxidation is discussed in Chapter 35, p. 919.

► You met electrocyclic reactions like this in Chapter 35.

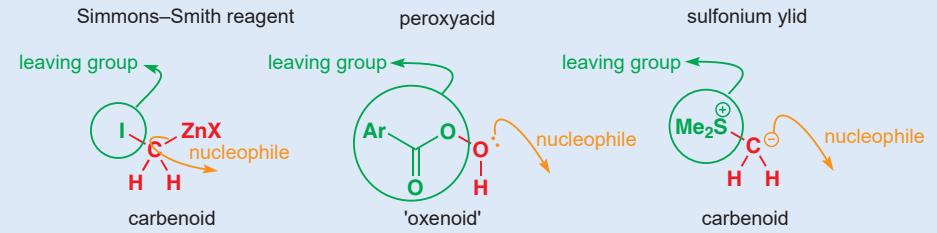


As you might imagine, carbenes like this, substituted with electron-withdrawing carbonyl groups, are even more powerful electrophiles than carbenes like :CCl<sub>2</sub>, and will even add to the double bonds of benzene. The product is not stable, but immediately undergoes electrocyclic ring opening.



### Comparison of '-enoid' reagents

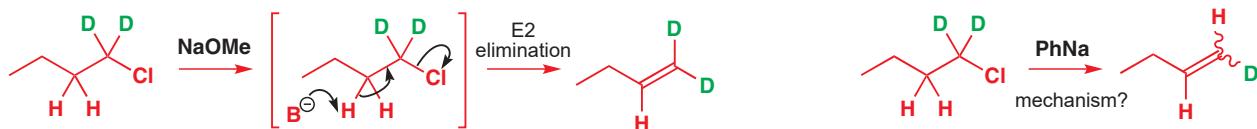
Before we leave this section on cyclopropanes, we want you to take a step back from simply thinking about carbenes, and consider the types of reagents that form three-membered rings generally. They all have something in common, which we could call '-enoid' character. Cyclopropanes form when a carbene (which, in the singlet state, has an empty, electrophilic p orbital and a full, nominally nucleophilic sp<sup>2</sup> orbital) attacks alkenes. The Simmons-Smith carbenoid is not a carbene, but nonetheless has a carbon atom with joint nucleophilic (alkyl zinc) and electrophilic (alkyl iodide) character. When you think about it, the same is true for peroxyacid epoxidation, which forms the oxygen analogue of a cyclopropane by attacking an alkene using an oxygen atom bearing both a lone pair (nucleophilic) and a carboxylate leaving group (electrophilic). It's an 'oxenoid'. In Chapter 27 you met other reagents that form cyclopropanes and epoxides by transferring CH<sub>2</sub>—sulfonium ylids. These yet again have a carbon atom carrying both a negative charge and a leaving group. You can consider them to be particularly stable carbenoids.



### Insertion into C—H bonds

We said that the formation of cyclopropanes by addition of substituted carbenes to alkenes was rare—in fact, alkyl-substituted carbenes undergo very few intermolecular reactions at all because they decompose very rapidly. When primary alkyl halides are treated with base, alkenes are formed by elimination. Having read Chapter 17, you should expect

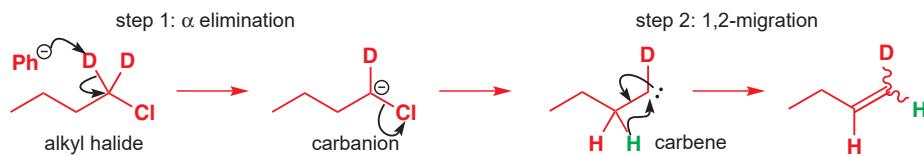
the mechanism of this elimination to be E2 and, if you started with a deuterated compound like this, the alkene product would be labelled with two deuterium atoms at its terminus.



This is indeed what happens if the base is sodium methoxide ( $pK_a[\text{MeOH}]$  about 16). If, however, it is phenyllsodium ( $pK_a[\text{benzene}]$  about 50), only 6% of the product is labelled in this way while 94% of the product has only one deuterium atom.

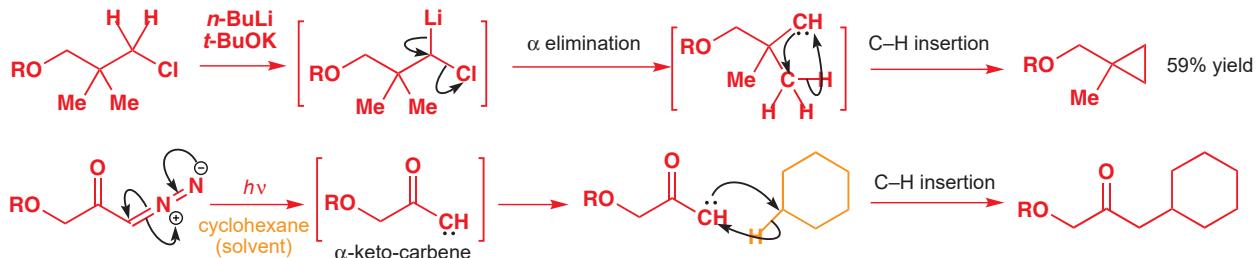
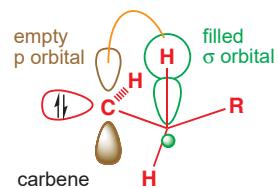
Evidently a hydrogen atom has ‘migrated’ from the 2-position to the 1-position. The overall mechanism of the elimination with very strong bases like phenyllsodium is thought to be: (1) formation of a carbene by  $\alpha$  elimination and then (2) 1,2-migration of a hydrogen atom on to the carbene centre. Carbenes with  $\beta$  hydrogens undergo extremely rapid 1,2-migration of hydrogen to the carbene centre, giving alkenes.

► Migrations were covered in detail in Chapter 36. You met examples there of migrations on to electrophilic carbocationic centres, but the reactions are in essence very similar to these migrations to carbenes.



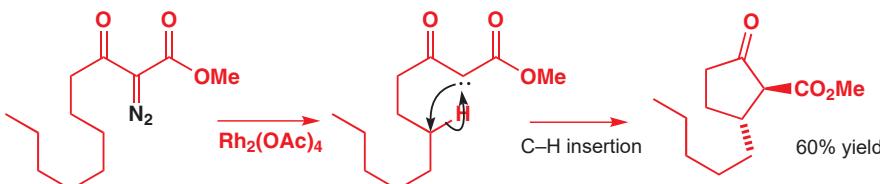
The reason for the rapid migration is that the electrophilic carbene has found a nearby source of electrons—the HOMO of the C–H bond—and it has grabbed the electrons for itself, ‘inserting’ into the C–H bond, as shown in the margin.

This type of reaction is better demonstrated by two examples in which the ‘insertion reaction’ is a bit more obvious: when there are no  $\beta$  hydrogens, the carbene inserts into C–H bonds a little further away in the same molecule or even in the solvent (cyclohexane in the second example). In the first case, the carbene is formed by  $\alpha$  elimination (using one of the ‘Schlosser bases’, see p. 1008) and, in the second case, by photolysis of a diazoketone.



Because these insertion reactions create new bonds at completely unfunctionalized centres, they can be very useful in synthesis. This next carbene is created between two carbonyl groups from a diazocompound with rhodium catalysis and selectively inserts into a C–H bond five atoms away to form a substituted cyclopentanone.

► Interactive mechanism for carbene insertion into C–H bonds



### Pentalenolactone synthesis using carbenes

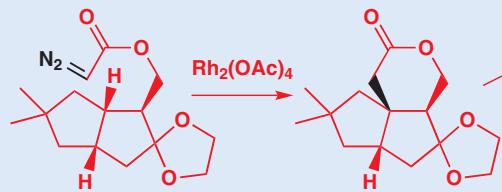
Pentalenolactone is the name given to an antibiotic extracted from *Streptomyces* fungi with an interesting tricyclic structure.



Two groups of chemists, within one year of each other, published syntheses of this compound using rhodium-promoted carbene insertions into C–H bonds. Cane's insertion reaction (route 1) proceeds stereospecifically with *retention* of

stereochemistry. This is excellent evidence for a concerted singlet carbene reaction. In Taber's synthesis, the carbene inserts into the six-membered tetrahydropyran ring selectively to give the less strained 5,5-*trans* ring junction.

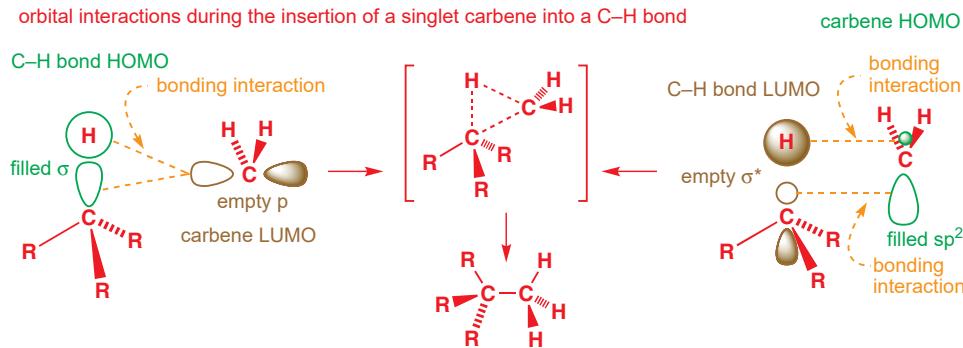
route 1: Cane's synthesis of pentalenolactone



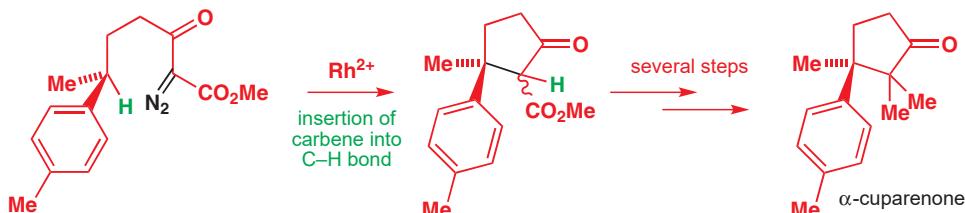
route 2: Taber's synthesis of pentalenolactone



In these C–H insertion reactions, the similarity with cyclopropane formation by insertion into alkenes is clear, and the mechanisms mirror one another quite closely. As with the cyclopropanation reactions, the mechanism depends on whether the carbene is a singlet or triplet. Singlet carbenes can insert in a concerted manner, with the orbitals overlapping constructively provided the carbene approaches side-on.



This mechanism implies that, if the C–H bond is at a stereogenic centre, the stereochemistry at that centre will be retained through the reaction, as in Cane's synthesis of pentalenolactone (see box above). A nice example of this result is this ingenious synthesis of  $\alpha$ -cuparenone using a stereospecific carbene insertion.

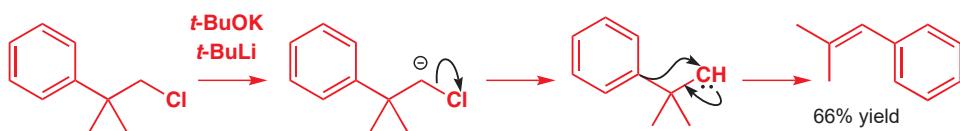


### Rearrangement reactions

We talked just at the beginning of this section about migration reactions of hydrogen on to carbenes to give alkenes, and said that these reactions can be viewed as insertion reactions of

■ In principle, triplet carbene insertions should follow a two-step radical pathway analogous to their insertion into alkenes. However, very few triplet carbene insertions into C–H bonds have been observed, and the stereochemical consequence of the two-step mechanism (which should result in mixtures of stereoisomers on insertion into a C–H bond at a stereogenic centre) has never been verified.

carbenes into adjacent C–H bonds. Carbenes with no  $\beta$  hydrogens often insert into other C–H bonds in the molecule. However, carbenes with no  $\beta$ -hydrogen atoms can also undergo rearrangement reactions with alkyl or aryl groups migrating.



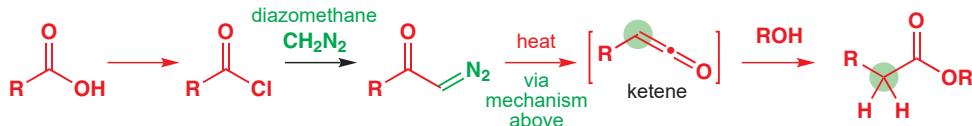
The most common example of this type of migration is that in which the carbene is adjacent to a carbonyl group. The initial product of what is known as the Wolff rearrangement is a ketene, which cannot be isolated but is hydrolysed to the acid in the work-up. Wolff rearrangement is a typical result of heating diazoketones, although as you saw above (p. 1019) these species also undergo intramolecular C–H insertion reactions.

the Wolff rearrangement



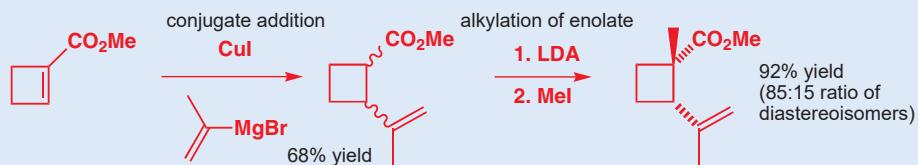
One important application of this reaction is the chain extension of acyl chlorides to their homologous esters, known as the Arndt–Eistert reaction. Notice that the starting material for the Wolff rearrangement is easily made from  $\text{RCO}_2\text{H}$  by reaction of the acyl chloride with diazomethane; the product is  $\text{RCH}_2\text{CO}_2\text{H}$ —the carboxylic acid with one more carbon atom in the chain. A  $\text{CH}_2$  group, marked in green, comes from diazomethane and is inserted into the C–C bond between R and the carbonyl group.

the Arndt–Eistert homologation

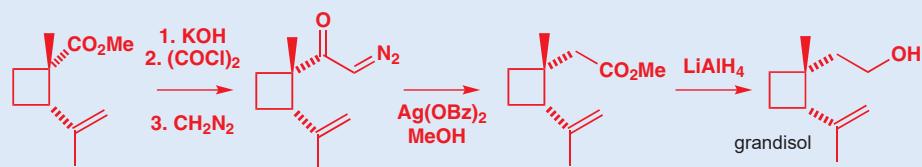


### A synthesis of grandisol using the Arndt–Eistert chain extension

The boll weevil is a serious pest of cotton bushes, and it produces a sex pheromone known as grandisol. A common strategy for preventing insect damage in agriculture is to lure the weevils into a trap using synthetic versions of their own sex pheromones, and chemists soon showed that it was an easy matter to synthesize a related ester by a conjugate addition of an organocupper derivative (Chapter 22) and then alkylation of an ester enolate (Chapter 25). The enolate reacts with MeI on the face opposite the propenyl side chain—a good example of stereochemical control with cyclic compounds (Chapter 32).



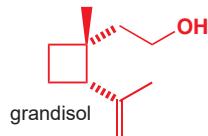
This ester is one carbon atom short of the full side chain of grandisol, so an Arndt–Eistert reaction was used to lengthen the chain by one atom. First, the ester was converted into the diazoketone with diazomethane and then the Wolff rearrangement was initiated by formation of the carbene with a silver(II) salt.



■ The migration of alkyl groups to carbene centres has much in common with the migration of alkyl groups to cationic centres discussed in Chapter 36—after all, both carbenes and carbocations are electron-deficient species with a carbon atom carrying only six electrons in its outer shell.

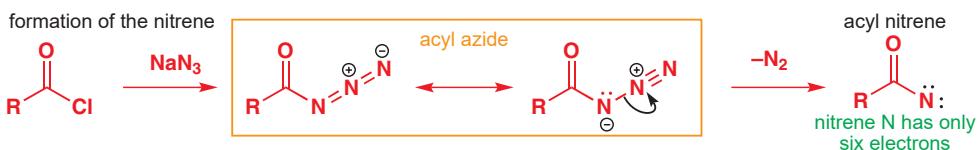
► You met ketenes in Chapter 34.

■ We discussed the structure and decomposition of diazoketones on p. 1001.



## Nitrenes are the nitrogen analogues of carbenes

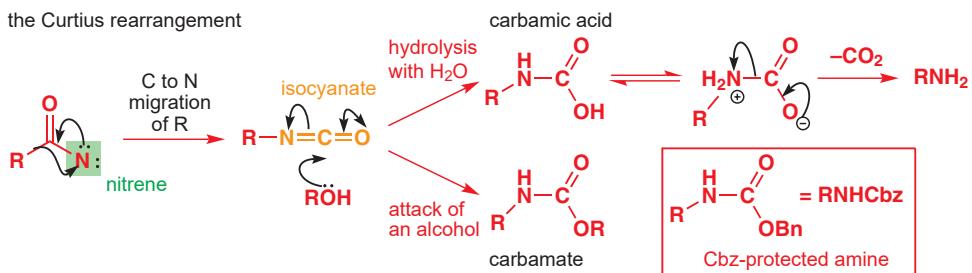
The Wolff rearrangement has some important cousins that we must now introduce to you—they deserve a mention because they bear a family likeness even though they do not, in fact, involve carbenes. They are a group of reactions that proceed through an intermediate *nitrene*—the nitrogen analogue of a carbene. The simplest to understand, because it is the direct nitrogen analogue of the Wolff rearrangement, is the Curtius rearrangement. It starts with an acyl azide, which can be made by nucleophilic substitution on an acyl chloride by sodium azide. The acyl azide is what you would get if you just replaced the  $-\text{CH}=\text{N}_2$  of a diazoketone with  $-\text{N}=\text{N}_2$ . And, if you heat it, it is not surprising that it decomposes to release nitrogen ( $\text{N}_2$ ), forming the nitrene. The nitrene N has only one bond and has two lone pairs, making six electrons in all, like a carbene.



Nitrenes, like carbenes, are immensely reactive and electrophilic, and the same Wolff-style migration (insertion into an adjacent C–C bond) takes place in which the substituent R migrates from carbon to the electron-deficient nitrogen atom of the nitrene. The product is an *isocyanate*. Isocyanates are unstable to hydrolysis: attack by water on the carbonyl group gives a carbamic acid, which decomposes to an amine. Alternatively, reaction with an alcohol gives a carbamate. If the alcohol is  $\text{BnOH}$ , the product is a Cbz-protected amine.

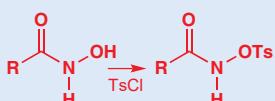
▶ See pp. 556–557 for a discussion of the Cbz group.

the Curtius rearrangement



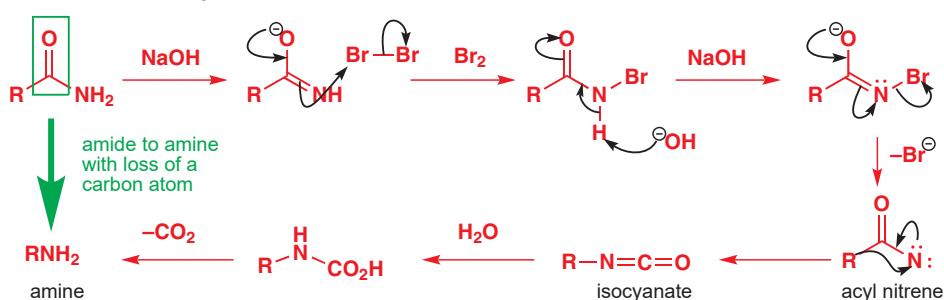
The Curtius rearrangement can be initiated directly from the carboxylic acid using diphenylphosphoryl azide (DPPA),  $(\text{PhO})_2\text{PON}_3$ .

Yet another related reaction is known as the Lossen rearrangement, which starts with the tosylation of a hydroxamic acid (that is, the amide of a hydroxylamine). You should be able to work out what happens next by analogy with the Hofmann rearrangement.



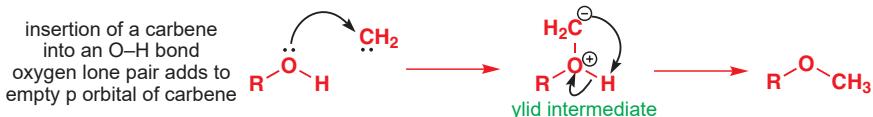
Overall, then, the Curtius rearrangement converts an acid chloride (or an acid) to an amine with loss of a carbon atom—very useful. Also useful is the related Hofmann rearrangement, which turns an amide into an amine with loss of a carbon atom. This time we start with a primary amide and make a nitrene by treatment with base and bromine. Notice how close this nitrene-forming reaction is to the carbene-forming reactions we talked about on p. 1008. The nitrene rearranges just as in the Curtius reaction, giving an isocyanate that can be hydrolysed to the amine.

the Hofmann rearrangement



### Attack of carbenes on lone pairs

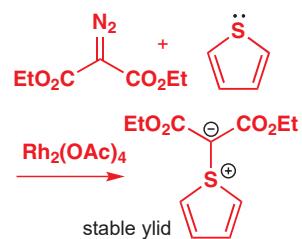
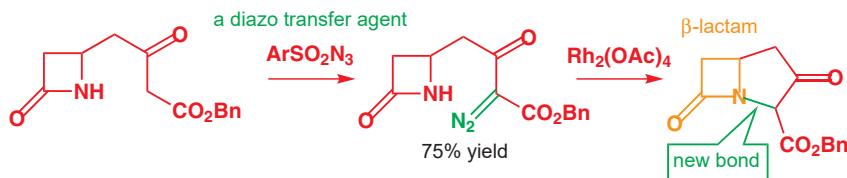
Wolff rearrangements, involving shifts of alkyl groups, are effectively intramolecular insertions into C–C bonds. Carbenes will also insert into other bonds, especially O–H and N–H bonds, although the mechanism in these cases involves initial attack on the lone pair of the heteroatom.



► Ylids (or ylides) are zwitterions in which the charges are on adjacent atoms—you met phosphorus and sulfur ylids in Chapter 27.

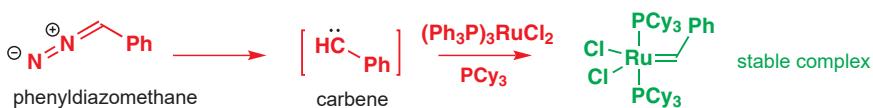
Carbene attack is followed by proton transfer to generate a neutral molecule from the first formed zwitterion (or 'ylid'). However, if the heteroatom does not carry a hydrogen, the ylid cannot rearrange in this way and this type of reaction is a very useful way of making reactive ylids that are inaccessible by other means.

As carbonyl-substituted carbenes (like carbonyl-substituted radicals) are electrophilic, their insertion into O–H and N–H bonds can be a useful way of making bonds in an *umpolung* (polarity-reversed, see Chapter 28) sense. Because of the difficulties in forming  $\beta$ -lactams (the four-membered rings found in the penicillin classes of antibiotics), the pharmaceutical company Merck decided to design a synthesis of the class of compounds known as carbapenems around a rhodium-catalysed carbene insertion into an N–H bond, building the five-membered ring on to the side of the four-membered ring.



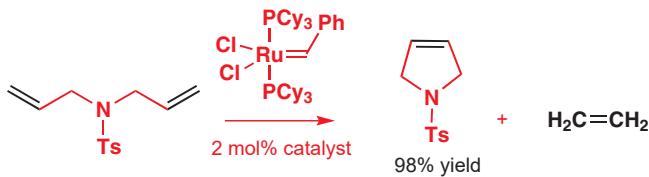
### Alkene metathesis

In this example, and in many before it, the formation of the carbene is initiated by a metal—often copper, rhodium, or silver. The carbene intermediates in these reactions are formed as reactive complexes with those metals, but in other cases the complexes are extremely stable. For example, decomposition of phenyldiazomethane in the presence of a ruthenium(II) complex gives a carbene complex stable enough to be isolated and stored for months. This complex, and a family of related Ru complexes, are among the most important of carbene-derived reagents because of a remarkable reaction known as alkene (or olefin) metathesis.



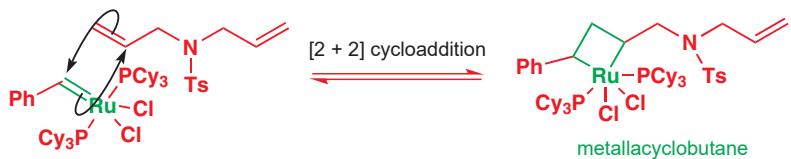
■ The Cy in these complexes represents the cyclohexyl group:  $\text{PCy}_3$  is tricyclohexylphosphine, the saturated analogue of triphenylphosphine.

The reaction is most easily understood when a simple diene reacts with a very small amount (in this case 2 mol%) of the catalyst. A cyclization reaction occurs and the product is also an alkene. It contains no atoms from the catalyst: indeed, it has lost two carbon atoms, which are given off as ethylene.

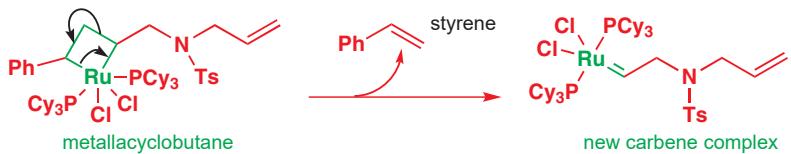


■ The same four carbon atoms in the starting material and in the product are highlighted in black.

What happens is a *metathesis*—an exchange of groups between the two arms of the molecule. But how? The mechanism is not difficult, but is unlike any other you have met before, except, perhaps, the Wittig reaction, which also forms alkenes. First, the carbene complex adds to one of the alkenes in what can be drawn as a [2 + 2] cycloaddition (Chapter 34) to give a four-membered ring with the metal atom in the ring (a ‘metallacyclobutane’).

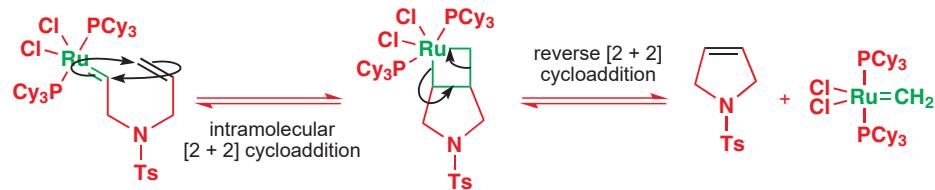


Now the same reaction happens in reverse, either unproductively to give back the starting materials or, by cleavage of the other two bonds, a new carbene complex and styrene.

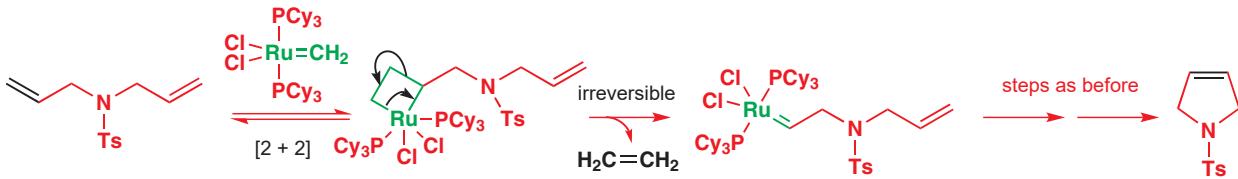


This new complex has the same reactivity as the catalyst we started with, so it will quickly find another alkene to undergo [2 + 2] cycloaddition with. There is now one in the same molecule, so a fast intramolecular reaction joins up the five-membered ring and produces a second metallacyclobutane. As before, there are two alternative ways for this metallacyclobutane to break down, and the productive one gives a third carbene complex and the cyclic product.

Interactive mechanism for alkene metathesis



This new carbene complex is then ready to attack another molecule of starting material and the cycle is repeated, with the minor difference that ethylene (ethene) is now lost instead of styrene in the first step.

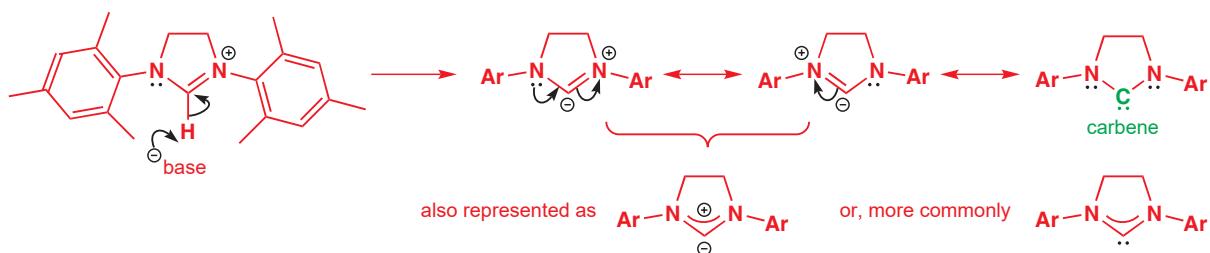


Not a lot can go wrong in this sequence, which is one reason why the yield is so high. Most of the steps are reversible, and the overall reaction is driven by the only irreversible step—the loss of ethylene as a gas. Even if the carbene complex adds the wrong way round to the alkene, nothing is lost because the only thing the resulting metallacycle can do is revert back to starting materials.



## Metathesis catalysts

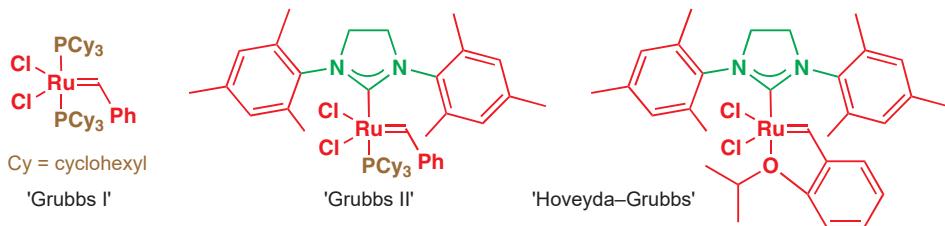
As you might imagine, the discovery of such a simple and efficient way of making new C=C bonds was a revolutionary point in organic chemistry, and earned a Nobel Prize in 2005 for the three chemists instrumental in its development—Yves Chauvin, Richard Schrock, and Robert Grubbs. The catalyst we have just been working with was developed by Grubbs and is often known by his name. The early years of the 21st century also saw a rapid improvement in the effectiveness of the catalysts used for metathesis. The most important development was the discovery of alternatives to the phosphine ligands, a change which increases the activity of the catalyst. The most important alternative ligands are themselves carbenes of the stable 'N-heterocyclic' type we introduced on p. 1006. Here is an important example, made by deprotonation of a heterocyclic cation:



There is a lot of delocalization in this structure, and usually these ligands are represented with a curved line to show the donation of both nitrogen lone pairs to the carbene C atom. You might prefer to include the formal + and – charges, but these compounds really do stretch the classical valence bond representation almost to breaking point, and conventionally the charges are not shown as they cancel out.

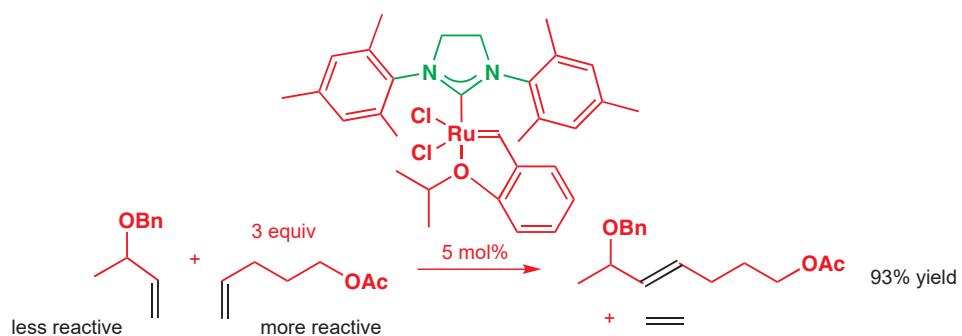
The remaining lone pair on carbon (which is not delocalized) can coordinate to Ru, just like the phosphine lone pair, giving a catalyst known as 'Grubbs II' (the 'second generation' of the 'Grubbs I' we made use of in the metathesis described above). In another widely used catalyst (known as the 'Hoveyda–Grubbs catalyst') the second phosphine is also replaced by intramolecular coordination.

common catalysts for metathesis

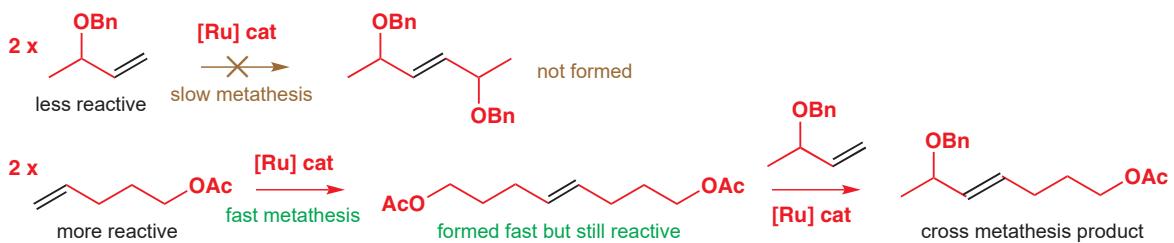


## Cross metathesis

The first metathesis we introduced you to is known, for obvious reasons, as a *ring closing metathesis* reaction, and the formation of rings—even of difficult ring sizes (see Chapters 16 and 31) is one of the supreme applications of metathesis chemistry. However, intermolecular metathesis reactions can also work under certain circumstances, especially when the coupling partners have very different electronic or steric properties. The challenge is of course avoiding each alkene coupling with itself. When one of the two partners is hindered and the other isn't, the cross metathesis reaction works well: the four carbons of the two alkenes swap partners and a new alkene is produced (as its *E* isomer), along with ethylene as a by-product.

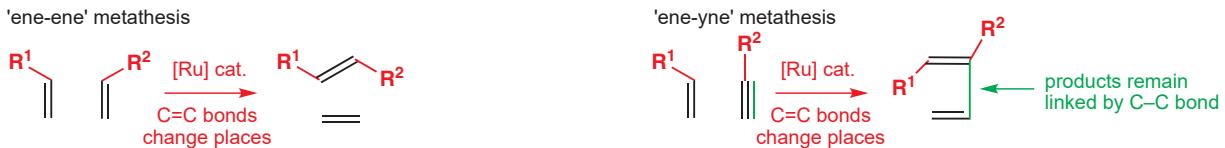


It's not difficult to understand why the less reactive and more hindered alkene doesn't react with itself, but why doesn't the more reactive alkene just dimerize? The point is...it does! But it doesn't matter because even the dimer is reactive as a metathesis substrate, and can still go on to form the product. All the metathesis steps proceed through the reversible [2 + 2] cyclo-addition mechanisms you saw earlier.



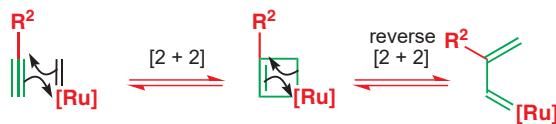
## Ene-yne metathesis

Before we leave metathesis, and carbenes, we need to introduce one final reaction where metathesis leads to a remarkable transformation. Metathesis works on any C=C  $\pi$  bond, but the  $\pi$  bonds need not be an alkene—it can be an *alkyne*. The scheme below shows what happens: the two C=C double bonds change places. When an alkene reacts with an alkene, the result is two new alkenes, but when an alkene reacts with an alkyne, there is still a single bond remaining from the original alkyne, which ends up linking the two products together as a diene.



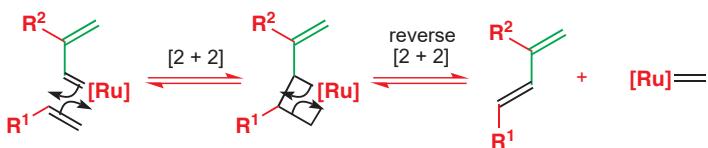
The mechanism follows exactly the same sequence of events as before. First the ruthenium carbene catalyst undergoes [2 + 2] cycloaddition with the alkyne. The intermediate is now a metallacyclobutene, and when the reverse [2 + 2] takes place the Ru carbene is still connected to the alkene product.

- Notice that this time we have started with the  $[Ru]=CH_2$  complex rather than  $[Ru]=CHPh$ —in reality, as shown on p. 1024, the very first time the cycle goes round, the catalyst will transfer styrene, but from then on the mechanism we show will operate.

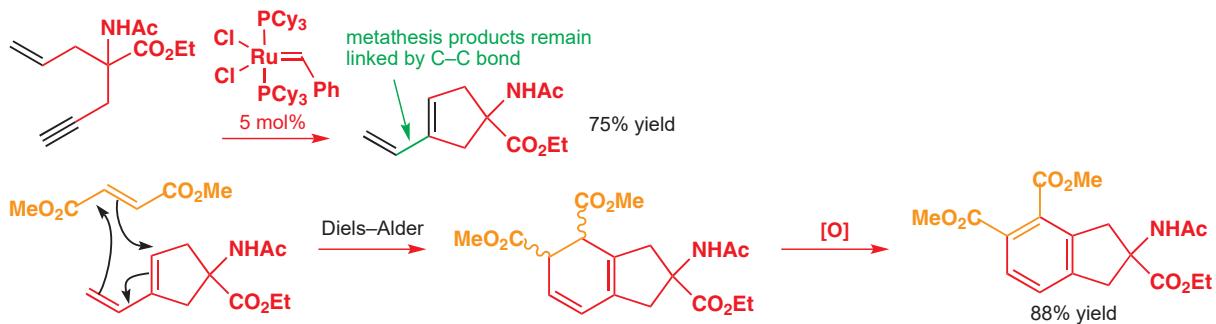


[Ru] represents the ruthenium complex

Now the new carbene can undergo [2 + 2] cycloaddition and reverse [2 + 2] cycloaddition again, this time with the alkene component, and out comes the diene, plus a Ru carbene ready to start the cycle again.

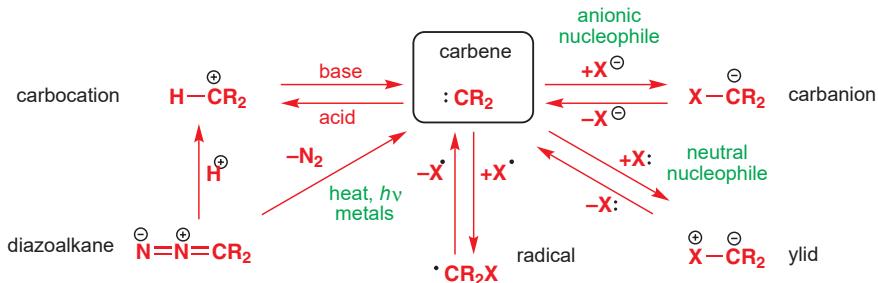


Ene-yne metathesis is therefore a valuable way of constructing dienes—of the type you might require for a Diels–Alder reaction, for example. Unlike more reactive organometallics such as organolithiums and Grignard reagents, the Ru carbenes are fully compatible with acidic NH and OH bonds and with electrophilic carbonyl groups. You will meet more of the mild chemistry possible with organometallics in Chapter 40.



## Summary

We have seen in this chapter how carbenes can be formed from many other reactive intermediates, such as carbocations, carbanions, and diazoalkanes, and how they can react to give yet further reactive intermediates such as ylids. Here is a summary of the main relationships between a carbene  $:CR_2$  and these other compounds.



In the last few chapters we have concentrated a lot on what we call reactive intermediates, species like radicals, carbenes, or carbocations that are hard to observe but that definitely exist. Much of the evidence for their existence derives from the study of the mechanisms of reactions. We have discussed some aspects of this as we have met the species concerned, but in the next chapter we will look in detail at how mechanisms are elucidated and the methods used to determine more precisely the structure of reactive intermediates.

## Further reading

*Reactive Intermediates*, C. J. Moody and G. H. Whitham, Oxford Primer, OUP, Oxford, 2001, has a section on carbenes. A more advanced book is G. Bertand, *Carbene Chemistry*, Fontis Media and Marcel Dekker, 2002. Rules for cross-metathesis are in R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360.

Reviews on metathesis by the chief stars are R. H. Grubbs, *Tetrahedron*, 2004, **60**, 7117 and R. R. Schrock and A. H. Hoveyda, *Angew. Chem. Int. Ed.*, 2003, **42**, 4592.

## Check your understanding

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To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 确定反应机理

## 联系

### 基础

- Mainly builds on ch12
- Acidity and basicity ch8
- Carbonyl reactions ch6, ch10, & ch11
- Nucleophilic substitution at saturated carbon ch15
- Controlling stereochemistry ch14, ch32, & ch33
- Eliminations ch17
- Electrophilic and nucleophilic aromatic substitution ch21 & ch22
- Cycloadditions ch34
- Rearrangements ch35 & ch36
- Fragmentations ch36
- Saturated heterocycles and stereoelectronics ch31
- Chemistry of S, B, Si, and Sn ch27

### 目标

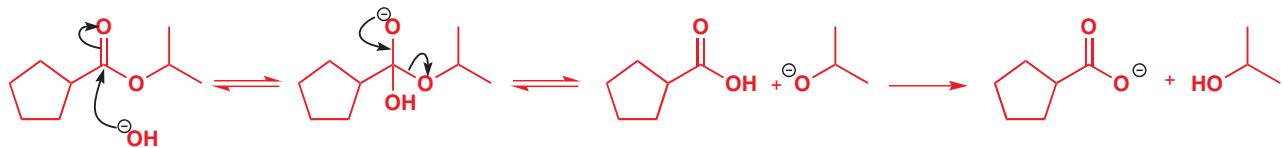
- Classes and types of mechanisms
- Importance of proposing a mechanism
- Structure of the product is all-important
- Labelling and double labelling
- Systematic structure variation and electronic demand
- The Hammett relationship explained
- Deuterium isotope effect (kinetic and solvent)
- Specific acid and specific base catalysis
- General acid and general base catalysis
- Detecting and trapping intermediates
- Why stereochemistry matters

### 展望

- Asymmetric synthesis ch41
- The chemistry of life ch42

## There are mechanisms and there are mechanisms

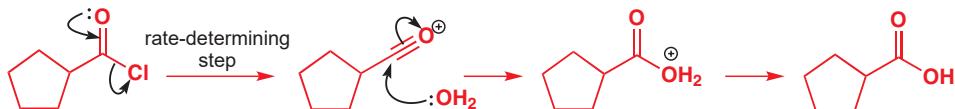
There are two types of answer to the question ‘What is the mechanism of this reaction?’. If you were asked to draw the mechanism of an ester hydrolysis in basic solution you should have no trouble in giving a good answer of the first type. It wouldn’t matter if you had never seen this particular ester before or even if you knew that it had never actually been made, because you would recognize that the reaction belonged to a class of well-known reactions (carbonyl substitution reactions, Chapter 10) and you would assume that the mechanism was the same as that for other ester hydrolyses. And you would be right—nucleophilic attack on the carbonyl group to form a tetrahedral intermediate is followed by loss of the alkoxide leaving group and formation of the anion of the carboxylic acid.



Yet someone at some time had to determine this mechanism in full detail. That work was done in the 1940s to 1960s and it was done so well that nobody seriously challenges it.

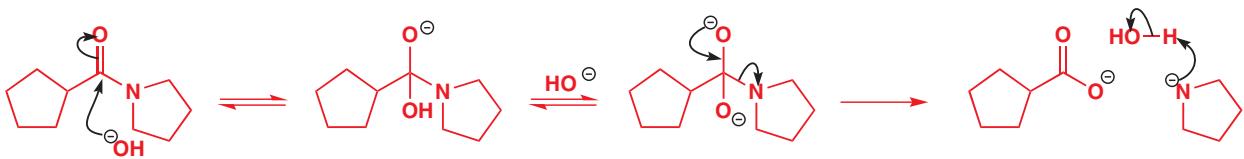
► This mechanism is described on p. 259.

You might also recall from Chapter 12 that, if we change the carbonyl compound to an acid chloride, the mechanism may change to an  $S_N1$  reaction with an acylium ion intermediate because the leaving group is now much better:  $\text{Cl}^-$  is more stable (less basic) than  $\text{RO}^-$ . It would not be worth using hydroxide for this reaction: as the first step is the slow step, water will do just as well. Again someone had to determine this mechanism, had to show which was the slow step, and had to show that leaving group ability depended on the  $pK_a$  of its conjugate base.



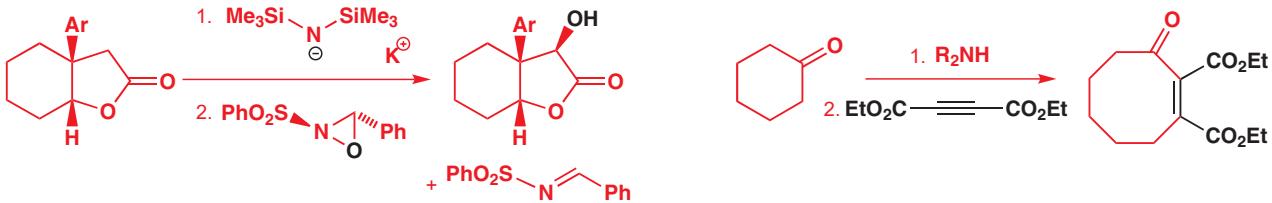
► Third-order kinetics, and this amide hydrolysis mechanism, were discussed on p. 260.

If the reaction were the hydrolysis of an amide, you might remember from Chapter 12 that third-order kinetics are often observed for the expulsion of such bad leaving groups and that this extra catalysis makes it worthwhile using concentrated base. Again, someone had to find out that: (1) the slow step is now the decomposition of the tetrahedral intermediate, (2) there are third-order kinetics involving two molecules of hydroxide, and (3) the first molecule acts as a nucleophile and the second as a base.



These three mechanisms are all versions of the same reaction. For you, writing these mechanisms chiefly means recognizing the type of reaction (nucleophilic substitution at the carbonyl group) and evaluating how good the leaving group is. For the original chemists, determining these reaction mechanisms meant: (1) determining exactly what the product is (that may sound silly, but it is a serious point), (2) discovering how many steps there are and the structures of the intermediates, (3) finding out which is the slow (rate-determining) step, and (4) finding any catalysis. This chapter describes the methods used in this kind of work—the detailed, second type of answer to ‘What is the mechanism of this reaction?’.

Now, suppose you were asked what the mechanisms of the next two reactions might be. This is a rather different sort of problem as you may well not recognize any of these reagents and you probably cannot fit any of the reactions into one of the classes you have seen so far. You may not even see at once which of the three main classes of mechanism you should use: ionic, pericyclic, or radical.



You may do your best to write a mechanism based on your understanding of organic chemistry, moving the electrons from nucleophiles to electrophiles, choosing sensible intermediates, and arriving at the right products. You would not claim any authority for the result, but you would hope, as an organic chemist, to propose one or more reasonable possibilities.

This process of proposing reasonable mechanisms is actually an essential preliminary to answering the question in the second way—finding the real, experimentally verified, mechanism for the reaction. We will now look at some of the techniques used to find such answers with an old curiosity of a reaction, the Cannizzaro reaction, as an example.

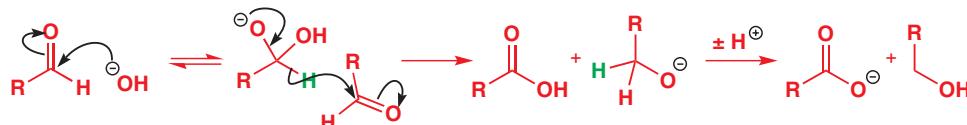
## Determining reaction mechanisms: the Cannizzaro reaction

So how do we know the mechanism of a reaction? The simple answer is that we don't for certain. Organic chemists have to face situations where the structure of a compound is initially thought to be one thing but later corrected to be something different. The same is true of mechanisms. It is the nature of science that all we can do is try to account for observations by proposing a hypothesis. We then test the hypothesis by experiment and, when the experiment does not fit the hypothesis, we must start again with a new hypothesis. This is exactly the case with mechanisms. When a new reaction is discovered, one or more mechanisms are proposed; evidence is then sought for and against these mechanisms until one emerges as the best choice. That one then remains the accepted mechanism for the reaction until fresh evidence comes along that does not fit the mechanism.

We are going to look at one reaction, the Cannizzaro reaction, and use this to introduce the different techniques used in elucidating mechanisms so that you will be able to appreciate the different information each experiment brings to light and how all the pieces fit together to leave us with a probable mechanism. Under strongly basic conditions, an aldehyde with no  $\alpha$  hydrogens undergoes disproportionation to give half alcohol and half carboxylate. Disproportionation means one half of the sample is oxidized by the other half, which is itself reduced. In this case, half the aldehyde reduces the other half to the primary alcohol and in the process is oxidized to the carboxylic acid. Before the discovery of  $\text{LiAlH}_4$  in 1946, this was one of the few reliable ways to reduce aldehydes and so was of some use in synthesis.

Here is a simple mechanistic scheme of what happens—the sort of thing you might reasonably propose if you had not seen the reaction before.

► The Cannizzaro reaction first appeared in Chapter 26.



It's not the only possible mechanism by any means—and you may spot that it is slightly different from the one in Chapter 26, where we showed a dianion as an intermediate. We'll now work through some of the alternative mechanisms that have been proposed for the Cannizzaro reaction, along with the evidence for or against them. Most of these alternatives have been eliminated, leaving just the ones you have already met. Finally, we will see that even these mechanisms do not explain everything absolutely.

### Proposed mechanism A: a radical mechanism

Early on it was thought that the hydrogen transfer might be taking place via a radical chain reaction. If this were the case, then the reaction should go faster if radical initiators are added and it should slow down when radical inhibitors are added. When this was tried, there was no change in the rate, so this proposed mechanism was ruled out.

► For some examples of radical initiators and inhibitors, see Chapter 37. Radical inhibitors are usually stable radicals, such as those on p. 975.

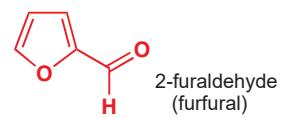
### Kinetic evidence for an ionic mechanism

The first piece of evidence that must be accounted for is the rate law. For the reaction of benzaldehyde with hydroxide, the reaction is first order with respect to hydroxide ions and second order with respect to benzaldehyde (third order overall).

$$\text{rate} = k_4[\text{PhCHO}]^2[\text{HO}^-]$$

For some aldehydes, such as formaldehyde and furfural, the order with respect to the concentration of hydroxide varies between one and two depending on the exact conditions. In high concentrations of base it is fourth order.

$$\text{rate} = k_4[\text{RCHO}]^2[\text{HO}^-]^2$$



At lower concentrations of base the rate law is a mixture of both third- and fourth-order terms.

$$\text{rate} = k_3[\text{RCHO}]^2[\text{HO}^-] + k_4[\text{RCHO}]^2[\text{HO}^-]^2$$

► See p. 261 for an explanation of this important point.

Just because the overall order of reaction is third or fourth order, it does not mean that all the species must simultaneously collide in the rate-determining step. You saw in Chapter 12 that the rate law actually reveals all the species that are involved *up to and including* the rate-determining step.

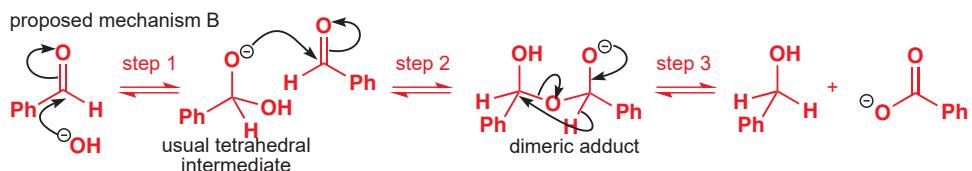
### Isotopic labelling

When the reaction is carried out in  $\text{D}_2\text{O}$  instead of in  $\text{H}_2\text{O}$  it is found that there are no C–D bonds in the products. This tells us that the hydrogen must come from the aldehyde and not from the solvent.

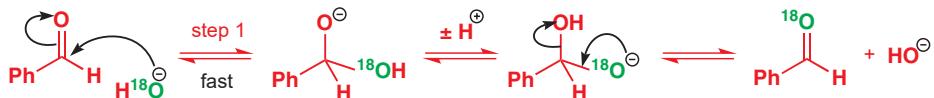


### Proposed mechanism B: formation of an intermediate dimeric adduct

A possible mechanism that fits all the experimental evidence so far involves nucleophilic attack of the usual tetrahedral intermediate on another aldehyde to give an intermediate adduct. This adduct could then form the products directly by hydride transfer. You may not like the look of this last step, but the mechanism was proposed and evidence is needed to disprove it.

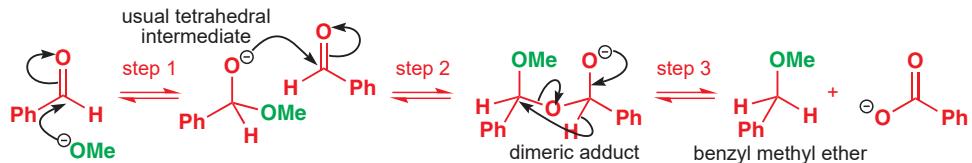


Which step would be rate determining for this mechanism? It could not be step 1 since, if this were the case, the rate law would be first order with respect to the aldehyde rather than the observed second-order relationship. Also, if the reaction is carried out in water labelled with oxygen-18, the oxygen in the benzaldehyde exchanges with the  $^{18}\text{O}$  from the solvent much faster than the Cannizzaro reaction takes place. This can only be because of a *rapid* equilibrium in step 1 and so step 1 cannot be rate determining.



So, for mechanism B, either step 2 or step 3 could be rate determining—either case would fit the observed rate law. Step 2 is similar to step 1: in both cases an oxyanion nucleophile attacks the aldehyde. Since the equilibrium in step 1 is very rapid, it is reasonable to suggest that the equilibrium in step 2 should also be rapid and thus that the hydride transfer in step 3 must be rate determining. So mechanism B can fit the rate equation.

How can mechanism B be ruled out? One way is to change the attacking nucleophile. The Cannizzaro reaction works equally well if methoxide is used in a mixture of methanol and water. If mechanism B were correct, the reaction with methoxide would be as follows.

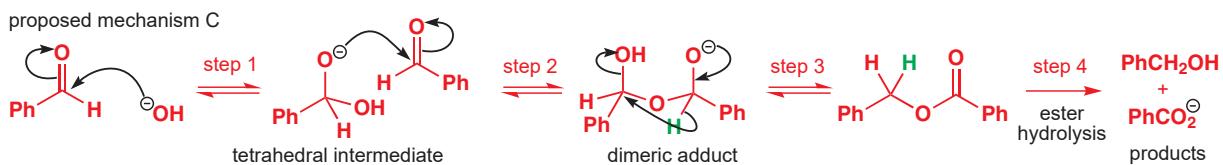


One of the products would be different by this mechanism: benzyl methyl ether would be formed instead of benzyl alcohol. None is observed experimentally. Moreover, under the conditions of the experiment, benzyl methyl ether does not react to form benzyl alcohol, so it cannot be the case that the ether is formed but then reacts to form the products. Mechanism B can therefore be ruled out.

→ We shall discuss this kind of technique as well as other evidence used to evaluate an intermediate towards the end of this chapter.

### **Proposed mechanism C: formation of an ester intermediate**

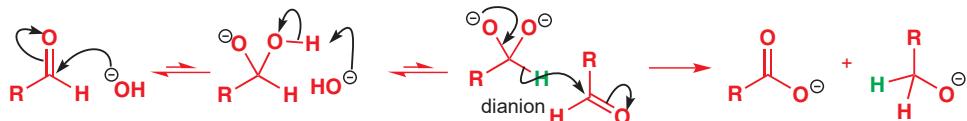
This mechanism is like mechanism B but the hydride transfer in the adduct formed in step 2 displaces OH<sup>-</sup> to form an ester (benzyl benzoate) that is then hydrolysed to the products. This was at one time held to be the correct mechanism for the Cannizzaro reaction. One piece of evidence for this, and at first glance a very good one, is that by cooling the reaction mixture and avoiding excess alkali, some benzyl benzoate could be isolated during the reaction. An important point is that this does not mean that the ester must be an *intermediate* in the reaction—it might be formed at the end of the reaction, for example. However, it does mean that any mechanism we propose must be able to account for its formation. For now though we want to try to establish whether the ester is an intermediate rather than a by-product in the Cannizzaro reaction.



An early objection to mechanism C was that the ester would not be hydrolysed fast enough. When someone actually tried it under the conditions of the experiment, they found that benzyl benzoate is very rapidly hydrolysed (the moral here is ‘don’t just think about it, try it!’). However, just because the ester *could* be hydrolysed, it still did not show that it actually was an intermediate in the reaction. How this was eventually shown was rather clever. The argument goes like this. We can measure the rate constant for step 4 by seeing how quickly pure benzyl benzoate is hydrolysed to benzyl alcohol and benzoate under the same conditions as those of the Cannizzaro reaction. We also know how quickly these products are formed during the Cannizzaro reaction itself. Since, if this mechanism is correct, the only way the products are formed is from this intermediate, it is possible to work out how much of the intermediate ester must be present at any time to give the observed rate of formation of the products. If we can measure the amount of ester that is actually present and it is significantly less than that which we predict, then this cannot be the correct mechanism. It turned out that there was never enough ester present to account for the formation of the products in the Cannizzaro reaction and mechanism C could be ruled out.

## The correct mechanism for the Cannizzaro reaction

The only mechanism that has not been ruled out and that appears to fit all the evidence is the one we have already given (p. 1031). The fact that the rate law for this mechanism is overall third and sometimes fourth order depending on the aldehyde and the conditions can be explained by the involvement of a second hydroxide ion deprotonating the tetrahedral intermediate to give a dianion. When methoxide is used in a methanol/water mix, some methyl ester is formed. This does not stay around for long—under the conditions of the experiment it is quickly hydrolysed to the carboxylate.



### Even this mechanism does not quite fit all the evidence

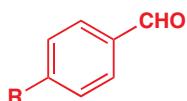
We said earlier that we can never prove a mechanism—only disprove it. Unfortunately, just as the ‘correct’ mechanism seems to be found, there are some observations that make us doubt this mechanism. In Chapter 37 you saw how a technique called **electron spin resonance (ESR)** (or electron paramagnetic resonance, EPR) detects radicals and gives some information about their structure. When the Cannizzaro reaction was carried out with benzaldehyde and a number of substituted benzaldehydes in an ESR spectrometer, a radical was detected. For each aldehyde used, the ESR spectrum proved to be identical to that formed when the aldehyde was reduced using sodium metal. The radical formed was the radical anion of the aldehyde.



Our mechanism does not explain this result, but small amounts of radicals are formed in many reactions in which the products are actually formed by simple ionic processes. Detection of a species in a reaction mixture does not prove that it is an intermediate. Few chemists think that radicals are involved in the Cannizzaro reaction. Most think the mechanism we have given is correct.

### Variation in the structure of the aldehyde

Before leaving the Cannizzaro reaction, look at these rates of reactions for aromatic aldehydes with different substituents in the *para* position. These aldehydes may be divided into two classes: those that react faster than unsubstituted benzaldehyde and those that react more slowly. Those that go slower all have something in common—they all have substituents on the ring that donate electrons.



Rate of Cannizzaro reaction with aromatic aldehydes

R =	Rate relative to benzaldehyde at 25°C	Rate relative to benzaldehyde at 100°C
H	1	1
Me	0.2	0.2
MeO	0.05	0.1
Me <sub>2</sub> N	very slow	0.0004
NO <sub>2</sub>	210	2200

We have already seen how substituents on a benzene ring affect the rate of electrophilic substitution (Chapter 21). Electron-donating groups such as MeO and Me<sub>2</sub>N dramatically speed up the rate at which an aromatic ring is attacked by an electrophile, whereas electron-withdrawing groups, particularly nitro groups, slow the reaction down. The Cannizzaro reaction is not taking place on the benzene ring itself, but substituents on the ring still make their presence known. The fact that the Cannizzaro reaction goes much *slower* with electron-donating groups and faster with electron-withdrawing groups tells us that, for this reaction, rather than a positive charge developing, as in the case of electrophilic substitution on an aromatic ring, there must be negative charge accumulating somewhere near the ring. The accumulation of more negative charge is disfavoured by the presence of a group that is already offloading electron density into the ring. In agreement with this, our mechanism has mono- and dianion intermediates, which are stabilized by electron-withdrawing groups and destabilized by electron-donating groups.

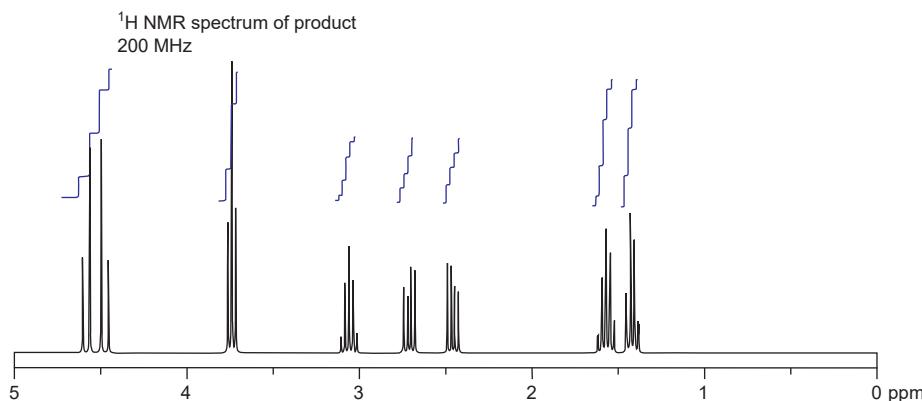
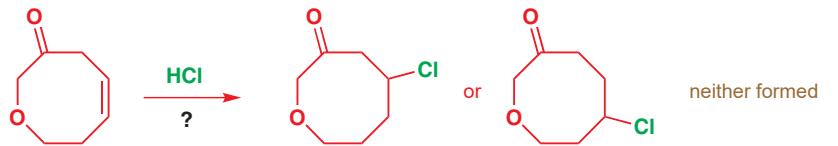
► Later in the chapter you will see a more quantitative treatment of this variation of structure.

The rest of the chapter is devoted to discussions of methods similar to those we have briefly surveyed for the Cannizzaro reaction, with examples of the use of each method. You can assume that the mechanisms we have discussed in this book have been verified (not, of course, proved) by these sorts of methods.

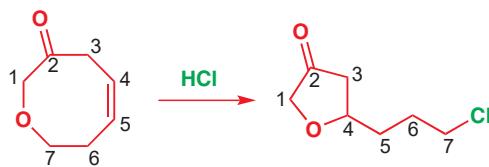
## Be sure of the structure of the product

This seems a rather obvious point. However, there is a lot to be learned from the detailed structure of the product: its connectivity (which atom goes where) as well as its stereochemistry. You will see that it may be necessary to alter the structure of the starting material in subtle ways to make sure that we know exactly what happens to all its atoms by the time it reaches the product.

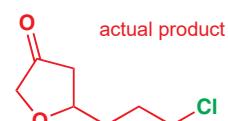
Suppose you are studying the addition of HCl to this alkene. You find that you get a good yield of a single adduct and you might be a bit surprised that you do not get a mixture of the two obvious adducts. You may wonder if there is some participation of the ether oxygen or whether perhaps the ketone enolizes during the reaction and controls the outcome.

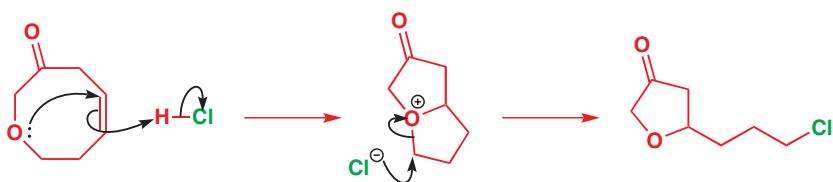


If you are cautious you might check on the structure of the product before you start a mechanistic investigation. The NMR spectrum (above) tells you at once that the product is neither of these suggestions. It contains a  $(\text{CH}_2)_3\text{Cl}$  unit and can no longer have an eight-membered ring. A ring contraction has given a five-membered ring and a mechanistic investigation is hardly needed. Simply knowing what the product is allows us to propose a mechanism. A rearrangement has occurred and we could use the method suggested in Chapter 36: number the atoms in the starting material and find them in the product. This is quite easy as only one numbering system makes any sense.



This numbering suggests that the carbon skeleton is unaffected by the reaction, that protonation has occurred at C5, that the ether oxygen has acted as an internal nucleophile across the ring at C4, and that the chloride ion has attacked C7. The mechanism is straightforward.

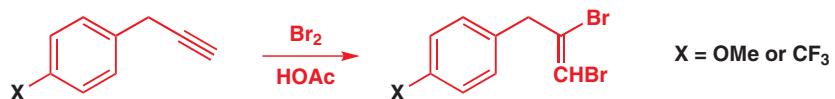




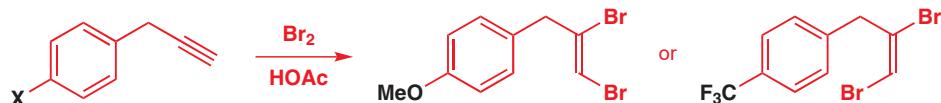
It may be disappointing to find that every step in this mechanism is well known and that the reaction is exactly what we ought to have expected with an eight-membered ring as these rings are famous for their transannular (across-ring) reactions to form 5/5 fused systems. However, it is good that a prolonged investigation is not necessary.

- Find out for sure what the structure of the product is before you start a mechanistic investigation.

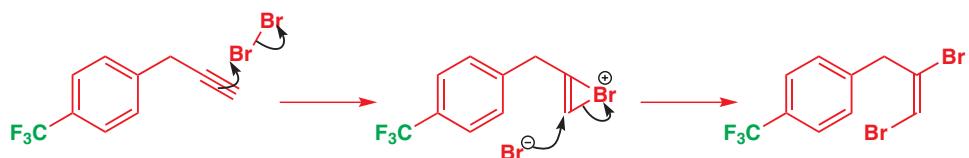
A more subtle distinction occurred in a study of the bromination of alkynes. Bromination of benzyl alkynes in acetic acid gave the products of addition of one molecule of bromine—the 1,2-dibromoalkenes. The reaction was successful with a variety of *para* substituents and there seems at first to be no special interest in the structure of the products.



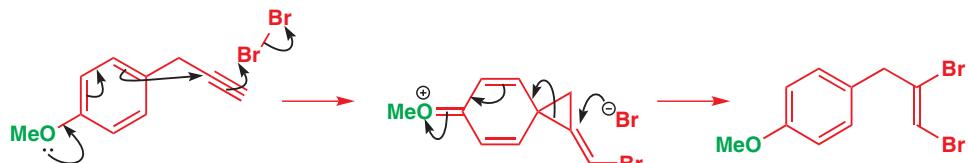
Closer investigation revealed an extraordinary difference between them, not at all obvious from their NMR spectra: the compound from  $X=OMe$  was the *Z*-dibromoalkene from *cis* addition of bromine while the product from  $X=CF_3$  was the *E* alkene from *trans* addition. What mechanism could explain this difference?



The *anti* addition is more easily explained: it is the result of formation of a bromonium ion, similar, in fact, to the normal mechanism for the bromination of alkenes. Bromine adds from one side of the alkene and the bromide ion must necessarily form the *E*-dibromo product regardless of which atom it attacks.



So why does the *p*-methoxy-substituted compound behave differently? It cannot react by the same mechanism and a reasonable explanation is that the much more electron-donating ring participates in the reaction to give a carbocyclic three-membered ring intermediate that is attacked in an *anti* fashion to give the *Z* alkene. Both intermediates are three-membered ring cations and both are attacked with inversion but the *p*-MeO compound undergoes double inversion by participation of the ring.

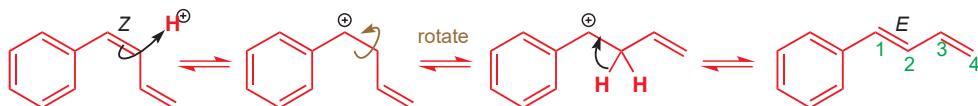


► A similar aryl participation in saturated compounds, giving a 'phenonium ion' intermediate, appears in Chapter 36, p. 936.

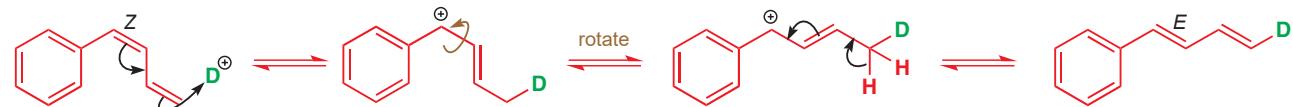
## Labelling experiments reveal the fate of individual atoms

It often happens that the atoms in starting material and product cannot be correlated without at least one of them being labelled. The fact that many elements exist as different isotopes provides us with a perfect way of doing this: a neutron more or less in the nucleus affects the physics (and hence the spectroscopic features) of an atom, but not its chemistry.

The isomerization of Z-1-phenylbutadiene to the E diene in acid looks like a simple reaction. Protonation of the Z alkene would give a stabilized secondary benzylic cation that should last long enough to rotate. Loss of the proton would then give the more stable E diene.

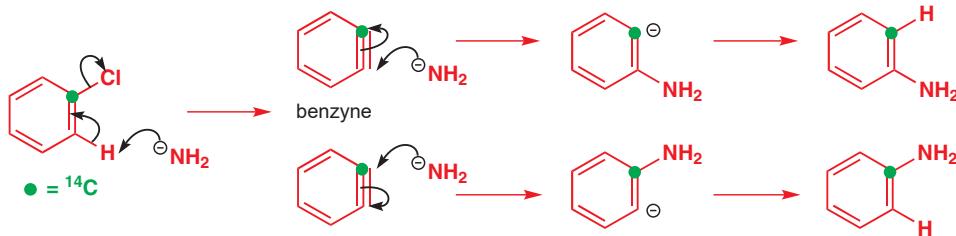


However, reaction with D<sup>+</sup> in D<sub>2</sub>O reveals that this mechanism is incorrect. The product contains substantial amounts of deuterium at C4, not at C2 as predicted by the proposed mechanism. Protonation must occur at the end of the conjugated system to produce the more stable conjugated cation, which rotates about the same bond and loses H or D from C4 to give the product. More H than D will be lost, partly because there are two Hs and only one D, but also because of the kinetic isotope effect, of which more later.

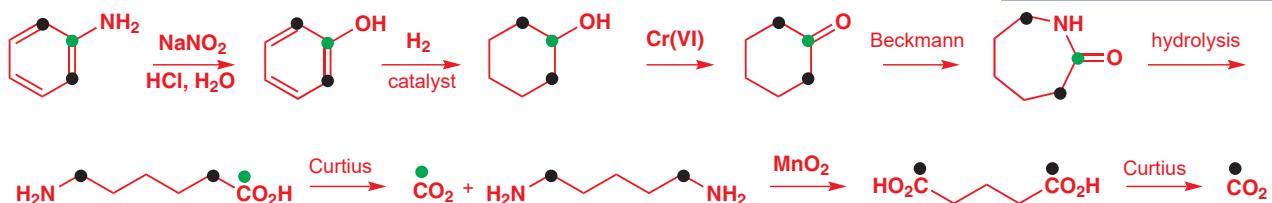


The easiest labels to use for this job are D for H, <sup>13</sup>C, and <sup>18</sup>O. None of these is radioactive; all can be found by mass spectrometry, while D and <sup>13</sup>C can be found by NMR. Older work on mechanisms used radioactive tracers such as T (tritium, <sup>3</sup>H) for H and <sup>14</sup>C.

The first evidence for benzyne as the intermediate in the reaction of chlorobenzene with NH<sub>2</sub><sup>-</sup> came from radioactive labelling. If benzyne is an intermediate, the product should have 50% label at C1 and 50% at the two identical *ortho* carbons, as the scheme below shows.



The labelled aniline was degraded by the reactions shown here, which you must agree was a lot of work for the chemists concerned. Each potentially labelled carbon atom had to be isolated from any other labelled atom and the radioactivity measured. We shall follow the fate of the two labelled atoms with black and green spots. Since the two *ortho* positions are identical, we must put a black spot on both of them.



Most of these reactions are well known—the Beckmann rearrangement is described in Chapter 36 and the Curtius reaction in Chapter 38—but the oxidation of the diamine to the

■ In fact a feature known as the *kinetic isotope effect* means that isotopes of an element can have subtly different chemistry, as we will explain on p. 1050.

■ Radioactive isotopes are, of course, more dangerous to use but they can at least always be found. The real disadvantage is that, to discover exactly where they are in the product, the molecule must be degraded in a known fashion. Radioactive isotopes are rarely used now except in determining biological mechanisms, as you will see in Chapter 42. Tritium and <sup>14</sup>C are β emitters—they give off electrons—having half-lives of 12 and over 5000 years, respectively. Tritium is made on a large scale by neutron irradiation of <sup>6</sup>Li in a nuclear reactor.

► Interactive mechanism showing benzyne intermediate

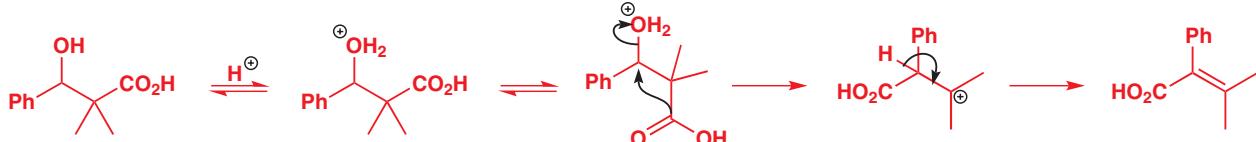
► Benzyne is discussed in Chapter 22 as an intermediate in nucleophilic aromatic substitution.

■ Other symmetrical intermediates originally identified by radioactive labelling include the cyclopropanone in the Favorskii rearrangement in Chapter 36, p. 950, and a spirocyclic intermediate in electrophilic substitution on an indole in Chapter 29, p. 746.

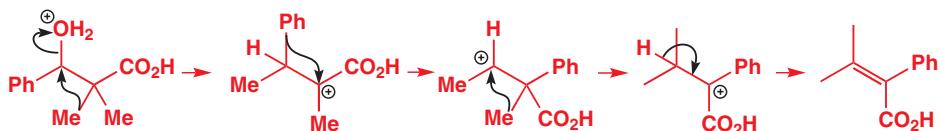
dicarboxylic acid is not a standard procedure and is not recommended. All the label came out in the  $\text{CO}_2$  and almost exactly half of it was from the black and half from the green labelled carbons. This was the original evidence that convinced organic chemists in 1953 that benzene was involved in the reaction. The evidence presented in Chapter 22 is much more modern.

### The value of double labelling experiments

An altogether more modern approach to a labelling study was used in the surprising rearrangement of a hydroxy-acid in acidic solution. The structure of the product suggests a  $\text{CO}_2\text{H}$  migration as the most likely mechanism. This mechanism resembles closely the cationic rearrangements of Chapter 36.

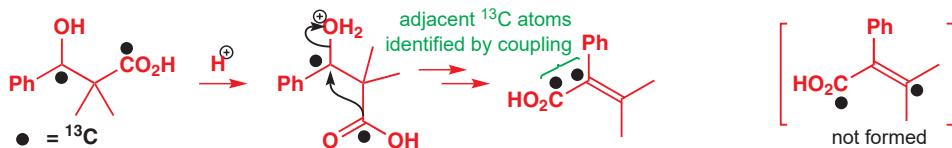


But there are other possibilities: received wisdom (Chapter 36) suggests that the best migrating group in cationic rearrangements is the one best able to bear a positive charge, by which logic the more familiar Ph and Me migrations ought to be preferred. A more elaborate mechanism can be written: it involves two methyl migrations and one phenyl migration and it also needs consideration.



■ We don't normally see  $^{13}\text{C}$ - $^{13}\text{C}$  coupling because in most molecules only 1.1% of the C atoms are  $^{13}\text{C}$ , so there's little chance of two of them finding themselves adjacent to one another. But when both C atoms are always  $^{13}\text{C}$ , the coupling becomes evident.

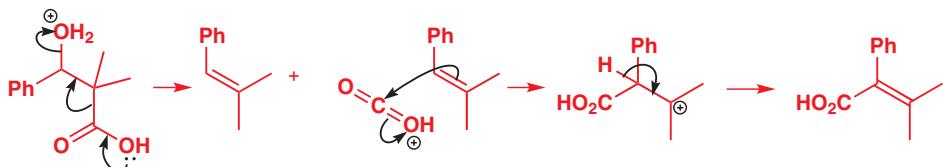
These mechanisms can be tested by finding out whether the  $\text{CO}_2\text{H}$  group remains attached to its original position or becomes attached to the other carbon in the skeleton of the molecule. This can be done by double labelling. If a compound is prepared with two  $^{13}\text{C}$  labels, one on the  $\text{CO}_2\text{H}$  group itself and one on the benzylic carbon, the NMR spectrum of the product will show what has happened. In fact, the two  $^{13}\text{C}$  labels end up next to each other with a coupling constant  $^1J_{\text{CC}} = 71 \text{ Hz}$ . It is the  $\text{CO}_2\text{H}$  group that has migrated.



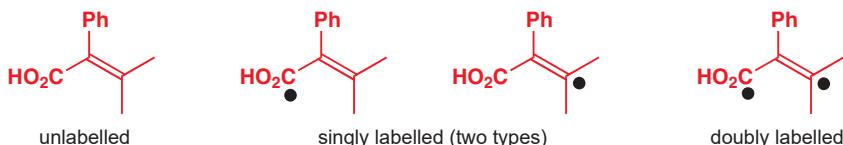
So why does the  $\text{CO}_2\text{H}$  group migrate? It does so not because it is a good migrating group, but because it cannot bear to be left behind. The rearranged cation from  $\text{CO}_2\text{H}$  migration is a stable tertiary alkyl cation. The cation from Me migration is a very unstable cation, with the positive charge next to the  $\text{CO}_2\text{H}$  group. Such cations are unknown as the carbonyl group is very electron withdrawing.

### 'Crossover' experiments

There is still one tiny doubt. Supposing the reaction is not intramolecular at all, but *intermolecular*. The  $\text{CO}_2\text{H}$  group might be lost from one molecule as protonated  $\text{CO}_2$  and be picked up by another molecule of alkene. No migration would be involved at all.



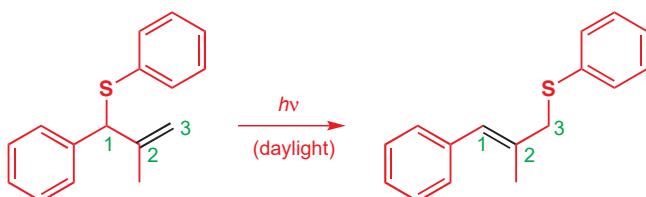
This mechanism can be checked by using a 50:50 mixture of doubly labelled and unlabelled starting material. The molecule of alkene that captures the roving protonated labelled  $\text{CO}_2$  might happen to be labelled too but equally well it might be unlabelled. If this last mechanism is correct, we should get a mixture of unlabelled, singly labelled, and doubly labelled product in the ratio 1:2:1 as there are two types of singly labelled product. The two singly labelled compounds are called the crossover products and the experiment is called a crossover experiment as it discovers whether any parts of one molecule cross over to another.



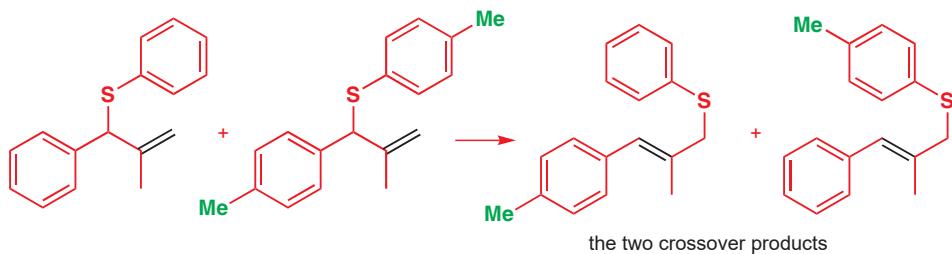
There is an example of a crossover experiment proving that an  $S_N2$  reaction is intermolecular in Chapter 31, p. 811 and one proving the mechanism of a rearrangement on pp. 959–960.

In fact, no singly labelled compounds were found: NMR analysis showed that the product consisted entirely of unlabelled or doubly labelled molecules. The  $\text{CO}_2\text{H}$  group remains attached to the same molecule (though not to the same atom) and the first mechanism is correct.

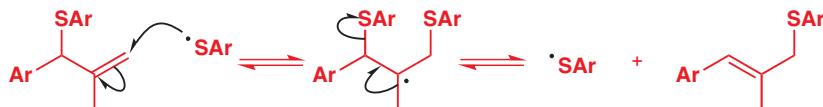
Crossover experiments demand some sort of double labelling, which does not have to be isotopic. An example where crossover products are observed is the light-initiated isomerization of allylic sulfides.



This is formally a [1,3] sigmatropic shift of sulfur (Chapter 35) but that is an unlikely mechanism (and you should be able to suggest why). A crossover experiment was carried out in which the two molecules had either two phenyl groups or two *para*-tolyl groups. The mixture was allowed to rearrange in daylight and the products were examined by mass spectroscopy. There was a roughly 1:2:1 mixture of products having two phenyl groups, one phenyl and one *para*-tolyl group, and two *para*-tolyl groups. The diagram shows the starting materials and the two crossover products only.



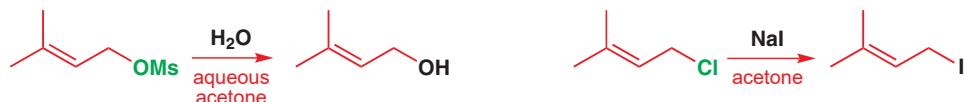
Clearly, the  $\text{ArS}$  group had become separated from the rest of the molecule and the most likely explanation was a radical chain reaction (Chapter 37) with the light producing a small amount of  $\text{ArS}^\bullet$  to initiate the chain. The *para*-methyl group acts as a label. The whole system is in equilibrium and the more highly substituted alkene is the product.



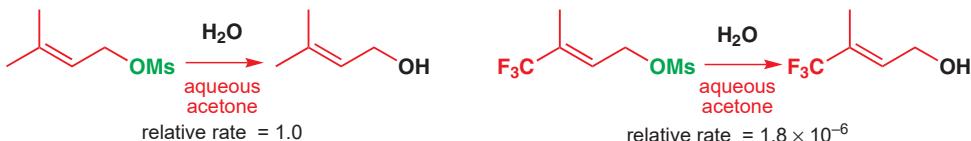
## Systematic structural variation

In this last example, the hope is that the *para*-methyl group will have too weak an electronic or steric effect and in any case will be too far away to affect the outcome. It is intended to make nearly as slight a change in the structure as an isotopic label. Many structural investigations have exactly the opposite hope. Some systematic change is made in the structure of the molecule in the expectation of a predictable change in rate. A faster or slower reaction will lead to some definite conclusion about the charge distribution in the transition state.

Allylic compounds can react efficiently with nucleophiles by either the S<sub>N</sub>1 or S<sub>N</sub>2 mechanisms (Chapter 15). Here are two examples.



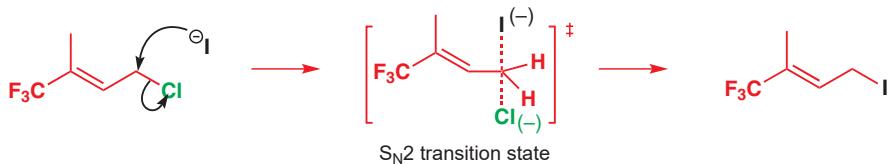
The carbon skeleton is the same in both reactions but the leaving groups and the nucleophiles are different. These reactions might both go by S<sub>N</sub>1 or S<sub>N</sub>2 or one might go by S<sub>N</sub>1 and the other by S<sub>N</sub>2. One way to find out is to make a large change in the electronic nature of the carbon skeleton and see what happens to the rate of each reaction. In these experiments one of the methyl groups was changed for a CF<sub>3</sub> group—exchanging a weakly electron-donating group for a strongly electron-withdrawing group. If a cation is an intermediate, as in the S<sub>N</sub>1 reaction, the fluorinated compound will react much more slowly. Here is the result in the first case.



The fluorinated compound reacts half a million times more slowly so this looks very much like an S<sub>N</sub>1 mechanism. The slow step in an S<sub>N</sub>1 mechanism is the formation of a carbocation so any group that destabilizes the positive charge would have (and evidently does have) a large effect on the rate. Rate ratios of several powers of ten often are worth noticing and a rate ratio of nearly 10<sup>6</sup> is considerable. In the second case the rate difference is much less.



A rate ratio of 11 is not worth noticing. The point is not that the fluorinated compound reacts faster but that the two compounds react at about the same rate. This strongly suggests that no charge is generated in the transition state and an S<sub>N</sub>1 mechanism is not happening. The S<sub>N</sub>2 mechanism makes good sense with its concerted bond formation and bond breaking requiring no charge on the carbon skeleton.



The CF<sub>3</sub> group works well here as a mechanistic probe because it is held well out of the way of the reaction site by a rigid π system but is connected electronically by that same allylic system. Steric effects should be minimized and electronic effects clearly seen. This approach is clearly limited by the small number of groups having properties like those of the CF<sub>3</sub> group and the small number of reactions having such favourable carbon skeletons. We will now present the most important serious correlation between structure and reactivity.

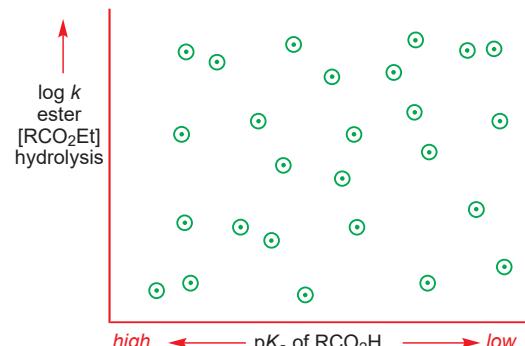
## The Hammett relationship

What we would ideally like to do is find a way to quantify the effects that electron-donating or -withdrawing groups have on the transition state or intermediate during the course of a reaction. This will then give us an idea of what the transition state is really like. The first question is: can we define exactly how efficient a given group is at donating or withdrawing electrons? Hammett took the arbitrary decision to use the  $pK_a$  of an acid as a guide. For example, the rate of hydrolysis of esters might well correlate with the  $pK_a$  of the corresponding acid.

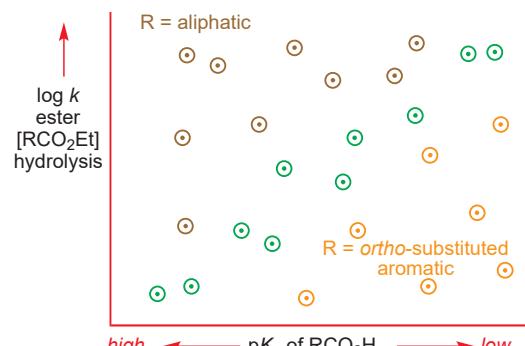


Louis P. Hammett (1894–1987) invented 'physical organic chemistry' and at Columbia University in 1935 derived the Hammett  $\sigma/\rho$  relationship. The impact was enormous and in the 1960s chemists were still working out more such correlations.

When Hammett plotted the rates of ethyl ester hydrolyses (as  $\log k$  since  $pK_a$  has a log scale) against the  $pK_a$ s of the corresponding acids, the initial results were not very encouraging as there was a random scatter of points over the whole graph.

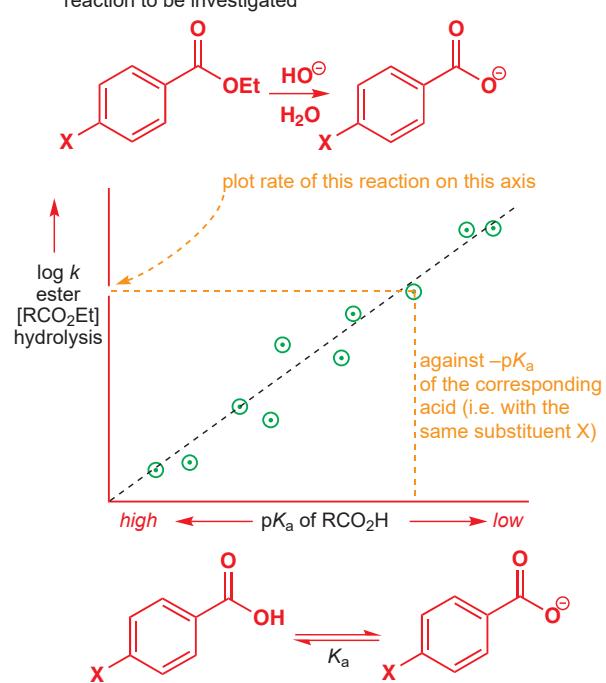


Hammett had used some aliphatic acids (substituted acetic acids) and some aromatic acids (substituted benzoic acids) and he noticed that many of the points towards the top of the graph belonged to the substituted acetic acids. Removing them (brown points) made the graph a lot better. He then noticed that the remaining aromatic compounds were in two classes: the *ortho*-substituted esters reacted more slowly than their *meta*- and *para*-isomers and came towards the bottom of the graph (orange points). Removing them made the graph quite good (remaining green points).



It was not a perfect correlation but Hammett had removed the examples where steric hindrance was important. Aliphatic compounds can adopt a variety of conformations (Chapter 16) and the substituent in some of them will interfere with the reaction. Similarly, in *ortho*-substituted aromatic compounds the nearby substituent might exert steric hindrance on the reaction. Only with *meta*- and *para*-substituted compounds was the substituent held out of the way, on a rigid framework, and in electronic communication with the reaction site through the flat but conjugated benzene ring.

Notice that the straight line is not perfect. This graph is an invention of the human mind. It is a correlation between things that are not directly related. If you determine a rate constant by plotting the right function of concentration against time and get an imperfect straight line, that is your fault because you haven't done your measurements carefully enough. If you make a Hammett plot and the points are not on a straight line (and they won't be) then that is *not* your fault. The points really don't fit on a perfectly straight line. As you will see soon, this doesn't actually matter.



### The Hammett substituent constant $\sigma$

■ You cannot push arrows from the negative charge of the carboxylate anion into the ring. Try it.

A quick glance at the  $pK_a$ s of some substituted benzoic acids in the table below will show how well they correlate electron donation with  $pK_a$ . The substituents at the top of the table are electron donating and the anions of the benzoic acids are correspondingly less stable so these are the weakest acids. At the bottom of the table we have the electron-withdrawing groups, which stabilize the anion and make the acid stronger. The whole range is not that great, only one pH unit or so, because the carboxylate anion is not conjugated with the ring.

Hammett decided not to use the  $pK_a$ s themselves for his correlation but defined a new parameter, which he called  $\sigma$ . This  $\sigma$  shows how electron donating or withdrawing a group is relative to H as a difference between the  $pK_a$ s of a benzoic acid derivative with the substituent and benzoic acid itself. If the acid required to determine  $\sigma$  for a new substituent was not available,  $\sigma$  could be determined by correlation with other reactions. Here are the equations and the table of  $\sigma$  values for the most important substituents. A different value of  $\sigma$  for any given substituent was needed for the *meta* and the *para* positions and these are called  $\sigma_m$  and  $\sigma_p$ , respectively.

$$\sigma_X = \log\left(\frac{K_a(XC_6H_4COOH)}{K_a(C_6H_5COOH)}\right) = pK_a(C_6H_5COOH) - pK_a(XC_6H_4COOH)$$

Substituent X	$pK_a$ of <i>p</i> -XC <sub>6</sub> H <sub>4</sub> COOH	$pK_a$ of <i>m</i> -XC <sub>6</sub> H <sub>4</sub> COOH	$\sigma_p$	$\sigma_m$	Comments
NH <sub>2</sub>	4.82	4.20	-0.62	0.00	groups that donate electrons have negative $\sigma$
OCH <sub>3</sub>	4.49	4.09	-0.29	0.11	
CH <sub>3</sub>	4.37	4.26	-0.17	-0.06	
H	4.20	4.20	0.00	0.00	there are no values for <i>ortho</i> substituents
F	4.15	3.86	0.05	0.34	
I	3.97	3.85	0.23	0.35	
Cl	3.98	3.83	0.22	0.37	$\sigma_p < \sigma_m$ for inductive withdrawal
Br	3.97	3.80	0.23	0.40	
CO <sub>2</sub> CH <sub>3</sub>	3.75	3.87	0.45	0.33	
COCH <sub>3</sub>	3.71	3.83	0.49	0.37	$\sigma_p > \sigma_m$ for conjugating substituents
CN	3.53	3.58	0.67	0.62	
NO <sub>2</sub>	3.43	3.47	0.77	0.73	groups that withdraw electrons have positive $\sigma$

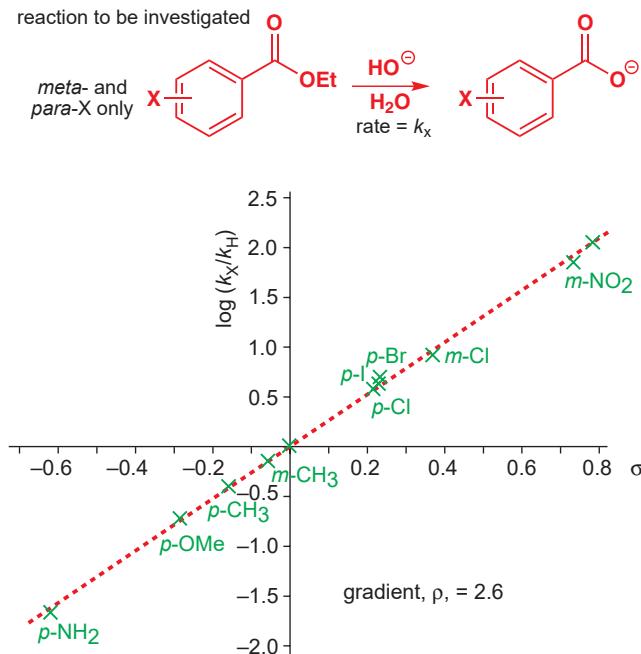
There is no point learning the precise figures in this table, but it will help if you form a general idea of what a  $\sigma$  value means. If  $\sigma = 0$  the substituent has no effect: it is electronically the same as H. If  $\sigma$  is positive, the substituent is electron withdrawing. This is unfortunate perhaps, but just remember that the comparison is with acid strength, and acids with electron-withdrawing substituents are stronger. Positive  $\sigma$  means a stronger acid so the substituent is electron withdrawing. The more positive the charge induced on the ring by a substituent, the larger its  $\sigma$  value. Negative  $\sigma$  means weaker acid and electron donation. Inductive effects from polarization of  $\sigma$  bonds are greater for  $\sigma_m$  than for  $\sigma_p$  because the substituent is nearer.

Conjugation is generally more effective in the *para* position (see Chapter 21) so  $\sigma_p > \sigma_m$  for conjugating substituents. Indeed, the  $\text{NH}_2$  group has a large negative  $\sigma_p$  and a zero  $\sigma_m$ . The  $\text{NH}_2$  group donates electrons strongly to the carbonyl group of benzoic acid from the *para* position but does not conjugate in the *meta* position where its donation happens just to balance the effect of electronegative nitrogen.

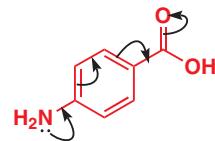
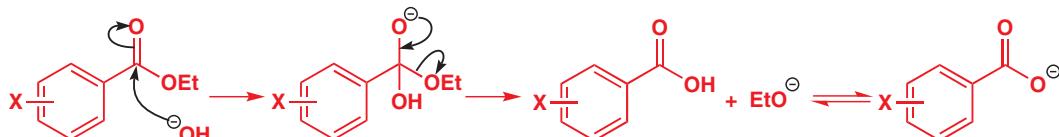
The OMe group has a negative  $\sigma_p$  but a positive  $\sigma_m$  because a weaker electron donation from the lone pairs is more important in the *para* position but the effect of very electronegative oxygen on the  $\sigma$  framework of the ring in the *meta* position is more important than lone pair donation that doesn't reach the carbonyl group. You do not need to learn any  $\sigma$  values but you should be able to work out the sign of  $\sigma$  for well-known substituents and estimate a rough value.

### The Hammett reaction constant $\rho$

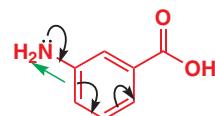
Now we can return to our reaction: the alkaline hydrolysis of various *meta*- and *para*-substituted ethyl benzoates. We sketched the graph earlier (p. 1041) but now we can add some more quantitative detail. The rate constants for this second-order reaction have been measured and shown here is a graph of  $\log(k_X/k_H)$  versus  $\sigma$ , where  $k_X$  is the rate constant for the reaction with the substituted benzoate and  $k_H$  is that for the unsubstituted reaction ( $X=H$ ).



We can see straight away that there is a good correlation between how fast the reaction goes and the value of  $\sigma$ ; in other words, the points lie more or less on a straight line. The gradient of this best-fit line, given the symbol  $\rho$  (rho), tells us how sensitive the reaction is to substituent effects in comparison with the ionization of benzoic acids. The gradient is  $\rho = +2.6$ . This tells us that the reaction responds to substituent effects in the same way (because it is +) as the ionization of benzoic acids but by much more ( $10^{1.6}$  times more) because it is 2.6 instead of 1.0. We already know what the mechanism of this reaction is:



strong conjugation into carbonyl group:  
large negative  $\sigma_p$



conjugation into ring  
not carbonyl group  
balances weak effect  
of electronegative N:  
zero  $\sigma_m$

### ■ Getting to grips with logs

A difference between two values of  $x$  log units means the values actually differ by a factor of  $10^x$ . From the graph for the hydrolysis of ethyl benzoates you can see that the *p*-NO<sub>2</sub> benzoate hydrolyses some  $10^2$  times faster than the unsubstituted benzoate, while the *p*-NH<sub>2</sub> benzoate hydrolyses some  $10^2$  times slower.

■ Hammett chose  $\sigma$  (Greek  $\sigma$ ) for substituent and  $\rho$  (Greek  $\rho$ ) for reaction.

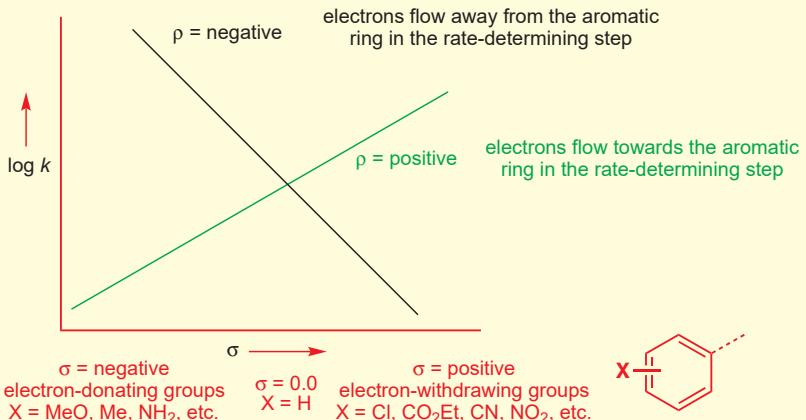
The first step is quite like the ionization of benzoic acid. A negative charge is appearing on the carbonyl oxygen atom and that negative charge will be stabilized by electron-withdrawing X groups. If the first step is rate determining, a positive  $\rho$  makes sense.

We need now to look at some other reactions to get a grasp of the meaning of the value of the Hammett  $\rho$ .

● **The Hammett reaction constant  $\rho$  measures the sensitivity of the reaction to electronic effects.**

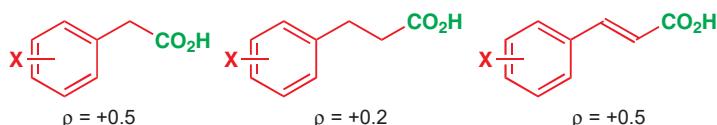
- A **positive  $\rho$**  value means **more electrons** in the transition state than in the starting material.
- A **negative  $\rho$**  value means **fewer electrons** in the transition state than in the starting material.

typical Hammett plots



### Equilibria with positive Hammett $\rho$ values

To take a simple example, let's just see what happens to  $\rho$  if we simply move the carboxylic acid away from the ring. The  $\rho$  value for ionization gets less. This is just what you would expect—the further it is from the aromatic ring, the less the acid cares about how electron rich or poor the ring is. With two saturated carbons between the benzene ring and the carboxylic acid, there is almost no effect on  $pK_a$ . But restore electronic communications with a double bond, and  $\rho$  goes back up again.



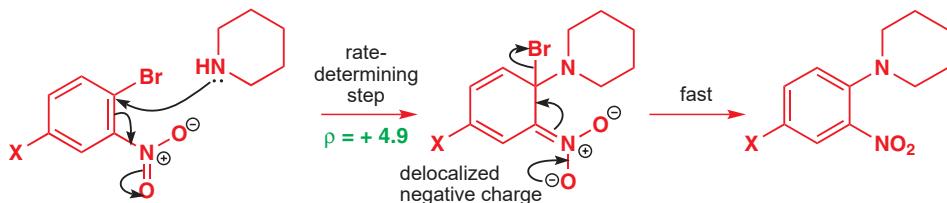
If the negative charge on the anion can actually be delocalized round the ring, as it can in substituted phenols, we should expect the size of  $\rho$  to increase. Both the phenol and the anion are delocalized but delocalization is more important for the anion. The effect is even more significant for the ionization of anilinium salts as the acid  $\text{ArNH}_3^+$  does not have a delocalized lone pair but the conjugate base ( $\text{ArNH}_2$ ) does.



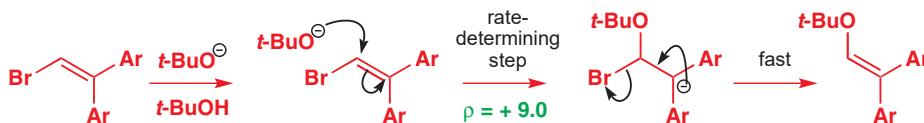
### Reactions with positive Hammett $\rho$ values

The size and sign of the value of  $\rho$  tell us about what is happening *in the rate-determining step* of a reaction. Any reaction that involves nucleophilic attack on a carbonyl group as the rate-

determining step is going to have a  $\rho$  value of about 2–3, the same as for the hydrolysis of esters, as we have already seen. Large positive  $\rho$  values usually indicate extra electrons in the transition state delocalized into the ring itself. A classic example is nucleophilic aromatic substitution by the addition–elimination mechanism (Chapter 22). The  $\rho$  value is +4.9, but even this large value does not mean a complete anion on the benzene ring as the nitro group, present in all cases, takes most of the negative charge. The substituent X merely helps.

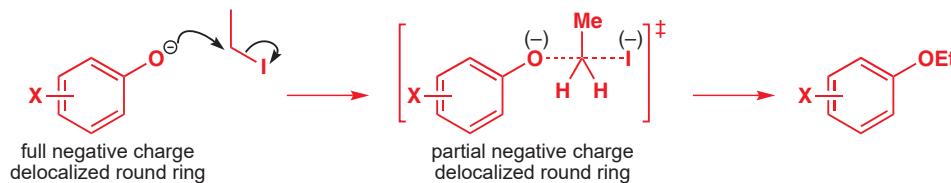


We get the full value when there are no nitro groups to take the brunt of the negative charge. This vinylic substitution has a  $\rho$  value of +9.0. It cannot be an  $S_N2$  reaction or it would have a small  $\rho$  value and it cannot be an  $S_N1$  reaction or it would have a negative  $\rho$  value (fewer electrons in the transition state). It must be an addition–elimination mechanism through a benzylic anion delocalized round both benzene rings.

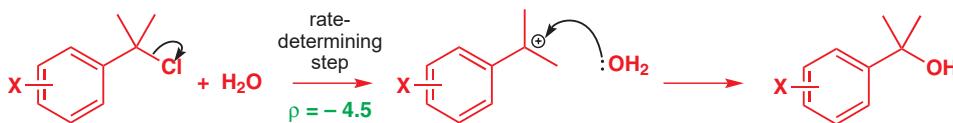


### Reactions with negative Hammett $\rho$ values

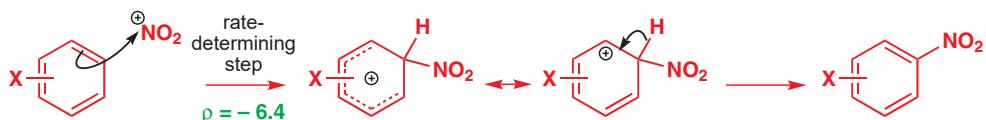
Negative  $\rho$  values mean electrons flowing away from the ring. A representative example is the  $S_N2$  displacement of iodide from EtI by phenoxide anions. This has a  $\rho$  value of exactly –1.0. Although the transition state has a negative charge, that charge is decreasing on the aromatic ring as the starting material approaches the transition state.



An  $S_N1$  reaction on the carbon atom next to the ring has a large negative  $\rho$  value. In this example, a tertiary benzylic cation is the intermediate and the rate-determining step is, of course, the formation of the cation. The cation is next to the ring but delocalized round it and the  $\rho$  value is –4.5, about the same value, though negative, as that for the nucleophilic substitution on nitrobenzenes by the addition–elimination mechanism that we saw in the last section.

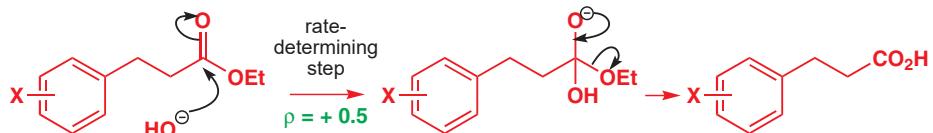


The largest negative  $\rho$  values come from electrophilic aromatic substitution (Chapter 21), where the electrons of the ring are used in the reaction, leaving a positive charge on the ring itself in the intermediate. Some of this charge is already there in the transition state. This simple nitration has  $\rho = -6.4$  and  $\rho$  values for electrophilic aromatic substitution are usually in the range –5 to –9. Negative  $\rho$  values mean electrons flowing out of the ring.

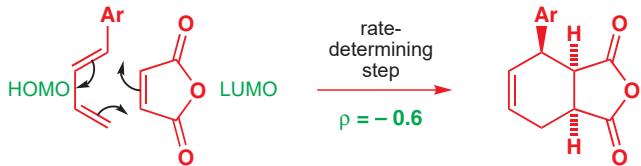


### Reactions with small Hammett $\rho$ values

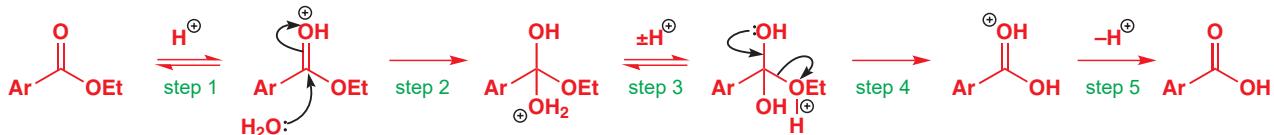
Small Hammett  $\rho$  values arise in three ways. The aromatic ring being used as a probe for the mechanism may simply be too far away for the result to be significant. This trivial case of the alkaline hydrolysis of the 3-aryl propionate ester has a  $\rho$  value of +0.5 and it is surprising that it is even that large.



The second case is the informative one where the reaction is not dependent on electrons flowing into or out of the ring. Pericyclic reactions are important examples and the Diels–Alder reaction of arylbutadienes with maleic anhydride shows a small negative  $\rho$  value of -0.6. The small value is consistent with a mechanism not involving charge accumulation or dispersal, but the sign is interesting. We explained this type of Diels–Alder reaction in Chapter 34 by using the HOMO of the diene and the LUMO of the dienophile. The negative sign of  $\rho$ , small though it is, supports this view because the reaction is somewhat faster with electron-donating groups on Ar, which raise the energy of the HOMO of the diene.



The third case is in many ways the most interesting. We have seen that the alkaline hydrolysis of ethyl esters of benzoic acids ( $\text{ArCO}_2\text{Et}$ ) has a  $\rho$  value of +2.6 and that this is a reasonable value for a reaction involving nucleophilic attack on a carbonyl group conjugated with the aromatic ring. The hydrolysis of the same esters in acid solution, which also involves nucleophilic attack on the same carbonyl group, has a  $\rho$  value of +0.1. In other words, substituted benzoic esters hydrolyse at more or less the same rate in acid solution, irrespective of their substituents. We need to look at the full mechanism to explain this remarkable result.



► We made this point in Chapter 12, p. 258.

Steps 1, 3, and 5 cannot be slow as they are just proton transfers between oxygen atoms, and proton transfer between electronegative atoms is always fast. That leaves only steps 2 and 4 as possible rate-determining steps. The bimolecular addition of the weak nucleophile water to the low concentration of protonated ester (step 2) is the most attractive candidate, as step 4—the unimolecular loss of ethanol and re-formation of the carbonyl group—should be fast. What  $\rho$  value would be expected for the reaction if step 2 were the rate-determining step? It would be made up of two parts. There would be an equilibrium  $\rho$  value for the protonation step and a reaction  $\rho$  value for the addition of water. Step 1 involves electrons flowing out of the molecule and step 2 involves electrons flowing in so the  $\rho$  values for these two steps would

have opposite charges. We know that the  $\rho$  value for step 2 would be about +2.5 (it's just like the step in the ester hydrolysis) and a value of about -2.5 for the equilibrium protonation is reasonable. This is indeed the explanation: step 2 is the rate-determining step and the  $\rho$  values for steps 1 and 2 almost cancel each other out. All steps before the rate-determining step are present in the rate equation and also affect the Hammett  $\rho$  value.

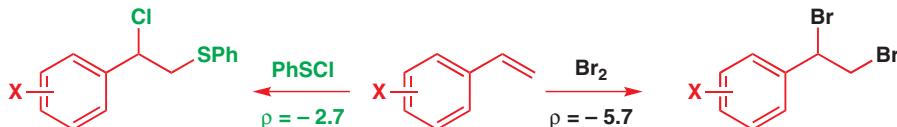
### ● Summary: interpreting Hammett $\rho$ values

-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6
large negative $\rho$ values		moderate negative $\rho$ values			small $\rho$ values			moderate positive $\rho$ values			large positive $\rho$ values	
positive charge on ring or delocalized round benzene ring		electrons flow out of transition state			1. Ar too far away 2. No electron change 3. Two $\rho$ -values cancel each other out			electrons flow into transition state			negative charge on ring or delocalized round benzene ring	
		positive charge near ring loss of conjugation						negative charge near ring loss of conjugation				

You should not, of course, learn the numbers in this scheme, but you need an idea of roughly what each group of values means. You should see now why it is unimportant whether the Hammett correlation gives a good straight line or not. We just want to know whether  $\rho$  is + or - and whether it is, say, 3 or 6. It is meaningless to debate the significance of a  $\rho$  value of 3.4 as distinct from one of 3.8.

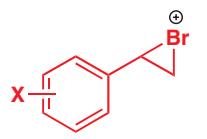
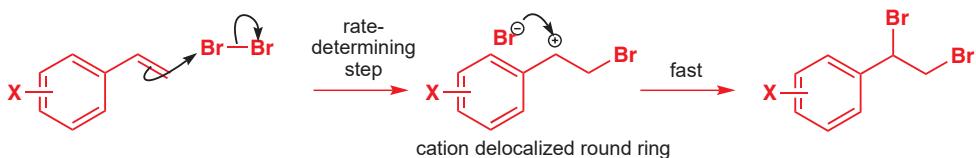
### Using the Hammett $\rho$ values to uncover mechanisms

Electrophilic attack on alkenes by bromine often goes through three-membered ring cyclic bromonium ions and we can sometimes tell that this is so by studying the stereochemistry. Here are two reactions of styrenes that look very similar—a reaction with bromine and another with PhSCl. With no further information, we might be tempted to assume that they both go by the same mechanism. However, the Hammett  $\rho$  values for the two reactions are rather different.

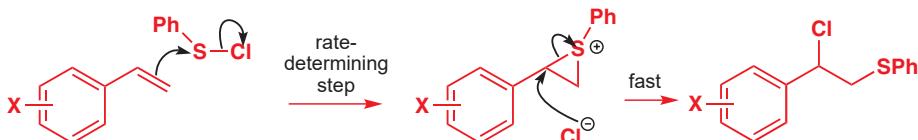


► Chapter 19 gives a full description of these mechanisms. There is more about these sulphenyl chlorides in Chapter 27, p. 658.

The  $\rho$  value for bromination is definitely in the 'large' range and can only mean that a positive charge is formed that is delocalized round the benzene ring. Bromine evidently does not form a bromonium ion with these alkenes but prefers to form a secondary benzylic cation instead, which can be stabilized more effectively by delocalization.

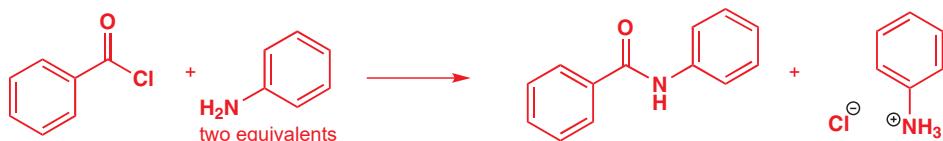


The sulfenylation, on the other hand, has a moderate negative  $\rho$  value. No cation is formed that is delocalized round the ring, but electrons flow out of the ring and we suspect some loss of conjugation. All this fits well with the formation of a three-membered ring intermediate. From experiments like this we learn that PhSCl is much more likely than bromine to react stereospecifically with alkenes through cyclic cation intermediates.

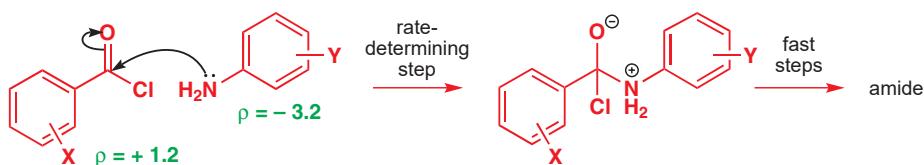


### A complete picture of the transition state from Hammett plots

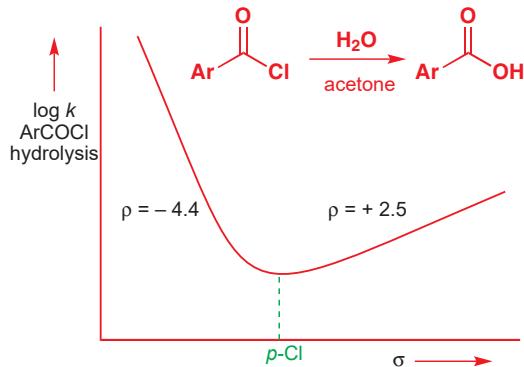
More information can be gained on the mechanism of the reaction if two separate experiments can be carried out with the mechanistic probe inserted at two different sites on the reagents. If we are studying a reaction between a nucleophile and an electrophile, it may be possible to make Hammett plots from the variation of substituents on both reagents. The acylation of amines with acid chlorides is an example.



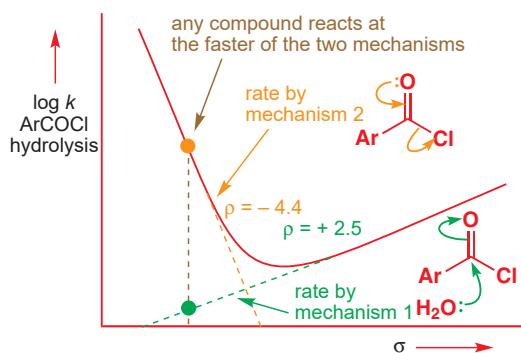
If we vary the structure of the acid chloride we get a  $\rho$  value of +1.2, typical of nucleophilic attack on the carbonyl group. If we vary the amine we get a  $\rho$  value of -3.2, typical of a reaction in which electrons that were conjugated round the ring move away to form a new bond. Comparing the numbers tells us the rate depends on the nucleophilicity of the amine 100 times more than on the electrophilicity of the acid chloride.



### Non-linear Hammett plots



The Hammett plot for hydrolysis of the acid chlorides of benzoic acids in aqueous acetone is very odd indeed. Hammett plots need not be perfectly linear to give useful information, but this one is clearly made up of two intersecting straight lines. This might look like disaster at first but, in fact, it tells us something rather important. The right-hand part of the curve, where the more electron-withdrawing substituents lie, has a slope of +2.5: just what we should expect for rate-determining attack of water on the carbonyl group. As we go to less electron-withdrawing substituents, the rate of the reaction suddenly starts to increase as we pass the *para*-chloro compound and the left-hand part of the curve has a slope of -4.4.



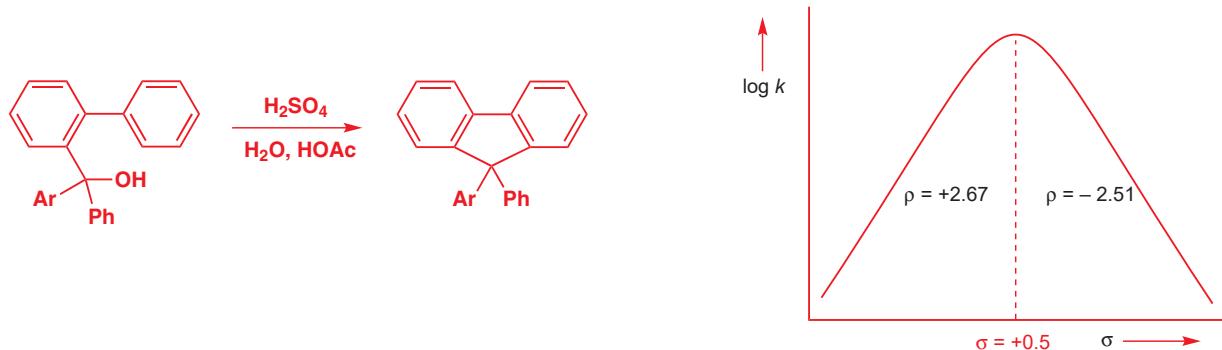
What can this mean? If the reaction becomes faster as we pass the discontinuity in the curve—and it gets faster whether we go from right to left or left to right—there must be a change in mechanism. If there is a choice between two mechanisms, the faster of the two will operate. Mechanism 1 is the rate-determining nucleophilic attack by water on the carbonyl group.

The new mechanism goes faster for more electron-donating substituents and has quite a large negative  $\rho$  value, suggesting the formation of a cation in the rate-determining step. This mechanism (mechanism 2) must surely be the  $S_N1$ -like preliminary formation of an acylium ion by loss of chloride ion.

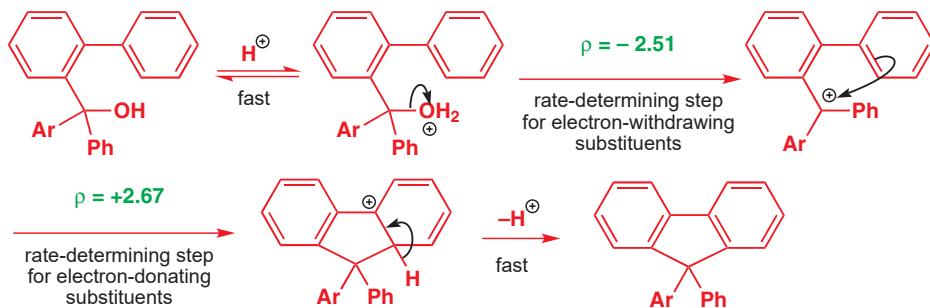
mechanism 2:



When the Hammett plot bends the other way, so that the rate of the reaction decreases as it passes the discontinuity, we have a single mechanism with a change in rate-determining step. A reaction goes by the fastest possible mechanism but its rate is limited by the slowest of the steps in that mechanism. An example is the intramolecular Friedel–Crafts alkylation of a diphenyl derivative where the alkylating agent is a diarylmethanol attached to one of the benzene rings in the *ortho* position.



The carbocation intermediate in the Friedel–Crafts reaction (Chapter 21) is rather stable, being tertiary and benzylic, and the formation of the cation, normally the rate-determining step, with inevitably a negative  $\rho$  value, goes faster and faster as the electron-donating power of the substituents increases until it is faster than the cyclization, which becomes the rate-determining step. The cyclization puts electrons back into the carbocation and has a positive  $\rho$  value. As the two steps have more or less the reverse electron flow to and from the same carbon atom, it is reasonable for the size of  $\rho$  to be about the same but of opposite sign.



- A reaction occurs by the faster of two possible mechanisms but by the slower of two possible rate-determining steps.

We shall see more examples of Hammett  $\rho$  values used in conjunction with other evidence as the chapter develops but now it is time to look at what other evidence is available.

## Other kinetic evidence for reaction mechanisms

### The kinetic isotope effect

You have seen how isotopes have different *physical* properties—their nuclear spin, for example, which affects how they behave in an NMR machine. We also showed you in Chapter 3 how IR stretching frequencies depend on mass, and there you saw that C–D bonds have lower stretching frequencies than C–H bonds. That fact is highly relevant to the explanation we are about to give you for the origin of kinetic isotope effects.

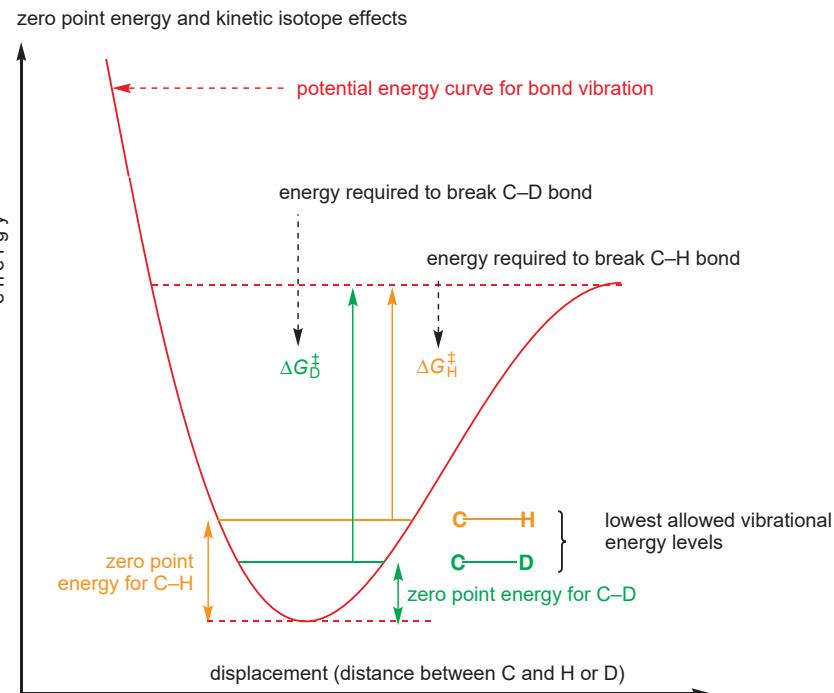
The full explanation of the theory of kinetic isotope effects is beyond the scope of this book but you can read about it in any book on physical organic chemistry.

Up to now you have probably (and rightly) assumed that isotopes of an element are chemically identical. They differ only in the number of neutrons in their nuclei: chemistry generally depends on charge, orbitals, and electrons. It may come as a surprise to find that this is not quite true. Isotopes may differ chemically, because some chemical properties do depend on atomic mass. However, this difference is only significant for hydrogen—no other element has one isotope twice as massive as another! *Kinetic isotope effects* are the changes in rate observed when a (<sup>1</sup>H) hydrogen atom is replaced by a (<sup>2</sup>D) deuterium atom in the same reaction. For any reaction, the kinetic isotope effect (KIE) is defined as

$$\text{KIE} = k_{\text{H}}/k_{\text{D}}$$

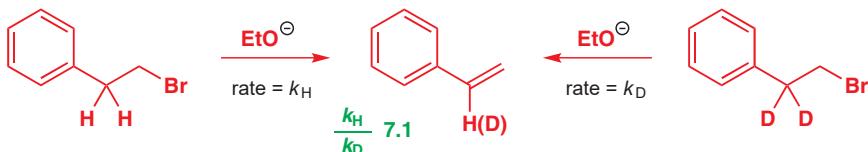
where  $k_{\text{H}}$  is the rate with a <sup>1</sup>H atom in the molecule and  $k_{\text{D}}$  is the rate with a <sup>2</sup>H (deuterium, D) atom in the molecule.

How do kinetic isotope effects come about? Even in its lowest energy state a covalent bond never stops vibrating. If it did it would violate a fundamental physical principle, Heisenberg's uncertainty principle, which states that position and momentum cannot be known exactly at the same time: a non-vibrating pair of atoms have precisely zero momentum and precisely fixed locations. The minimum vibrational energy a bond can have is called the zero point energy, and the zero point energy depends on the mass of the atoms attached to the bond—heavier atoms have a lower zero point energy than lighter ones.



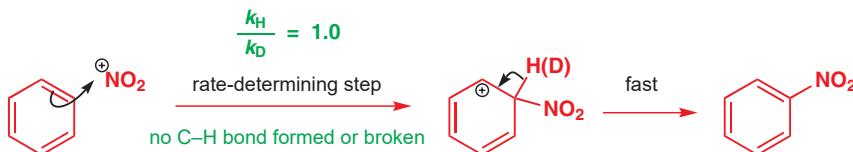
In order to break a covalent bond, a certain amount of energy is required to separate the nuclei from their starting position. This energy has to raise the vibrational state of the bond to the point where it breaks. For the sake of argument, imagine taking a C–H bond in its lowest energy state and breaking it—the diagram shows the amount of energy required, which we can call  $\Delta G^{\ddagger}_{\text{H}}$ . Now do the same for a C–D bond: because the zero point energy of a C–D bond is smaller than that for a C–H bond, the C–D bond needs that little bit more energy  $\Delta G^{\ddagger}_{\text{D}}$  to break: in other words a C–D bond is marginally stronger than a C–H bond. This means reactions in which C–H bonds break go faster than reactions in which C–D bonds break, *providing the bond to H (or D) is involved in the rate-determining step*. The theoretical maximum value of

the KIE is about 7 for reactions at room temperature in which a bond to H or D is being broken. For example, the rates of these two eliminations can be compared, and  $k_H/k_D$  turns out to be 7.1 at 25 °C.

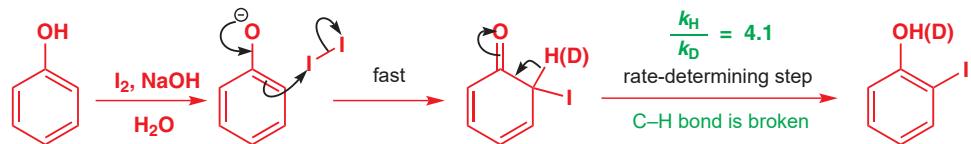


In this case the fact that the KIE is non-zero tells us that the C–H (or C–D) bond is being broken during the rate-determining step, and so the reaction must be an E2 elimination. In E1 eliminations, the rate-determining step does not involve a breaking C–H bond.

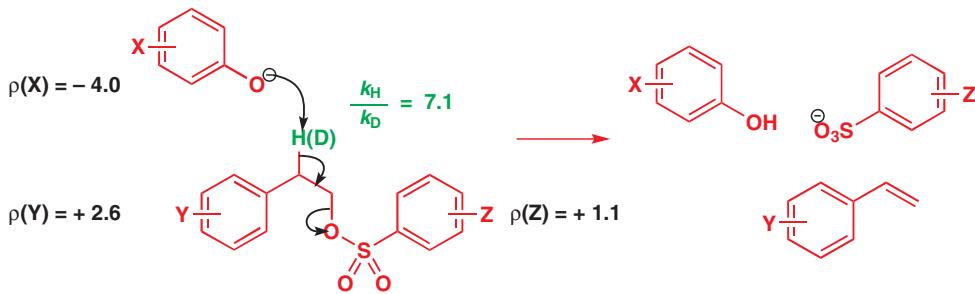
In Chapter 21 we told you that the rate-determining step in the nitration of benzene was the attack of the electrophile on the benzene ring. This is easily verified by replacing the hydrogen atoms round the benzene ring with deuteriums. The rate of the reaction stays the same, so the C–H (or C–D) bonds cannot be involved in the rate-determining step. If the second step, which does involve the breaking of a C–H bond, were the rate-determining step it would go more slowly if the H were replaced by D.



By contrast, for the iodination of phenol in basic solution there is a deuterium isotope effect of  $k_H/k_D = 4.1$ . Clearly, the loss of the proton from the intermediate must now be the rate-determining step—the phenolate ion reacts so rapidly that the first step is faster than the second.



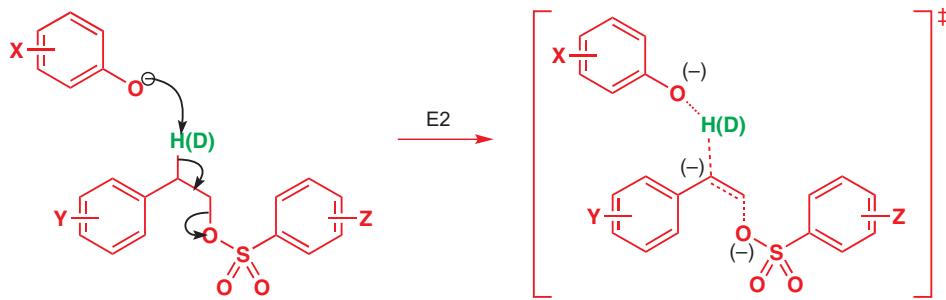
The deuterium isotope effect can add to the information from Hammett plots in building up a picture of a transition state. Three separate Hammett  $\rho$  values can be measured for the elimination reaction and this information is very valuable. In addition, a large KIE  $k_H/k_D = 7.1$  is observed for the hydrogen atom under attack.



It is no surprise that the base ( $\text{ArO}^-$ ) donates electrons and the leaving group ( $\text{ArSO}_3^-$ ) accepts them, as the  $\rho$  values indicate. The large deuterium isotope effect tells us that the reaction is E2, but additional information comes from the moderate positive  $\rho(Y)$  value for the aromatic ring adjacent to the proton being lost. It might have been expected that this ring is merely a spectator, but in fact the reaction must involve a build-up of negative charge, which can be stabilized by an electron-donating substituent Y. This can be explained if we assume

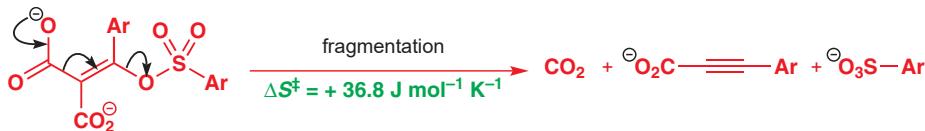
► E1 and E2 mechanisms were covered in Chapter 17.

that the removal of the proton is slightly more advanced at the transition state than loss of the leaving group.



### Entropy of activation

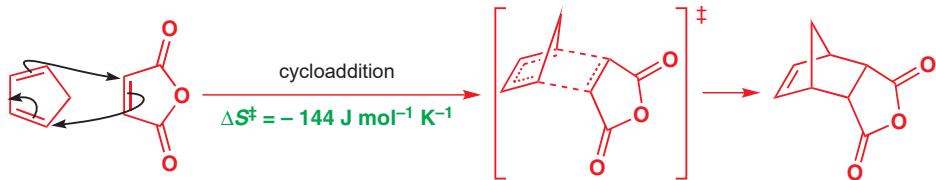
The entropy of activation,  $\Delta S^\ddagger$ , of a reaction tells us about the increase or decrease in order in a reaction as the starting material goes to the transition state. A positive  $\Delta S^\ddagger$  means an increase in entropy or a decrease in order, and a negative  $\Delta S^\ddagger$  means an increase in order. Normally, unimolecular reactions in which one molecule gives two products have a positive  $\Delta S^\ddagger$  and bimolecular reactions have a negative  $\Delta S^\ddagger$ . Fragmentations (Chapter 36), such as this decarboxylation in which one molecule fragments to three, have positive values of  $\Delta S^\ddagger$ , in this case  $\Delta S^\ddagger = +36.8 \text{ J mol}^{-1} \text{ K}^{-1}$ .



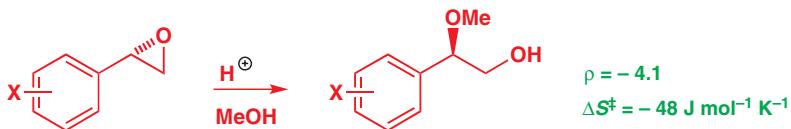
Entropies of activation are measured in units of  $\text{J mol}^{-1} \text{ K}^{-1}$ . All the values in this book are in  $\text{J mol}^{-1} \text{ K}^{-1}$  but in older books you will see 'entropy units' (e.u.), which are  $\text{cal mol}^{-1} \text{ K}^{-1}$ . Values in e.u. should be multiplied by 4.18 to get values in  $\text{J mol}^{-1} \text{ K}^{-1}$ .

Interactive mechanism for the Diels–Alder reaction

At the other extreme are cycloadditions (Chapter 34) such as the Diels–Alder reaction we examined a few pages back. Not only do two reagents become one product but a very precise orientation is required in the transition state, usually meaning a large negative  $\Delta S^\ddagger$ . Diels–Alder reactions usually have  $\Delta S^\ddagger$  of about  $-120$  to  $-160 \text{ J mol}^{-1} \text{ K}^{-1}$ . The classic cyclopentadiene addition to maleic anhydride has  $\Delta S^\ddagger = -144 \text{ J mol}^{-1} \text{ K}^{-1}$ .

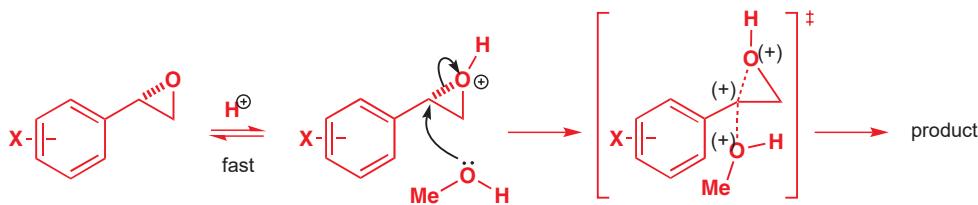


These numbers give you the range of entropies of activation you may expect to find. Large negative numbers are common but only small positive numbers are found. The largest negative numbers apply to bimolecular reactions where neither reagent is in great excess. Smaller negative numbers may mean a bimolecular reaction with solvent or some other reagent in large excess. The acid-catalysed opening of styrene oxides in methanol is a good example.



The Hammett  $\rho$  value of  $-4.1$  suggests a carbocation intermediate, as does the regioselectivity of the reaction (MeOH attacks the benzylic position) but the stereochemistry (the reaction occurs with inversion) and a modest negative entropy of activation ( $\Delta S^\ddagger = -48 \text{ J mol}^{-1} \text{ K}^{-1}$ )

suggest rather an  $S_N2$  reaction with a loose transition state having substantial positive charge at the benzylic carbon. Neither piece of evidence alone would be enough to define the mechanism.

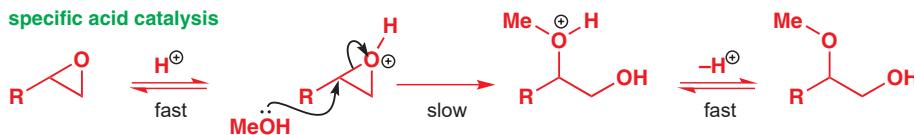


## Acid and base catalysis

As you have seen throughout this book, acids and bases provide the most widely used ways of speeding up reactions. If you want to make an ester—add some acid. If you want to hydrolyse an ester—add some base. We explained in Chapter 12 the ways in which acid and base catalysts help reactions along, and we introduced you to the terms **specific acid** and **specific base**, **general acid** and **general base**. We will now look in a little more detail at these types of catalysis and give some pointers as to how to establish which of them, if any, is operative in any given reaction.

As a preliminary, let's look at an example of **specific acid catalysis**. This is the kind operating in the reaction just above—epoxides don't react with methanol but, if we protonate the epoxide first, then the reaction works. Specific acid catalysis protonates electrophiles and makes them more electrophilic.

For the earlier discussion of acid and base catalysis, and an outline of what the terms **specific** and **general** acid/base catalysis mean, see Chapter 12, pp. 262–264.

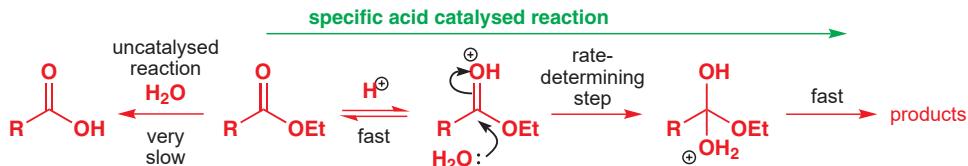


We could, on the other hand, have reasoned that although methanol is not a good enough nucleophile, deprotonating with a base will make it into the much more nucleophilic methoxide, and the reaction will also work. This sort of base catalysis—deprotonating nucleophiles to make them more nucleophilic—is **specific base catalysis**.



## Specific acid catalysis

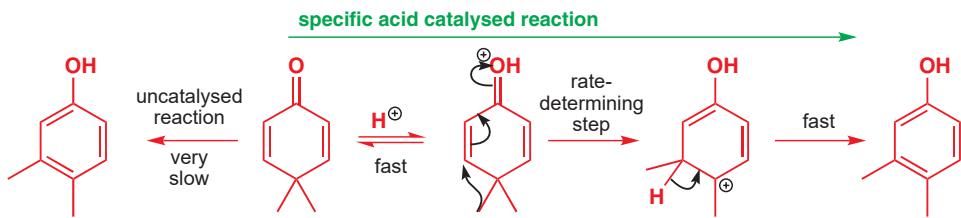
Specific acid catalysis (SAC) involves a rapid protonation of the compound followed by the slow step, which is accelerated in comparison with the uncatalysed reaction because of the greater reactivity of the protonated compound. You have just seen an example with an epoxide; ester hydrolysis (or formation) is another, as you saw in Chapter 12.



A more interesting reaction is the dienone–phenol rearrangement. Rearrangement in the absence of acid is very slow but once the ketone oxygen is protonated, it occurs very rapidly.

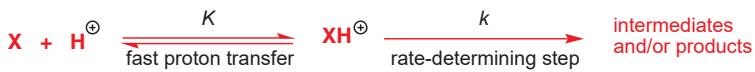
You met this rearrangement in Chapter 36.

Again we have fast equilibrium protonation, followed by a rate-determining step involving a reaction of the protonated species: this is SAC.



This catalysis depends only on the protonating power of the solution. The compound must be protonated to react, so the catalyst must be a strong enough acid to do the job. It is not necessary that every molecule is protonated—just enough to set the reaction going because the catalytic acid is regenerated at the end. In a specific acid catalysed reaction, the rate of the reaction depends on the pH of the reaction mixture. SAC works only if the pH is similar to, or below, the  $pK_a$  of the conjugate acid of the substrate, and the log of the rate of the reaction is proportional to the pH of the solution.

There is one rather remarkable experimental indication of this mechanism. If the reaction is carried out in a deuterated solvent ( $D_2O$  instead of  $H_2O$ ) the rate of the reaction increases. This is a *solvent isotope effect* rather than a kinetic isotope effect and needs some explanation. If you examine the three examples of SAC in the previous pages you will see that they share these characteristics: a fast proton exchange is followed by a rate-determining step that does *not* involve the making or breaking of any bonds to hydrogen. In general terms:



The rate of the reaction is the rate of the rate-determining step:

$$\text{rate} = k[XH^\oplus]$$

The concentration of the intermediate  $[XH^\oplus]$  is related to the pH and to the concentration of the substrate by the equilibrium constant,  $K$ , of the protonation. This gives us:

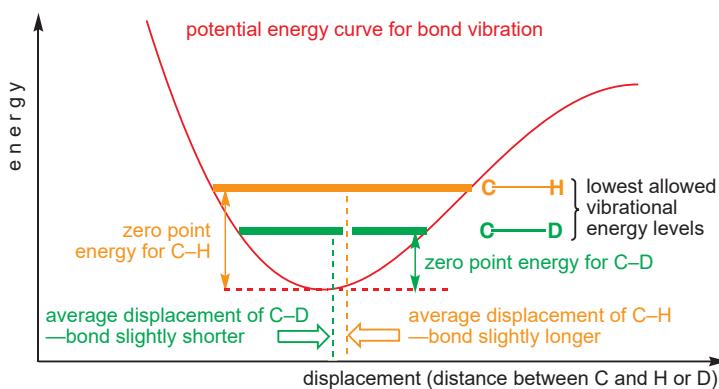
$$\text{rate} = kK[H^\oplus][X]$$

In the acid-catalysed reaction, the bond to H (or D) is not broken in the rate-determining step, so  $k$  cannot change when hydrogen is replaced by deuterium. That means that if a reaction goes faster in  $D_2O$  than in  $H_2O$  then it must be  $K$  that is different (i.e. larger) in  $D_2O$ . SAC is more effective with  $D_3O^+$  in  $D_2O$  than with  $H_3O^+$  in  $H_2O$  because more of the substrate is protonated at any one time.

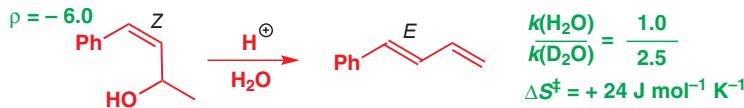
● An inverse solvent isotope effect ( $k[D_2O] > k[H_2O]$ ) is indicative of specific acid catalysis.

It is not, of course, possible to use  $D_3O^+$  in  $H_2O$  as H and D exchange very quickly. The solvent determines which acid is present.

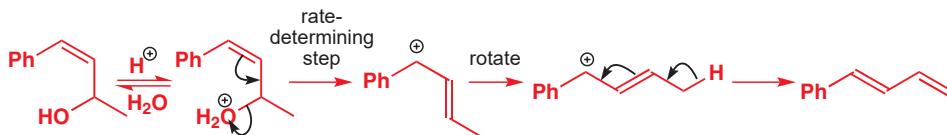
This is sometimes explained by saying that  $D_3O^+$  is a stronger acid than  $H_3O^+$ . This is partly true. The full truth is that  $D_3O^+$  in  $D_2O$  is a stronger acid than  $H_3O^+$  in  $H_2O$ . Water ( $H_2O$ ) is a better solvating agent for  $H_3O^+$  than  $D_2O$  is for  $D_3O^+$  because O–H bonds are longer than O–D bonds. Look again at the potential energy curve we showed you on p. 1050 and reproduced below, this time representing the energies of O–H and O–D bonds. The average length of a bond is the mid-point of the line in the potential energy well representing its energy level. You can easily see that the mid-point for the O–H is further out than the mid-point for the O–D bond because of the asymmetry of the well. O–H bonds are longer than O–D bonds, and can therefore make *stronger hydrogen bonds*. These hydrogen bonds are better at allowing solvation of  $H_3O^+$ , making  $H_3O^+$  in  $H_2O$  less willing to protonate a substrate than  $D_3O^+$  in  $D_2O$ .



Let's illustrate all this with an example. The *Z* allylic alcohol below dehydrates in acid solution to the *E* diene. We have lots of data on this mechanism, all summarized in the diagrams. You may like to note as well that the product contains no deuterium after dehydration in D<sub>2</sub>O.



The Hammett  $\rho$  value of  $-6.0$  suggests a carbocation intermediate and the positive entropy of activation suggests a rate-determining step in which disorder increases, perhaps one molecule breaking into two. The inverse solvent deuterium isotope effect (faster reaction in D<sub>2</sub>O than in H<sub>2</sub>O) strongly suggests SAC. Putting all this together we have a mechanism—a simple example of SAC. There is no protonation at carbon.



You can compare this mechanism with the isomerization of the same diene described earlier in this chapter.

### ● Summary of features of specific acid catalysis

- 1 Only H<sub>3</sub>O<sup>+</sup> is an effective catalyst; pH alone matters.
- 2 Usually means rate-determining reaction of protonated species.
- 3 Effective only at pHs near or below the pK<sub>a</sub> of the substrate's conjugate acid.
- 4 Proton transfer is not involved in the rate-determining step.
- 5 Only simple unimolecular and bimolecular steps—moderate + or  $-\Delta S^\ddagger$ .
- 6 Inverse solvent isotope effect  $k(\text{H}_2\text{O}) < k(\text{D}_2\text{O})$ .

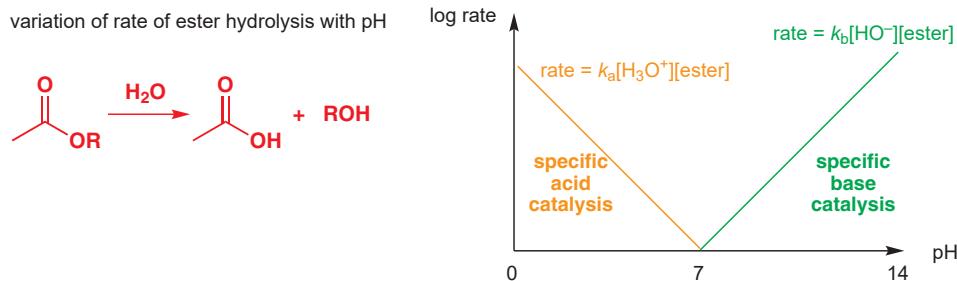
### Specific base catalysis

The other side of the coin is *specific base catalysis* (SBC). SBC usually involves the removal of a proton from the substrate in a fast pre-equilibrium step followed by a rate-determining reaction of the anion. Most of the base-catalysed reactions you are familiar with work by SBC. Examples include opening of epoxides with thiols.

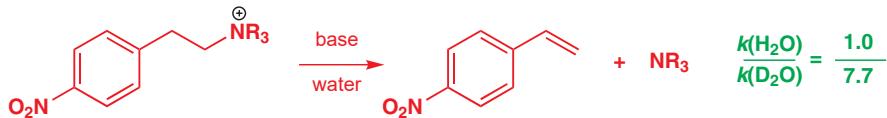


As with SAC, the rate of the reaction depends on the pH of the solution. If it is around or higher than the  $pK_a$  of the thiol, thiolate anion will be formed and this opens the epoxide much faster than does the unionized thiol. The nucleophile is then regenerated by the oxy-anion produced in the rate-determining step.

It is quite common for specific acid and specific base catalysis to operate on the same reaction, depending on the pH at which the reaction is carried out. In fact, you have already seen this for ester hydrolysis in Chapter 12. The pH–rate profile (Chapter 12) for the hydrolysis of a simple ester such as ethyl acetate shows just two straight lines meeting each other (and zero rate) at about neutrality. Ethyl acetate hydrolysis occurs by SAC or SBC only.

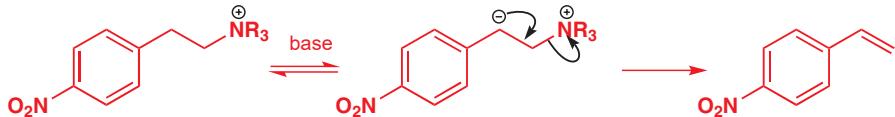


Removal of a proton from heteroatoms by heteroatom bases is never rate determining because it is always fast, but removal of a proton from carbon *can* be the rate-determining step. A remarkably large inverse solvent deuterium isotope effect was found with this elimination of a tertiary amine in basic solution.



► E1, E2, and E1cB mechanisms are described in Chapter 17.

The detailed mechanism cannot be E2 or the isotope effect, if any, would be the other way round. With SBC, however, the mechanism can be E1cB having a carbanion as an intermediate.



The isotope effect observed is certainly inverse (the reaction is faster with  $\text{H}_2\text{O}$  than  $\text{D}_2\text{O}$ ) but the magnitude of the effect is too large to be a *solvent* isotope effect and looks much more like an inverse *kinetic* isotope effect. And so it is. The tertiary amine is not a very good leaving group in spite of its positive charge ( $pK_a$  of  $\text{R}_3\text{NH}^+$  is about 10) so the carbanion mostly reverts to starting materials. The isotope effect is a kinetic isotope effect on this reverse step—the protonation of the carbanion. This reaction involves a proton transfer from  $\text{H}_2\text{O}$  or  $\text{D}_2\text{O}$  and will be much faster (7.7 times in fact) in  $\text{H}_2\text{O}$  due to an ordinary kinetic isotope effect. The *elimination* reaction goes faster in  $\text{D}_2\text{O}$  because the back reaction goes more slowly and more of the carbanion goes on to product.

#### ● Summary of features of specific base catalysis

- 1 Only  $\text{HO}^-$  is an effective catalyst; pH alone matters.
- 2 Usually means rate-determining reaction of deprotonated species.
- 3 Effective only at pHs near or above the  $pK_a$  of the substrate.
- 4 Proton transfer is not involved in the rate-determining step, unless C–H bonds are involved.
- 5 Only simple unimolecular and bimolecular steps—moderate  $+ \Delta S^\ddagger$ .
- 6 Inverse solvent isotope effect  $k(\text{H}_2\text{O}) < k(\text{D}_2\text{O})$ .

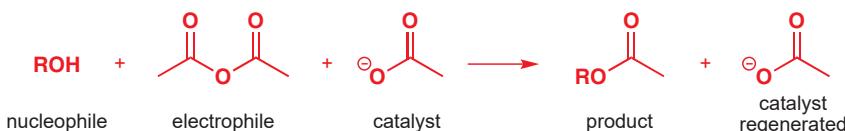
#### Microscopic reversibility

There is only one least-energy pathway between two interconverting compounds such as the starting material and the intermediate here. Every microscopic detail of the back reaction is exactly the same as that for the forward reaction. This is the principle of microscopic reversibility. Here we use evidence from the back reaction (slow proton transfer from water to the carbanion) to tell us about the forward reaction.

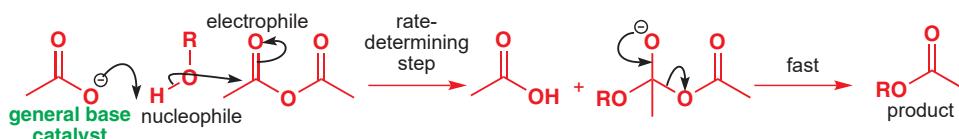
## General base catalysis

In Chapter 12 (p. 263) we pointed out that even weak bases—too weak to deprotonate a nucleophile by the mechanism we have just described for SBC—can still act as catalysts. Such catalysts are known as **general base catalysts**, and are the promoters of a parallel kind of acid–base catalysis called ‘general’ rather than ‘specific’. General base catalysis, abbreviated GBC, depends not only on pH (i.e. the concentration of hydroxide ion) but also on the concentration of other bases too. General acid catalysis, abbreviated GAC, likewise depends not only on pH (i.e. the concentration of  $\text{H}_3\text{O}^+$ ) but also on the concentration of other undissociated acids HA. General acid–base catalysis is a milder kind of catalysis and is characteristic of reactions catalysed by enzymes in the metabolism of living things.

In a general base-catalysed reaction, proton transfer is not complete before the rate-determining step (as it was in SBC) but occurs *during* the rate-determining step. A simple example is the catalysis by acetate ion of the formation of esters from alcohols and acetic anhydride.

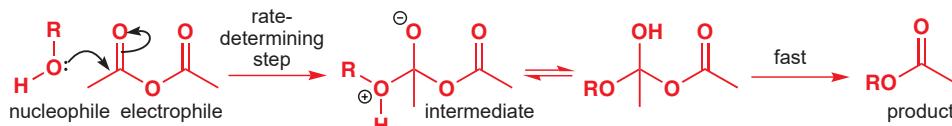


How can this catalysis work? At first sight there seems to be no mechanism available. Acetate cannot act as a specific base—it is far too weak ( $\text{pK}_a$  AcOH 4.7) to remove a proton from an alcohol ( $\text{pK}_a$  about 15). It can't operate as a nucleophile, as pyridine does (p. 200), as nucleophilic attack on acetic anhydride would be a non-reaction, simply regenerating starting materials. The only thing it can do is to remove the proton from the alcohol *as the reaction occurs*.



You will see at once that there is a great disadvantage in this mechanism: the rate-determining step is termolecular—three molecules have to collide. This comes out most clearly in the entropy of activation, which has an enormous negative value—around  $\Delta S^\ddagger = -168 \text{ J mol}^{-1} \text{ K}^{-1}$  for this reaction. For this reason, GBC or GAC reactions are normally effective only if one of the three molecules is present in large excess—this reaction might be done in  $\text{ROH}$  as a solvent, for example, so that  $\text{ROH}$  is always present. We would also expect a normal kinetic isotope effect for  $\text{ROD}$  compared with  $\text{ROH}$  as a bond to hydrogen is being formed and broken in the rate-determining step: it is  $k_{\text{H}}/k_{\text{D}} = 2.4$  here.

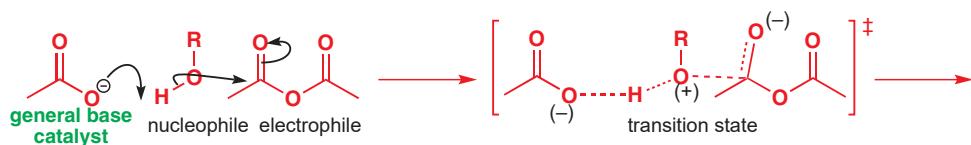
In understanding how this GBC works it is helpful to look at the mechanism without catalysis.



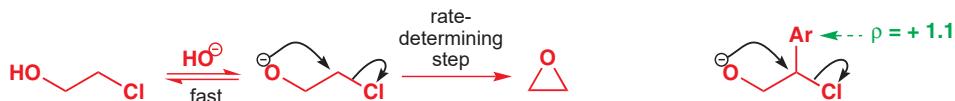
The acetate catalyst cannot remove a proton from the starting material but it can easily remove a proton from the intermediate, which has a complete positive charge on the alcohol oxygen atom. The starting material has a  $\text{pK}_a$  above the  $\text{pK}_a$  of HOAc but the product has a  $\text{pK}_a$  well below it. Somewhere in the middle of the rate-determining step, the  $\text{pK}_a$  of the ROH proton passes through the  $\text{pK}_a$  of acetic acid and then acetate is a strong enough base to remove it. The GBC is effectively deprotonating the transition state.

► There was some discussion of this reaction in Chapter 12. Chapter 10 refers to the difficulty of pinpointing proton transfers in mechanisms involving the carbonyl group.

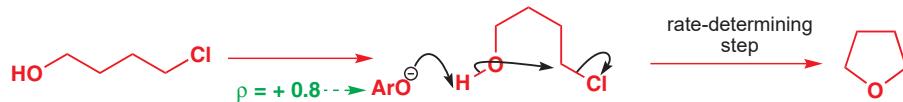
► The first time you met third-order kinetics (where it arose from a combination of more than one step, see p. 261) we pointed out how unlikely real termolecular steps are.



So how do we find GAC or GBC? Well, first we must remove the more powerful ‘specific’ style of catalysis by working at constant pH because SAC or SBC depends on pH alone. If we find that the rate of the reaction changes with the concentration of a weak base at constant pH, we have GBC. The formation of three- and five-membered cyclic ethers shows the contrast between GBC and SBC. The formation of epoxides is straightforward SBC with a simple linear dependence on pH between pH 8 and 12, and no acceleration at constant pH by carbonate ( $\text{CO}_3^{2-}$ ) ions. There is an inverse solvent isotope effect and an aryl substituent at the electrophilic carbon atom gives the small positive  $\rho$  value expected for  $\text{S}_{\text{N}}2$  with an anion.



Formation of tetrahydrofuran (THF) is also faster at higher pH but, by contrast, is additionally accelerated by various bases at constant pH. If anions of phenols ( $\text{ArO}^-$ ) are used as catalysts, a Hammett  $\rho$  value of +0.8 shows that electrons are flowing away from the aromatic ring. There is a small normal kinetic isotope effect  $k_{\text{H}}/k_{\text{D}} = 1.4$ . Both SBC and GBC are therefore operating in this reaction. Here is the mechanism with  $\text{ArO}^-$  as GBC.



Why are the two different? The THF is easy to form, the transition state is unstrained, and only a little help is needed to make the reaction go—GBC will do. The epoxide is very strained indeed and the starting material needs to be raised in energy before cyclization will occur. Only the most powerful form of catalysis—SBC—is good enough.

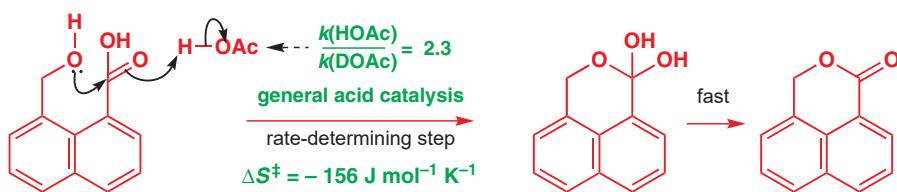
#### ● Summary of features of general base catalysis

- 1 Any base is an effective catalyst; pH also matters.
- 2 Proton transfer is involved in the rate-determining step.
- 3 Effective at neutral pHs even if below the  $\text{p}K_a$  of the substrate.
- 4 Catalyst often much too weak a base to deprotonate the reagent.
- 5 Catalyst removes a proton, which is becoming more acidic in the rate-determining step.
- 6 Some other bond making or bond breaking also involved unless proton is on carbon.
- 7 Often termolecular rate-determining step: large  $-\Delta S^\ddagger$ .
- 8 Normal kinetic isotope effect  $k(\text{H}) > k(\text{D})$ .

### General acid catalysis

GAC involves transfer of a proton from a weak acid (too weak to protonate the substrate completely) *during* the rate-determining step. A few examples will demonstrate to you how this works. They are all examples where GAC occurs because of a modification to a familiar reaction involving SAC.

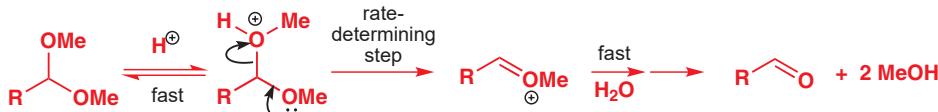
In the first one, the termolecular problem (i.e. the fact that in GAC and GBC three molecules have to come together in the transition state) is avoided by making a reaction intramolecular. Normally, ester formation and hydrolysis are specific-acid-catalysed only, but here there is catalysis by a weak acid: acetic acid. A normal kinetic isotope effect  $k(\text{HOAc})/k(\text{DOAc}) = 2.3$  shows that proton transfer occurs in the rate-determining step and there is a large negative  $\Delta S^\ddagger = -156 \text{ J mol}^{-1} \text{ K}^{-1}$ . This is GAC of nucleophilic attack on a carbonyl group, admittedly in a rather special molecule.



In Chapter 11 we emphasized the importance of the mechanism for the formation and hydrolysis of acetals. These are SAC reactions: alcohols are bad leaving groups and usually need to be fully protonated by strong acids before they will go, even with the help of the lone pair of another oxygen atom.

Nature often makes use of GAC and GBC since the catalysts required are compatible with the need to work at pH close to neutral. As in this example, enzymes manage to reduce the number of molecules required for GAC and GBC to operate by building the catalytic functional groups into their active sites.

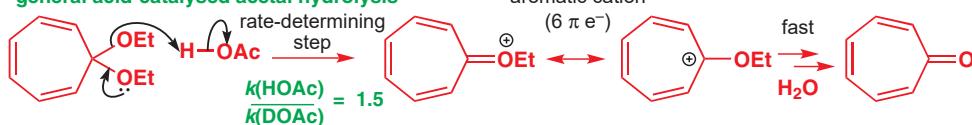
#### specific acid-catalysed acetal hydrolysis



If we speed up the slow step by adding to the molecule some feature that stabilizes the cation intermediate, GAC may be found. One example is the aromatic cation formed in the hydrolysis of cycloheptatrienone acetals. The normal kinetic isotope effect announces the appearance of GAC.

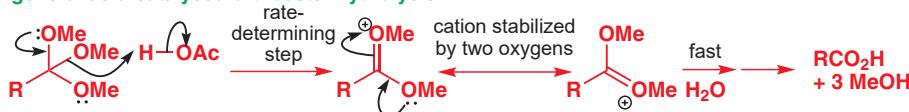
► In these examples the steps after the rate-determining step are omitted and you should look at Chapter 11 for the full details.

#### general acid-catalysed acetal hydrolysis



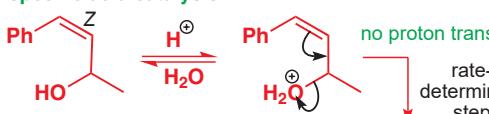
Even adding one extra alkoxy group so that we have an orthoester instead of an acetal is enough. These compounds show catalysis with a variety of weak acids at not very acidic pH (5–6). As one OMe group is protonated, two others help in pushing it out, and they both help to stabilize the intermediate cation. Nature prefers these milder methods of catalysis, as we will see in Chapter 42.

#### general acid-catalysed orthoester hydrolysis

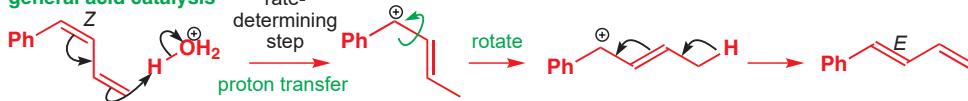


For another contrast between SAC and GAC we need only refer you back to the two Z/E isomerizations earlier in the chapter. Isomerization of the diene is GAC—protonation at carbon is the slow step—and isomerization of the allylic alcohol is SAC. What we didn't tell you earlier was that the GAC reaction has a normal kinetic isotope effect of  $k(\text{H})/k(\text{D}) = 2.5$  and a negative entropy of activation  $\Delta S^\ddagger = -36 \text{ J mol}^{-1} \text{ K}^{-1}$ —just what we should expect for a bimolecular reaction involving rate-determining proton transfer from oxygen to carbon. Notice that the intermediate cation is the same whichever the route; only the ways of getting there, including the rate-determining steps, are different.

#### specific acid catalysis



#### general acid catalysis



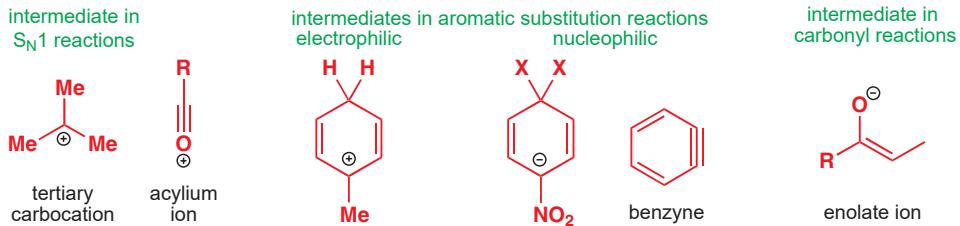
These examples show you that GAC is possible with strong acids, especially when protonation is at carbon and that in such cases no other bond-making or -breaking steps need be involved.

### ● Summary of features of general acid catalysis

- 1 Any acid is an effective catalyst; pH also matters.
- 2 Proton transfer is involved in the rate-determining step.
- 3 Effective at neutral pHs even if above the  $pK_a$  of the conjugate acid of the substrate.
- 4 Catalyst often much too weak an acid to protonate reagent.
- 5 Catalyst adds proton to a site that is becoming more basic in the rate-determining step.
- 6 Some other bond-making or bond-breaking also involved unless proton is on carbon.
- 7 Often termolecular rate-determining step: large  $-\Delta S^\ddagger$ .
- 8 Normal kinetic isotope effect  $k(H) > k(D)$ .

## The detection of intermediates

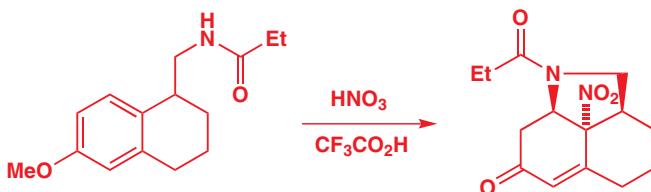
In earlier chapters we revealed how some reactive intermediates can be prepared, usually under special conditions rather different from those of the reaction under study, as a reassurance that some of these unlikely looking species can have real existence. Intermediates of this kind include the carbocation in the  $S_N1$  reaction (Chapter 15), the cations and anions in electrophilic (Chapter 21) and nucleophilic (Chapter 22) aromatic substitutions, and the enols and enolates in various reactions of carbonyl compounds (Chapters 20, 25, and 26). We have also used labelling in this chapter to show that symmetrical intermediates are probably involved in, for example, nucleophilic aromatic substitution with a benzyne intermediate (Chapter 22).



We have hedged this evidence around with caution since the fact that an intermediate can be prepared does not by any means prove that it is involved in a reaction mechanism. In this section we are going to consider other and better evidence for intermediates and at the same time revise some of the earlier material.

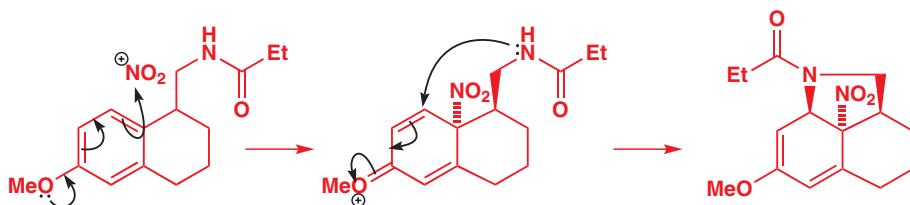
### Trapping reactions

A more impressive piece of evidence is the design of a molecule that has built into it a functional group that could react with the intermediate in a predictable way but could not reasonably react with other species that might be present. For example, aromatic ethers react with nitrating agents in the *ortho* or *para* positions (Chapter 21). The intermediate has a positive charge delocalized over three of the carbon atoms in the benzene ring. If a nucleophilic group is built into the structure in the right way, it might trap this intermediate and stop it reacting further.



If we try drawing a mechanism for the formation of this remarkable compound, we discover that a necessary intermediate is also an intermediate in our preferred mechanism for aromatic nitration. The amide has trapped the cation we would propose as an intermediate in aromatic

nitration, so we feel more confident about that mechanism. The product is an enol ether that will hydrolyse to the observed enone.



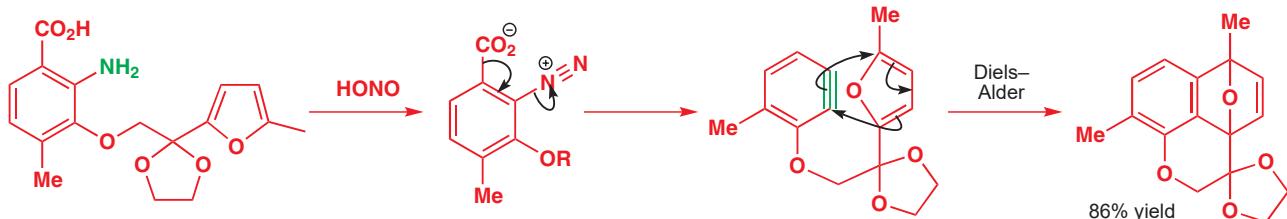
This mechanism explains everything, including the stereochemistry. The  $\text{NO}_2^+$  attacks the aromatic ring *para* to the  $\text{OMe}$  group and on the opposite side to the amide. The amide is now in the perfect position to capture the cation at the *meta* position and, because the tether is short, it must form a *cis* bridge.

To be convincing, evidence for an intermediate should include:

- detection of the intermediate in the reaction mixture, perhaps by a trapping reaction
- a demonstration that the intermediate gives the product when added to the reaction mixture (this also means that it must be prepared as an at least reasonably stable compound)
- kinetic evidence that the rate of formation and rate of disappearance are adequate
- other suitable evidence of the kind that we have been discussing in this chapter.

A neat intramolecular trap for a benzyne works in this way. A standard benzyne-generating reaction, the diazotization of an *ortho*-amino benzoic acid (Chapter 22), gives a zwitterion that loses nitrogen and  $\text{CO}_2$  to release the benzyne. A furan tethered to the next *ortho* position traps the benzyne in an intramolecular Diels–Alder reaction. The yield is impressive and the trap is very efficient.

Why the cyclic acetal? It makes the cyclization more efficient by the Thorpe–Ingold effect (see Chapter 31).

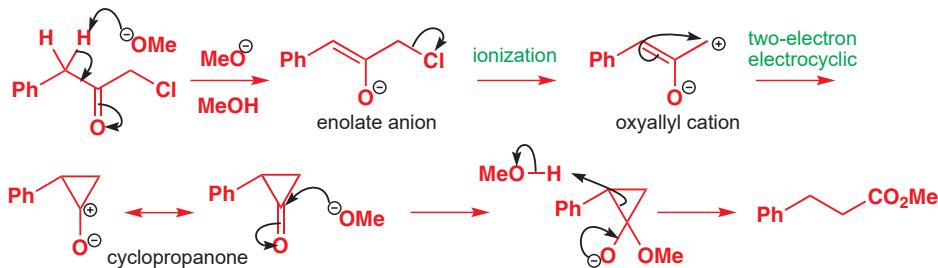


This reaction cannot really be explained without a benzyne intermediate. This same method of making benzyne is used on other *o*-amino benzoic acids and so we deduce that they presumably create benzenes too.

### A collection of reactions linked by a common intermediate

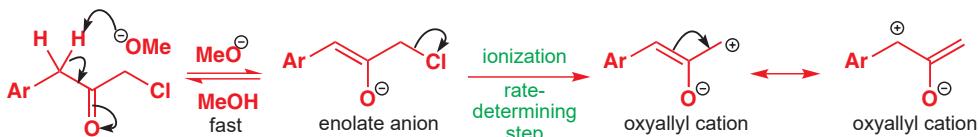
Particularly convincing evidence can develop when a number of chemists suggest the same intermediate for a number of different reactions and show that it is possible to trap the intermediate from one reaction, put it into the others, and get the normal products. We are going to describe one such set of related reactions. In Chapter 36 we suggested a mechanism for the Favorskii rearrangement involving a series of remarkable intermediates. Here is an example.

The Favorskii rearrangement is on p. 950.

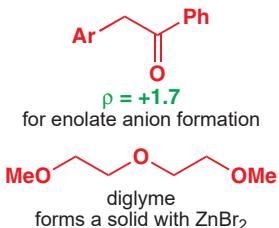


Interactive mechanism for the Favorskii rearrangement

We'll summarize the evidence on this particular example. If the reaction is run in MeOD instead of MeOH, the starting material becomes deuterated at the site of enolate formation, suggesting that this is a fast and reversible step. The entropy of activation for the reaction is  $\Delta S^\ddagger = +64 \text{ J mol}^{-1} \text{ K}^{-1}$ , suggesting that the slow step is one molecule breaking into two. There is only one such step—the second, ionization step. If various substituted phenyl groups are used, the Hammett  $\rho$  value is  $-5$ . This large negative value also suggests that the ionization is the slow step as the cation is delocalized into the benzene ring.

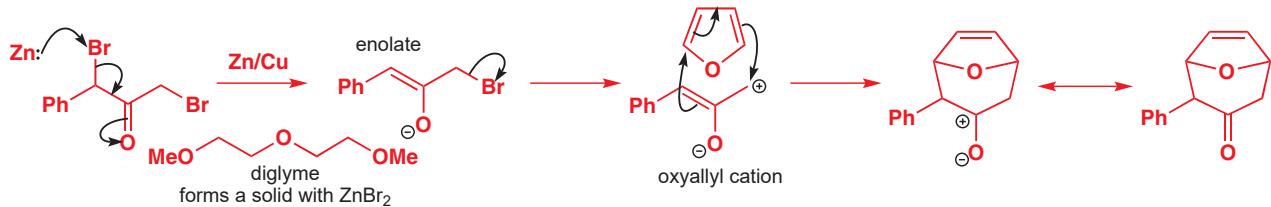


There is evidence for the first intermediate—the exchange of deuterium from the solvent. In fact formation of the enolate can even become the rate-determining step. If we merely add an extra methyl group to the chloroketone the reaction becomes 220 times faster and the rate-determining step changes. There is no longer any exchange of deuterium from the solvent and the Hammett  $\rho$  value changes from  $-5$  to  $+1.4$ . This small positive value, showing some modest increase in electron density near the ring, matches typical known  $\rho$  values for enolate formation.

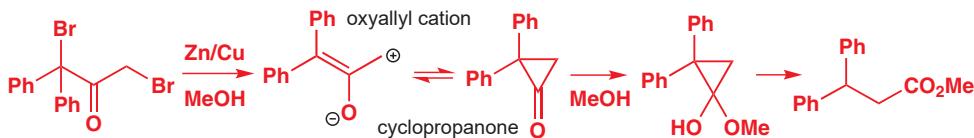


For related reactions, see Chapter 34, p. 894.

However, it's not too surprising that an enolate ion is formed from a ketone in basic solution. The oxyallyl cation is a much more unusual species. How can we be convinced that it really is an intermediate? One way is to make it by an alternative route. If basic nucleophiles such as the methoxide ion are avoided and reaction of zinc with an  $\alpha,\alpha'$ -dibromoketone in a non-nucleophilic solvent like diglyme is used instead, the oxyallyl cation can be trapped in a Diels–Alder reaction. This is the basis for a good synthesis of seven-membered rings.

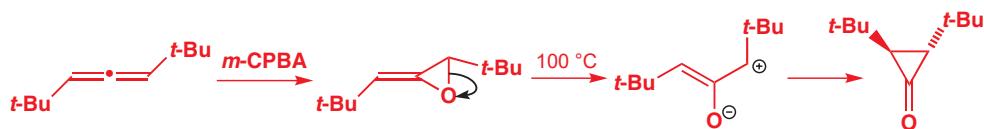


But does the oxyallyl cation go on to give cyclopropanones? In fact, there is good evidence that the two are in equilibrium. If the same method is used to create the diphenyl oxyallyl cation in methanol instead of in diglyme, the normal Favorskii product is produced. Evidently, methoxide is needed only to produce the enolate—methanol alone is enough to decompose the cyclopropanone.

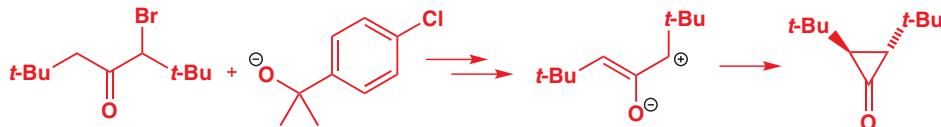


Further information comes from another reaction. If a suitable (1,3-di-*t*-butyl) allene is epoxidized with *m*-CPBA the unstable allene oxide can actually be isolated. On heating, this

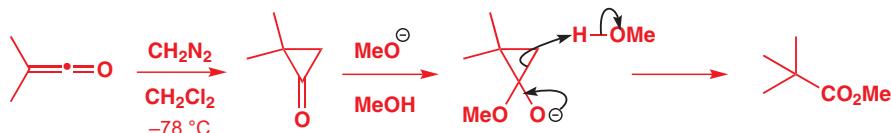
epoxide gives a stable *trans*-di-*t*-butylcyclopropanone. It is very difficult to see how this reaction could happen except via the oxyallyl cation intermediate.



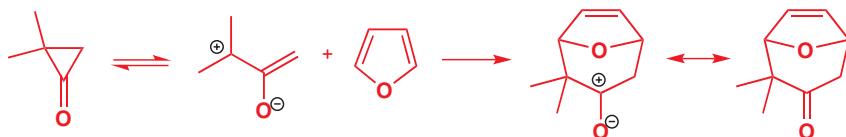
But can the same cyclopropanone be an intermediate in the Favorskii reaction? If the bromoketone is treated with methoxide in methanol, it gives the Favorskii product, but if it is treated with a much more hindered base, such as the potassium phenoxide shown, it gives the same cyclopropanone.



Other, less stable, cyclopropanones—such as this 2,2-dimethyl compound—can be made by carbene addition (Chapter 38) to ketenes. This compound did the Favorskii reaction with methoxide in methanol: the only product came from the expected loss of the less unstable carbanion. This will, of course, be general acid catalysed by methanol as no free carbanion can be released into an alcoholic solvent.



The same cyclopropanone gives a cycloadduct with furans—this must surely be a reaction of the oxyallyl cation and we can conclude that the isomeric reactive intermediates are in equilibrium, and react to give products according to the conditions they find themselves in.

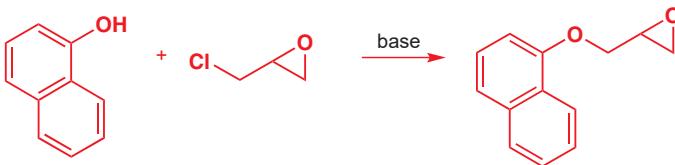


Although it is never possible to prove a mechanism, this interlocking network of intermediates, all known to be formed under the reaction conditions, all being trapped in various ways, and all known to give the products, is very convincing. If any part of the mechanism were not correct, that would throw doubt on all the other reactions as well.

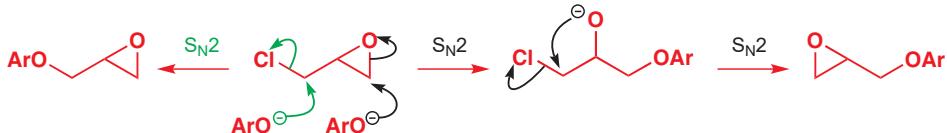
## Stereochemistry and mechanism

Although we have left stereochemistry to the last, it is one of the most important tools in unravelling complex mechanisms. You have already seen how inversion of configuration is a vital piece of evidence for an  $\text{S}_{\text{N}}2$  mechanism (Chapter 15) while retention of configuration is the best evidence for participation (Chapter 36). You have seen the array of stereochemical evidence for pericyclic mechanisms (Chapters 34 and 35). The chapters devoted to diastereoselectivity (32 and 33) give many examples where information about the mechanism follows from the stereochemistry. We shall not go over that material again, but summarize the types of evidence with new examples. The first example looks too trivial to mention.

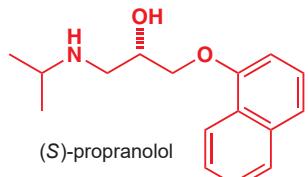
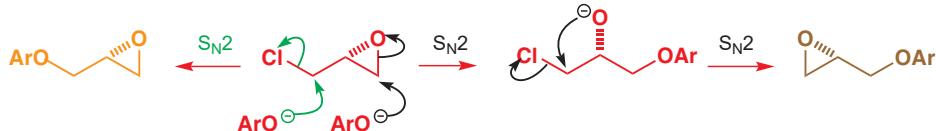
### Retention or inversion?



Although this reaction looks like a simple  $S_N2$  displacement by the naphthyloxide anion on the primary alkyl chloride, there is, in fact, a reasonable alternative—the opening of the epoxide at the less hindered primary centre followed by closure of the epoxide the other way round. The electrophile is known as epichlorohydrin and has two reasonable sites for nucleophilic attack.

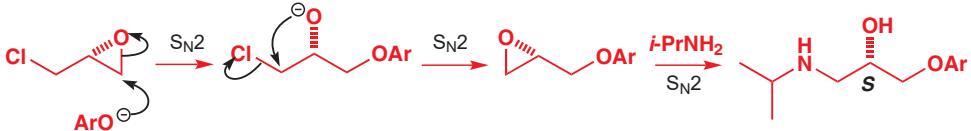


It looks difficult to tell these mechanisms apart since both involve the same kind of reaction. Stereochemistry is the answer. If enantiomerically pure epichlorohydrin is used, the two mechanisms give different enantiomers of the product. Although each  $S_N2$  reaction takes place at a primary centre and the stereogenic centre remains the same, the products shown in orange and in brown are obviously enantiomers.

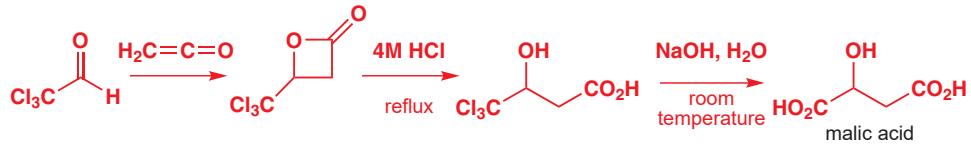


► A synthesis of propranolol is given in Chapter 28.

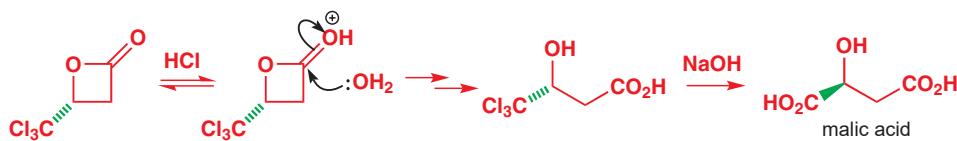
Finding out the mechanism of this process is not idle curiosity as a group of drugs used to combat high blood pressure and heart disease, such as propranolol, are made from epichlorohydrin and it is essential to know which enantiomer to use to get the right enantiomer of the drug. In fact, the epoxide is attacked initially, in preference to the chloride.



A more complicated example arises from the strange reactions used to make malic acid from chloral and ketene. An initial  $[2 + 2]$  cycloaddition is followed by acid treatment and then treatment with an excess of aqueous  $\text{NaOH}$ . Neutralization gives malic acid.

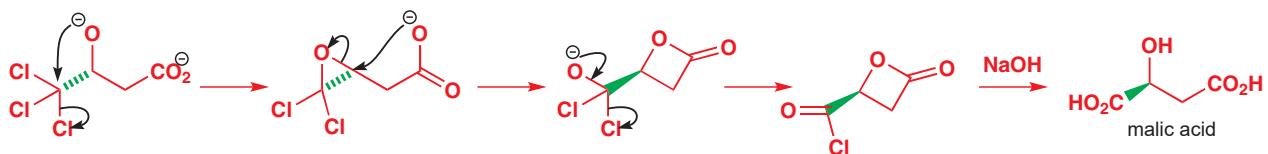


The mechanism of this reaction also looks straightforward: normal ester hydrolysis followed by hydrolysis of the  $\text{CCl}_3$  group to  $\text{CO}_2\text{H}$ . Caution suggests investigation, particularly as four-membered lactones sometimes hydrolyse by  $S_N2$  displacement at the saturated ester carbon rather than by attack on the carbonyl group, like the three-membered lactones discussed in Chapter 36 (p. 934). The solution was urgently needed when it was found that enantiomerically pure lactone could be prepared as a single enantiomer. The sequence was repeated with enantiomerically pure lactone: lactone hydrolysis occurred with retention of configuration and must be normal ester hydrolysis by attack of water at the carbonyl group. But the hydrolysis of the  $\text{CCl}_3$  group surprisingly occurred with inversion of configuration.



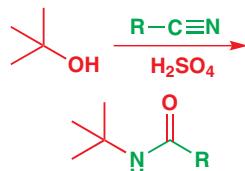
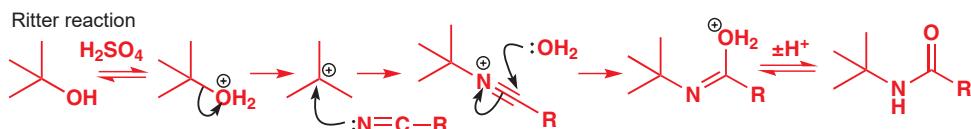
The answer must be a mechanism related to the one we have just seen for epichlorohydrin. Attack by hydroxide on  $\text{CCl}_3$  is almost unknown and it is much more likely that intramolecular attack by alkoxide should occur. The carboxylate anion can then invert the stereogenic centre by intramolecular  $S_N2$  displacement. Notice that the tether ensures attack at the nearer end of the epoxide. The second four-membered lactone also hydrolyses by attack at the carbonyl group.

► In Chapter 31 we discussed Baldwin's rules for ring closures such as these. The unreactivity of the trichloromethyl group is related to the unreactivity of dichloromethane: see p. 804.



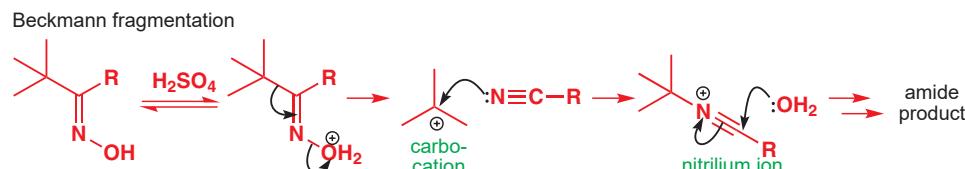
### The Ritter reaction and the Beckmann fragmentation

Another collection of related intermediates occurs in the Ritter reaction and the Beckmann fragmentation. The Ritter reaction involves the combination of a tertiary alcohol and a nitrile in acid solution and the proposed mechanism involves a series of intermediates.



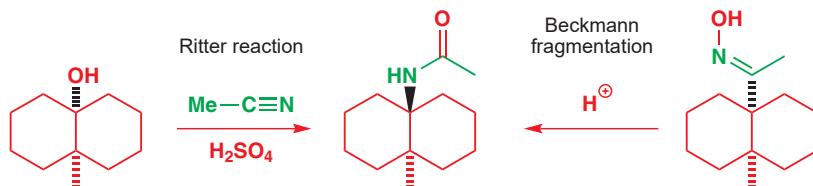
The Beckmann fragmentation also occurs in acid solution on the fragmentation of an oxime with a tertiary alkyl group *anti* to the OH of the oxime. The fragmentation step gives the same cation and the same nitrile together with a molecule of water and these three combine in the same way to give the same amide. We need evidence that the carbocation and the nitrilium ion are genuine intermediates and that the same sequence is found in both reactions.

► The Ritter reaction was introduced in Chapter 15 and the Beckmann fragmentation in Chapter 36.

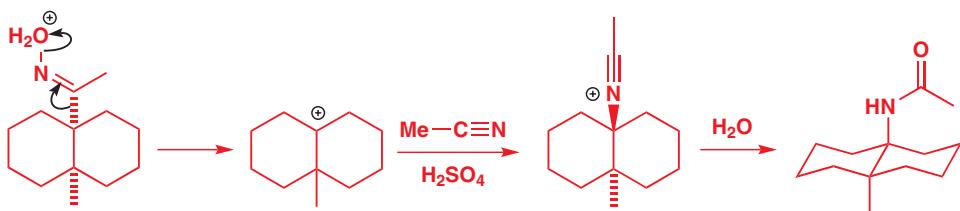


► Interactive mechanism for the Beckmann fragmentation

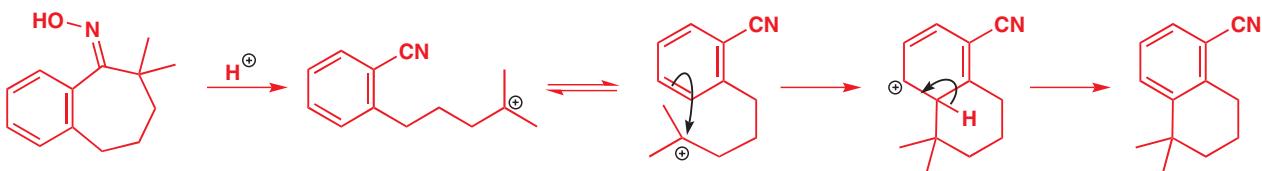
Evidence that the two reactions are intimately related comes from the formation of the same amide from two different starting materials: a tertiary alcohol and an oxime, both based on the decalin skeleton. The oxime has its OH group *anti* to the ring junction to minimize steric hindrance as oxime formation is under thermodynamic control (Chapter 11).



The experiments also provide stereochemical evidence that a carbocation is an intermediate in both reactions. Both starting materials are *cis*-decalins but the product is a *trans*-decalin. The carbocation intermediate has no stereochemistry and can react with the nitrile from either face: since axial attack is preferred the product is the more stable *trans*-decalin. Here's the mechanism for the Beckmann fragmentation:

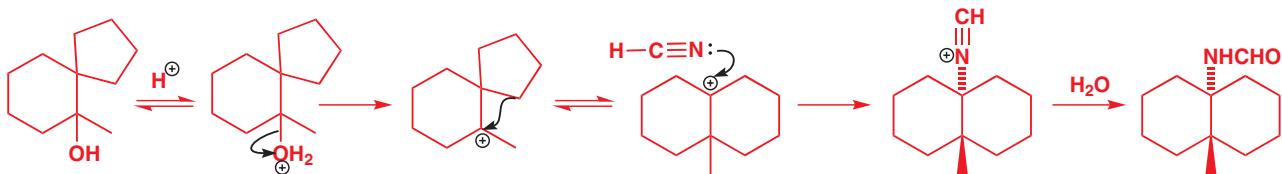


It is also possible to trap the carbocation in other ways. The Beckmann fragmentation of this oxime of an aryl seven-membered ring ketone gives a tertiary carbocation that might be expected to cyclize to give an amide. However, this reaction would give an unfavourable eight-membered ring (see Chapter 32) and does not happen. Instead, the chain twists round the other way and forms a much more stable six-membered ring by intramolecular Friedel–Crafts alkylation.



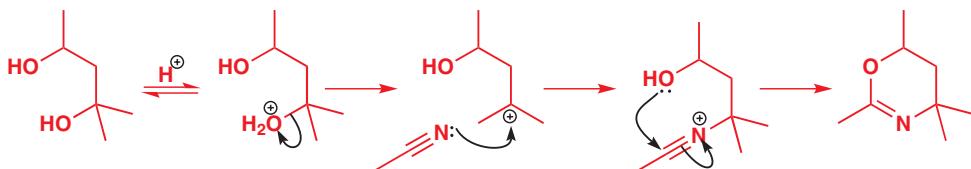
► Rearrangements of carbocations were described in Chapter 36, pp. 940–947.

In the Ritter reaction a rather different kind of evidence for the cation is the fact that families of isomeric alcohols all give the same product. In all these cases, rearrangements of the first-formed carbocation can easily account for the products. An example in the decalin series is this Ritter reaction with KCN as the nitrile in acidic solution so that HCN is the reagent. The starting material is a spirocyclic tertiary alcohol but the product is a *trans*-decalin formed by rearrangement.

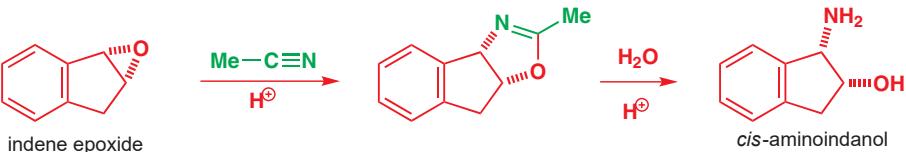


■ It's worth pointing out here that use of cyanides in acid is extremely dangerous.

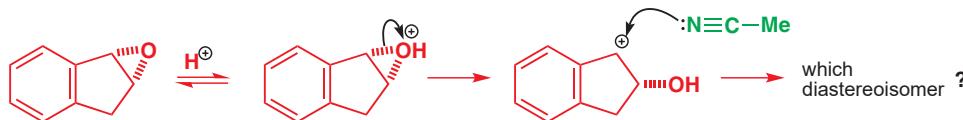
Trapping the nitrilium cation is also possible. A famous example is the heterocycle (an oxazine, Chapter 32) produced by intramolecular capture of the nitrilium ion with a hydroxyl group. Note that the tertiary alcohol reacts to give the cation while the secondary alcohol acts as the nucleophilic trap.



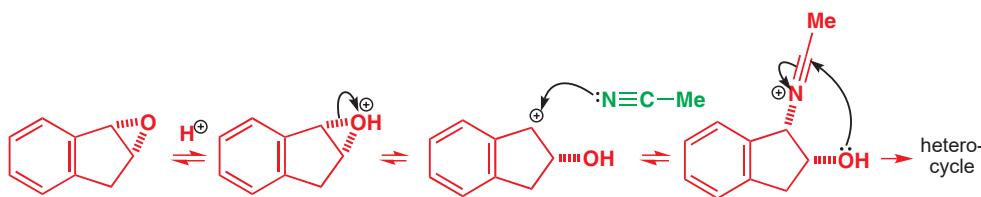
An important example in which the diastereoisomer produced was critical in determining the mechanism is the synthesis of *cis*-aminoindanol, a part of Merck's anti-HIV drug Crixivan (indinavir). The reaction involves treatment of indene epoxide with acetonitrile (MeCN) in acidic solution. The product is a *cis* fused heterocycle. It is easy to see which atoms have come from the nitrile (green) but the substitution of nitrogen for oxygen at one end of the epoxide has occurred with retention of configuration as the *cis*-epoxide has given the *cis* product. Clearly, we have some sort of Ritter reaction and the nitrilium ion has been trapped with an OH group.



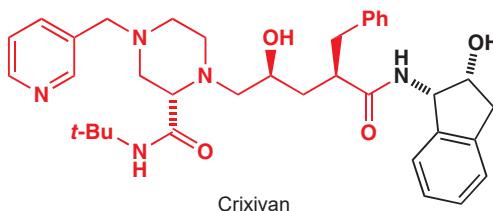
What about the regioselectivity? The obvious explanation is that a cation is formed from the epoxide by a specific acid-catalysed ring opening. But why should the nitrile attack the bottom face of the cation? We should expect it to attack the top face preferentially as the hydroxyl group partly blocks the bottom face.



A reasonable suggestion is that the nitrile adds *reversibly* to the cation. Every time it adds to the top face, it drops off again as the OH group cannot reach round to form the heterocycle. But every time it adds to the bottom face (which may well be less often), it is quickly captured by the OH group because 5,5 fused rings are favourable when the ring junction is *cis*. Eventually, all the compound is converted to the heterocycle.



The mechanism of this reaction is of great importance because it is the foundation stone of the synthesis of Crixivan (indinavir)—an anti-HIV drug that has saved thousands of lives.



► The last step looks a long stretch, but you saw in Chapter 31 that 5-*endo*-dig cyclizations are favourable (p. 813).

► Interactive mechanism for the formation of *cis*-aminoindanol by the Ritter reaction

► The story of indinavir is recounted in Chapter 43.

## Summary of methods for the investigation of mechanism

This brief summary is for guidance only and the figures quoted are approximate ranges only. The full text above should be used for detail. All methods would not be used in one investigation.

### 1. Make sure of the structure of the product

- Basic structure (Chapters 3, 13, and 18) and stereochemistry (Chapter 31) by spectroscopic methods.
- Detail of the fate of individual atoms by labelling with D,  $^{13}\text{C}$ , and  $^{18}\text{O}$ . Double labelling may help.
- The stereochemical course of the reaction (enantio- or diastereoselectivity) may be critical.

### 2. Kinetic methods

- Rate equation gives the composition of main transition state.
- Deuterium isotope effect:  $k_{\text{H}} > k_{\text{D}}$  shows bond to H formed and/or broken in transition state. Values of  $k_{\text{H}}/k_{\text{D}}$  of 2–7 typical.
- Entropy of activation shows increase ( $\Delta S^\ddagger$  positive) or decrease ( $\Delta S^\ddagger$  negative) in disorder. Typical values and deductions:
  - $\Delta S^\ddagger$  positive (rarely larger than  $+50 \text{ J mol}^{-1} \text{ K}^{-1}$ ): one molecule breaks into two or three
  - moderate negative values: no change in number of molecules (one goes to one etc.) or bimolecular reaction with solvent

- large negative values: two molecules go to one or unimolecular reaction with ordered transition state (cycloaddition, etc.)

### 3. Correlation of structure and reactivity

- Replace one group by another of similar size but different electronic demand ( $\text{CF}_3$  for  $\text{CH}_3$  or  $\text{OMe}$  for  $\text{CH}_3$ ).
- Systematic Hammett  $\sigma/\rho$  correlation with *m*- and *p*-substituted benzenes:
  - sign of  $\rho$ :  $+\rho$  indicates electrons flowing into and  $-\rho$  electrons flowing out of ring in transition state
- magnitude of  $\rho$  shows effect on the benzene ring:
  - large (around 5), charge on ring ( $+\rho$ , anion;  $-\rho$ , cation)
  - moderate (around 2–4), charge on atom next to ring—may be gain or loss of conjugation
  - small (<1), ring may be distant from scene of action or  $\rho$  may be balance of two  $\rho$ s of opposite sign.

### 4. Catalysis

- pH-rate profile reveals specific acid or base catalysis.
- Rate variation with  $[\text{HA}]$  or  $[\text{B}]$  at constant pH reveals GAC or GBC.
- Deuterium isotope effect: normal ( $k_{\text{H}} > k_{\text{D}}$ ) shows GA/BC, inverse solvent  $k(\text{D}_2\text{O}) > k(\text{H}_2\text{O})$  shows SA/BC.
- GA/BC is termolecular and has large negative entropy of activation.

### 5. Intermediates

- Independent preparation or, better, isolation from or detection in reaction mixture helps.
- Must show that intermediate gives product under reaction conditions.
- Designed trapping experiments often most convincing.

## Further reading

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An excellent modern and rather more advanced book is E. V. Anslyn and D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books, Sausalito, CA, 2005.

## Check your understanding

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To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 金属有机化学

## 联系

### 基础

- Nucleophilic substitution at saturated carbon ch15
- Conjugate addition ch22
- Controlling stereochemistry ch14, ch32, & ch33
- Oxidation and reduction ch23
- Chemistry of Si and Sn ch27
- Aromatic heterocycles ch29 & ch30
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### 目标

- Transition metals form organic compounds
- The structure of  $\sigma$  and  $\pi$  complexes and the meaning of  $\eta$  numbers
- The bonding is described with the usual orbitals
- Most stable complexes have 18 valence electrons
- Metals catalyse ‘impossible’ reactions
- Oxidative insertion, reductive elimination, and ligand migration from metal to carbon are key steps
- Carbon monoxide inserts into metal–carbon bonds
- Palladium is the most important metal
- C–C, C–O, and C–N bonds can be made with Pd catalysis
- Cross-coupling of two ligands is common
- Allyl cation complexes are useful electrophiles

### 展望

- Asymmetric synthesis ch41
- The chemistry of life, especially nucleic acids ch42

## Transition metals extend the range of organic reactions

Some of the most exciting reactions in organic chemistry make use of transition metals, and in recent years three Nobel prizes have been awarded for work in this area. How about this example? It is a **Heck reaction**, which allows nucleophilic addition to an unactivated alkene. Just a catalytic amount of palladium is needed to make the reaction go: the most useful organometallic reactions are those in which the metal acts catalytically.



Reagents and complexes containing transition metals are important in modern organic synthesis because they allow apparently impossible reactions to occur easily. Their chemistry complements traditional functional group chemistry and significantly broadens the range of

True to our beliefs that explanations are more important than facts, we have given mechanisms for most reactions. You should understand that it is much more difficult to be certain about these mechanisms than in some other areas of chemistry: a great deal of work goes into establishing mechanisms for important organometallic transformations, but many remain speculative. The mechanisms we give are meant to help you understand what is going on and may well turn out not to be correct in every detail.

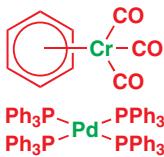
reactions a chemist can expect to use to make molecules. This chapter introduces the concepts of metal–ligand interaction, describes the most important reactions that can occur while ligands are bound to the metal, and demonstrates the power of organometallic chemistry in synthesis. The efficiency of transition metal-catalysed reactions means that they are routinely used in industrial synthesis. It is important that you understand the rules by which organometallic chemistry works.

## The 18 electron rule

There is a contradiction in what is required of a metal complex for it to be useful to us. Initially, it will need to be stable and have a long enough lifetime to enable study and, ideally, storage. But once it enters the reaction vessel, stability is a disadvantage: instead we want reactivity. Our ideal catalyst is a complex that is stable in the resting state, but quickly becomes activated in solution—perhaps by loss of a ligand—so that it can interact with the substrate. Fortunately, there is a simple guide to the stability of transition metal complexes: **the 18 electron rule**. If a complex satisfies the 18-electron rule it means that the metal at the centre of the complex has the noble gas configuration of 18 electrons in the valence shell, and the complex is likely to be stable. The requirement for 18 electrons comes from the need to fill one ‘s’ orbital, five ‘d’ orbitals, and three ‘p’ orbitals with two electrons in each. The 18 electrons we need can come from those the metal already possesses plus those donated by any coordinating ligands.

The table below gives you the number of valence electrons each metal starts with before it acquires any ligands. Notice that the ‘new’ group numbers 1–18 give you the answer without any calculation. The most important are highlighted.

Group	IVB (4)	VB (5)	VIB (6)	VIIB (7)	VIIIB (8, 9, and 10)	1A (11)		
Number of valence electrons	4	5	6	7	8	9	10	11
3d electrons	Ti	V	Cr	Mn	Fe	Co	Ni	Cu
4d electrons	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag
5d electrons	Hf	Ta	W	Re	Os	Ir	Pt	Au



18-electron complexes



a 16-electron Pd(II) complex

Metals to the left-hand side of this list obviously need many more electrons to make up the magic 18. Chromium, for example, forms stable complexes with a benzene ring, giving it six electrons, and three molecules of carbon monoxide, giving it two each:  $6 + 6 + 2 + 2 + 2 = 18$ . Palladium is happy with just four triphenylphosphines ( $\text{Ph}_3\text{P}$ ) giving it two each:  $10 + 2 + 2 + 2 + 2 = 18$ .

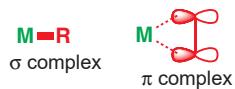
You may already know from your study of inorganic chemistry that there are exceptions to the 18-electron rule, particularly among complexes of Ti, Zr, Ni, Pd, and Pt, which can all form stable 16-electron complexes. The important 16-electron Pd(II) complex with two chlorides and two acetonitriles (MeCN) will feature heavily in this chapter. The so-called platinum metals Ni, Pd, and Pt are extremely important in catalytic processes, as you will see later on. Their stable 16-electron configuration results from a high-energy vacant orbital caused by the complex adopting a square planar geometry.

## Ligands can be attached in many different ways

Transition metals can have a number of ligands attached to them and each ligand can be attached in more than one place. This affects the reactivity of the ligand and the metal because each additional point of attachment means the donation of more electrons. We can show the number of atoms involved in bonding to the metal by a **hapto number**  $\eta$ . A simple Grignard reagent is  $\eta^1$  (pronounced ‘eta-one’) as the magnesium is attached only to one carbon atom. A metal–alkene complex is  $\eta^2$  because both carbon atoms of the alkene are equally involved in bonding to the metal. In these cases the  $\eta$  designation is not very informative as there are no alternatives, and it is usually omitted.



The bonding in these two complexes is very different. In the first there is a simple  $\sigma$  bond between the metal and the alkyl group as in a Grignard reagent  $R\text{-MgBr}$  and this type of complex is called a  $\sigma$  complex. In the alkene complex, bonding is to the p orbitals only. There are no  $\sigma$  bonds to the metal, which sits in the middle of the  $\pi$  bond in between the two p orbitals. This type of complex is called a  $\pi$  complex.



### Representing bonds in transition metal complexes

It is difficult to know exactly how to draw the bonding in metal complexes and there are often several different acceptable representations. There is no problem when the metal forms a  $\sigma$  bond to atoms such as Cl or C as the simple line we normally use for covalent bonds means exactly what it says. The problems arise with ligands that form  $\sigma$  bonds by donating both their electrons, and with  $\pi$  complexes. Everyone writes phosphine–borane complexes with two charges but we normally draw the same sort of bond between a phosphine and, say, Pd as a simple line with no charges.

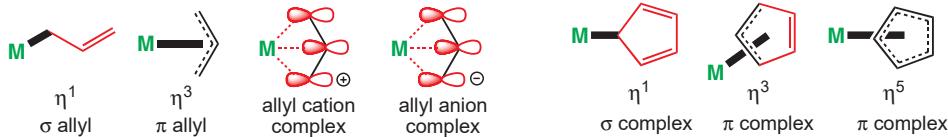


You will sometimes see  $\pi$  complexes drawn with simpler dotted lines going to the middle of the  $\pi$  bond, sometimes with dotted  $\pi$  bonds, and sometimes with bonds (simple or dotted) going to the ends of the old  $\pi$  bond. These are all acceptable as the bonding is complex, as you will see. We might almost say that the ambiguity is helpful: we often don't know either the exact nature of the bonding or the number of other ligands in the complex. In the diagrams in this section we have shown the main bond from metal to ligand as a heavy line in the simplest representation but we also offer alternatives with simple and dotted bonds. Don't worry about this—things will become clearer as the chapter develops. When you have to draw the structure of a complex but you don't know the exact bonding, just draw a line from metal to ligand.

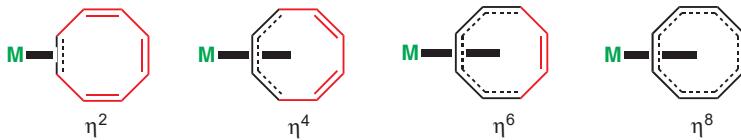
different acceptable ways  
to draw  $\pi$  complexes



These labels are useful where there is a choice of type of bonding, as with allylic ligands. The metal can either form a  $\sigma$  bond to a single carbon (hence  $\eta^1$ ), or form a  $\pi$  complex with the p orbitals of all three carbons of the allyl system—this would be  $\eta^3$ . If the  $\pi$  complex is made from an allyl cation, the ligand has two electrons, but it has four if it is made from an allyl anion. Similarly, a cyclopentadienyl anion can act as a  $\sigma$  ligand ( $\eta^1$ ), an allyl ligand ( $\eta^3$ ), or, most usually, as a cyclopentadienyl ligand ( $\eta^5$ ). The distinction is very important for electron counting as these three different situations contribute two, four, or six electrons, respectively, to the complex.



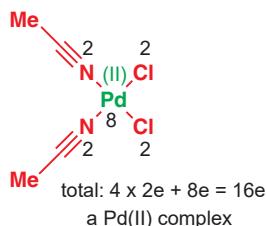
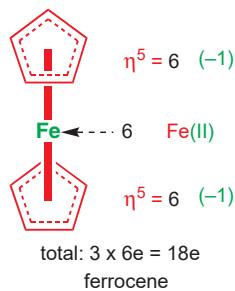
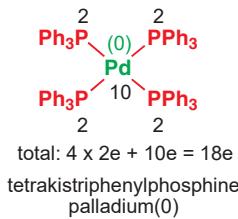
Neutral ligands can also bond in a variety of ways. Cyclooctatetraene can act as an alkene ( $\eta^2$ ), a diene ( $\eta^4$ ), a triene ( $\eta^6$ ), or a tetraene ( $\eta^8$ ), and the reactivity of the ligand changes accordingly. These are all  $\pi$  complexes with the metal above or below the black portion of the ring and with the thick bond to the metal at right angles to the alkene plane.



To determine the number of electrons around the transition metal in a complex the valence electrons from the metal ion are added to those contributed by all the ligands. The numbers of electrons donated by various classes of ligands are summarized in the table. Anions such as halides, cyanide, alkoxide, hydride, and alkyl donate two electrons, as do neutral ligands with a lone pair such as phosphines, amines, ethers, sulfides, carbon monoxide, nitriles, and

isonitriles. Unsaturated ligands can contribute as many as eight electrons and can be neutral or negatively charged. If the overall total is 18, then the complex is likely to be stable. If the overall total is less than 18 the complex is called *coordinatively unsaturated*.

Ligand characteristics		Formal charge	Electrons donated
anionic ligands			
$\text{Cl}^-$	$\text{Br}^-$	$\text{I}^-$	$\text{CN}^-$
$\text{OR}^-$	$\text{H}^-$	$\text{alkyl}^-$	-1
neutral $\sigma$ -donor ligands			
$\text{R}-\ddot{\text{P}}(\text{R})_2$	$\text{R}-\ddot{\text{N}}(\text{R})_2$	$\text{R}-\ddot{\text{O}}-\text{R}$	$\text{R}-\ddot{\text{S}}-\text{R}$
$\text{C}\equiv\text{O}$	$\text{N}\equiv\text{C}$	$\text{C}\equiv\text{N}$	0
			2
Organic ligands			
	Hapto number	Formal charge	Electrons donated
unsaturated $\sigma$ - or $\pi$ -donor ligands			
aryl, $\sigma$ -allyl	$\eta^1$	-1	2
alkenes	$\eta^2$	0	2
$\pi$ -allyl cation	$\eta^3$	+1	2
$\pi$ -allyl anion	$\eta^3$	-1	4
diene—conjugated	$\eta^4$	0	4
dienyls, cyclopentadienyls (anions)	$\eta^5$	-1	6
arenes, trienes	$\eta^6$	0	6
triennyls, cycloheptatrienyls (anions)	$\eta^7$	-1	8
cyclooctatetraene	$\eta^8$	0	8
carbene, nitrene, oxo	$\eta^1$	0	2



### Electron counting helps to explain the stability of metal complexes

Counting electrons in most complexes is simple using the table of ligand characteristics above in conjunction with the table on p. 1070. Take tetrakis(triphenylphosphine)palladium(0): each neutral phosphine donates two electrons, making a total of eight, and palladium still has its full complement of 10 valence electrons as it is in the zero oxidation state. Overall, the complex has a total of 18 electrons and is a stable complex—in fact too stable: it has to lose a  $\text{PPh}_3$  ligand before it can enter into reactions.

All of the different classes of ligands listed in the table above can be treated in this way. In ferrocene, the cyclopentadienyl ligands contribute six electrons each and have a formal negative charge, shown in green, which means that the iron in ferrocene is in the +2 oxidation state and will have six valence electrons left. The total for the complex is again 18 and ferrocene is an extremely stable complex.

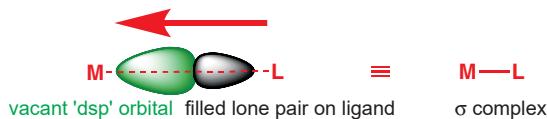
The useful complex  $(\text{MeCN})_2\text{PdCl}_2$  has palladium in the +2 oxidation state because of its two chlorine atoms and the number of electrons is eight for the Pd(II) oxidation state and another two each from the four ligands, making 16 in all. This complex does not fulfil the 18-electron rule and is stable yet reactive.

### The oxidation state of metals in complexes

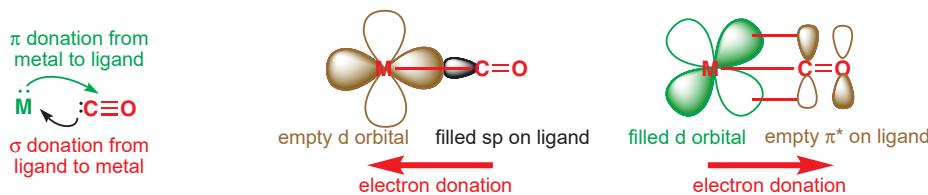
As well as the problem of bond drawing, there is a potential problem over oxidation states too. You can either say that ferrocene is a complex of  $\text{Fe}(II)$ , having two fewer electrons than the normal eight, with two cyclopentadienyl anions contributing six electrons each, or you can say that it is a complex of  $\text{Fe}(0)$ , having eight electrons, with two cyclopentadienyl ligands each contributing five electrons. The simplest approach is to say that a metal is in the (0) oxidation state unless it has  $\sigma$  bonds to ligands such as Cl, AcO, or Me that form bonds with shared electrons. Neutral ligands such as  $\text{Ph}_3\text{P}$  that provide two of their own electrons do not affect the oxidation state of the metal.

## Bonding and reactions in transition metal complexes

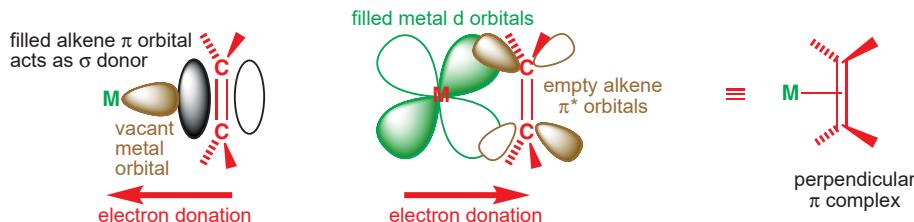
The majority of ligands have a lone pair of electrons in a filled  $sp^n$  type orbital that can overlap with a vacant metal 'dsp' orbital, derived from the vacant d, p, and s orbitals of the metal, to form a conventional two-electron two-centre  $\sigma$  bond. Ligands of this type increase the electron density on the central metal atom.



A bonding interaction is also possible between any filled d orbitals on the metal and vacant ligand orbitals of appropriate symmetry such as  $\pi^*$  orbitals. This leads to a reduction of electron density on the metal and is known as **back-bonding**. An example would be a complex with carbon monoxide. Many metals form these complexes and they are known as **metal carbonyls**. The ligand (CO) donates the lone pair on carbon into an empty orbital on the metal while the metal donates electrons into the low-energy  $\pi^*$  orbital of CO. Direct evidence for this back-bonding is an increase in the C–O bond length and a lowering of the infrared stretching frequency from the population of the  $\pi^*$  orbital of the carbonyl.



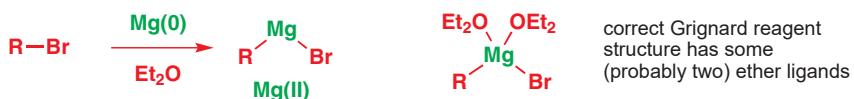
When an unsaturated ligand such as an alkene approaches the metal sideways to form a  $\pi$  complex, similar interactions lead to bonding. The filled  $\pi$  orbitals of the ligand bond to empty d orbitals of the metal, while filled d orbitals on the metal bond to the empty  $\pi^*$  orbitals of the ligand. The result is a  $\pi$  complex with the metal–alkene bond perpendicular to the plane of the alkene. The bond has both  $\sigma$  and  $\pi$  character.



Coordination to a metal by any of these bonding methods changes the reactivity of the ligands dramatically and this is exploited in the organometallic chemistry we will be discussing in the rest of the chapter. You do not need to understand all the bonding properties of metal complexes but you need to be able to count electrons, to recognize both  $\sigma$  and  $\pi$  complexes, and to realize that complexes show a balance between electron donation and electron withdrawal by the metal.

### Oxidative addition inserts metal atoms into single bonds

Potential ligands that do not have a lone pair or filled  $\pi$ -type orbital are still able to interact with transition metal complexes but only by breaking a  $\sigma$  bond. This is the first step in a wide variety of processes and is described as **oxidative addition** because the formal oxidation state of the transition metal is raised by two, for example M(0) to M(II), in the process. This is the result of having two extra ligands bearing a formal negative charge. You have seen this process in the formation of Grignard reagents (Chapter 9).



The number of coordinated ligands also increases by two so the starting complex is usually in low oxidation state (0 or 1; the diagram shows 0) and **coordinatively unsaturated**, that is, it has an empty site for a ligand and, say, only 16 electrons, like  $(\text{MeCN})_2\text{PdCl}_2$ , whereas the product is usually **coordinatively saturated**, that is, it cannot accept another ligand unless it loses one first.



► You will see why Wilkinson's catalyst and its derivatives are important catalysts of homogeneous hydrogenation in Chapter 41.

Oxidative addition occurs for a number of useful neutral species, including molecular hydrogen, carbon–hydrogen bonds, and silanes as well as polarized bonds or electrophilic species containing at least one electronegative atom. The resulting species with metal–ligand bonds allow useful chemical transformations to occur. Important examples include the oxidative addition of Pd(0) to aryl iodides and the activation of Wilkinson's catalyst for hydrogenation in solution by oxidative addition to a hydrogen molecule.



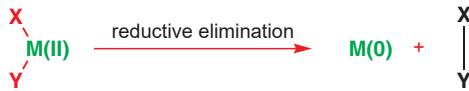
### Vaska's complex

There are a number of possible mechanisms for oxidative addition and the precise one followed depends on the nature of the reacting partners. Vaska's complex  $[\text{Ir}(\text{PPh}_3)_2\text{COCl}]$  has been extensively studied and it reacts differently with hydrogen and methyl iodide. Hydrogen is added in a *cis* fashion, consistent with concerted formation of the two new iridium–hydrogen bonds. The 16e (count them!) d<sup>8</sup>, Ir(I) complex becomes a new 18e, d<sup>6</sup>, Ir(III) species. With methyl iodide the kinetic product is that of *trans* addition, which is geometrically impossible from a concerted process. Instead, an S<sub>N</sub>2-like mechanism is followed involving nucleophilic displacement of iodide followed by ionic recombination.

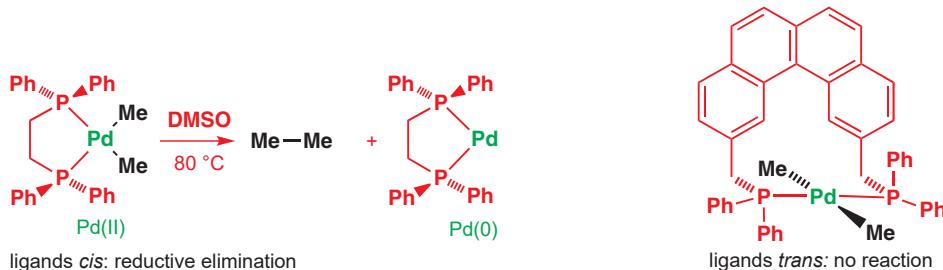


### Reductive elimination removes metal atoms and forms new single bonds

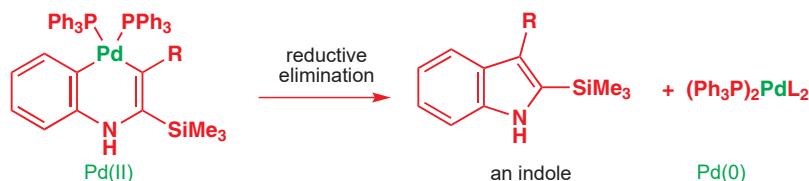
If we want to use organometallic chemistry to make organic compounds other than those containing metals, we must be able to remove the ligands from the coordination sphere of the metal at the end of the reaction. Neutral organic species such as alkenes, phosphines, and carbon monoxide can simply dissociate in the presence of other suitable ligands but those that are bound to the metal with shared electrons require a more active process. Fortunately, most reactions that occur around a transition metal are reversible and so the reverse of oxidative addition, known as **reductive elimination**, provides a simple route for the release of neutral organic products from a complex. Our general reaction shows M(II) going to M(0), releasing X–Y. These two ligands were separate in the complex but are bound together in the product. A new X–Y σ bond has been formed.



The ligands to be eliminated must be *cis* to one another for reductive elimination to occur. This is because the process is concerted. Two examples from palladium chemistry make this point clear. Warming in DMSO causes ethane production from the first palladium complex because the two methyl groups are *cis* in the square planar complex. The more elaborate second bisphosphine forces the two methyl groups to be *trans* and reductive elimination does not occur under the same conditions.



Of course, no one wants to make ethane that way (if at all) but many other pairs of ligands can be coupled by reductive elimination. Reductive elimination is one of the most important methods for the removal of a transition metal from a reaction sequence, leaving a neutral organic product. We will see many examples as the chapter develops but here is an indole synthesis that depends on a reductive elimination at palladium as a last step. In the starting material, palladium has two  $\sigma$  bonds sharing electrons with C, and is Pd(II). In the reaction the two C substituents bond together to form the indole ring and a Pd(0) species is eliminated.



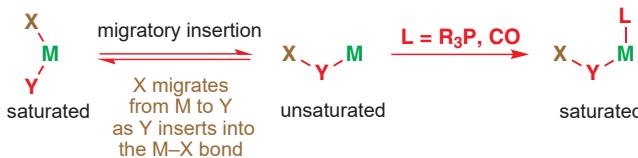
### L and L<sub>n</sub>

We know that the Pd product here must carry more than just the two ligands it is left with after the reductive elimination, but the scheme we have here doesn't tell us what they are. It's quite conventional in such cases—where we are more interested in the structure of the organic product than the remains of the complex—to indicate a general metal ligand '*L*', or '*L*<sub>n</sub>' for an undefined number of unknown ligands.

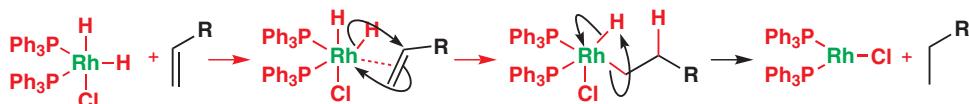
### Migratory insertion builds ligand structure

Two ligands can also react together to produce a new complex that still has the composite ligand attached to the metal, ready for further modification. This process involves migration of one of the ligands from the metal to the other ligand, and insertion of one of the ligands into the other metal–ligand bond. It is known as **migratory insertion**. The insertion process is reversible and, as the metal effectively loses a ligand in the process, the overall insertion may be driven by the addition of extra external ligands (*L*) to produce a coordinatively saturated complex. As with reductive elimination, a *cis* arrangement of the ligands is required and the migrating group (*X*) retains its stereochemistry (if it has any) during the migration.

→ Migration normally occurs with retention; see Chapter 36.

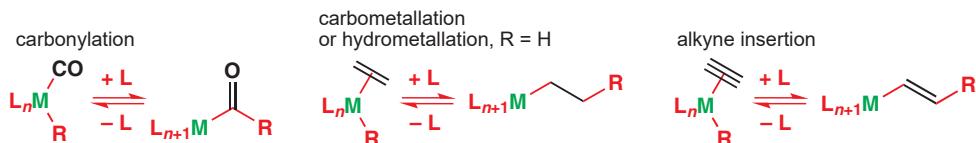


Wilkinson's catalyst is used in homogeneous hydrogenation of alkenes. The catalyst is soluble in many organic solvents such as EtOH, chloroform, or some hydrocarbons. The alkene complexes with the metal and migratory insertion forms an alkyl metal complex by hydrogen transfer. The next step, reductive elimination, usually follows rapidly to give the alkane and a complex that adds a hydrogen molecule to regenerate the catalyst.



► Polymerization is covered in an additional chapter you will find online.

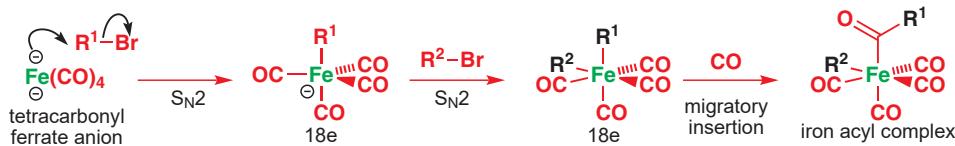
Migratory insertion is the principal way of building up the chain of an organic ligand before elimination. The group to be inserted must be unsaturated in order to accommodate the additional bonds and common examples include carbon monoxide, alkenes, and alkynes, producing metal–acyl, metal–alkyl, and metal–alkenyl complexes, respectively. In each case the insertion is driven by additional external ligands, which may be an increased pressure of carbon monoxide in the case of carbonylation or simply excess phosphine for alkene and alkyne insertions. In principle, the chain extension process can be repeated indefinitely to produce polymers by Ziegler–Natta polymerization.



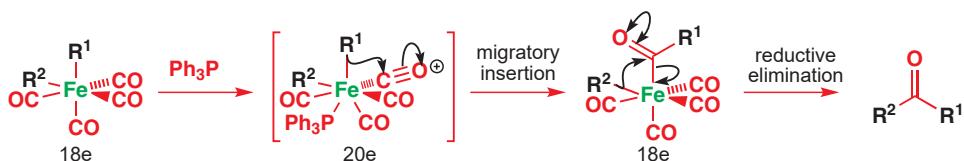
An example of the carbonylation process is the reaction of the tetracarbonyl ferrate dianion  $[\text{Fe}(\text{CO})_4]^{2-}$  with alkyl halides. This reagent is made by dissolving metal reduction of the 18-electron  $\text{Fe}(0)$  compound  $\text{Fe}(\text{CO})_5$ . Addition of two electrons would give an unstable 20-electron species but the loss of one of the ligands with its two electrons restores the stable 18-electron structure.



This iron anion is a good soft nucleophile for alkyl halides and can be used twice over to produce first a monoanion with one alkyl group and then a neutral complex with two alkyl groups and four CO ligands. Each of these complexes has 18 electrons. If extra CO is added by increasing the pressure, CO inserts into one Fe–C bond to form an iron acyl complex. Finally, reductive elimination couples the acyl group to the other alkyl group in a conceptually simple ketone synthesis. It does not matter which Fe–C bond accepts the CO molecule: the same unsymmetrical ketone is produced at the end.

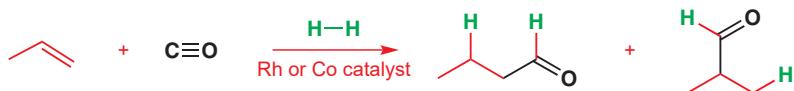


Any good two-electron ligand will cause the CO insertion:  $\text{Ph}_3\text{P}$  is often used instead of an increased CO pressure. The phosphine adds to the iron and pushes out the poorest ligand (one of the alkyl groups) on to a CO ligand in a process of **ligand migration**. We can represent this as the mechanism below, although the phosphine addition and alkyl migration may well be concerted to avoid the formation of a 20-electron complex as an intermediate.

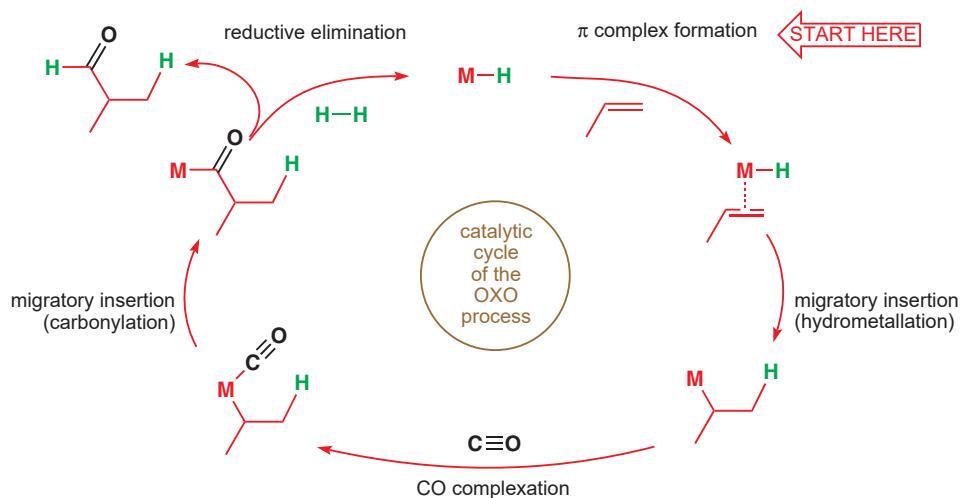


## Carbon monoxide incorporation extends the carbon chain

**Carbonylation** (the addition of carbon monoxide to organic molecules) is an important industrial process as carbon monoxide is a convenient one-carbon feedstock and the resulting metal–acyl complexes can be converted into aldehydes, acids, and their derivatives. The **OXO process** is the hydroformylation of alkenes such as propene and uses two migratory insertions to make higher value aldehydes. Although a mixture is formed, this is acceptable from very cheap and abundant starting materials. Here the metal complex is a catalyst, not a stoichiometric reagent.

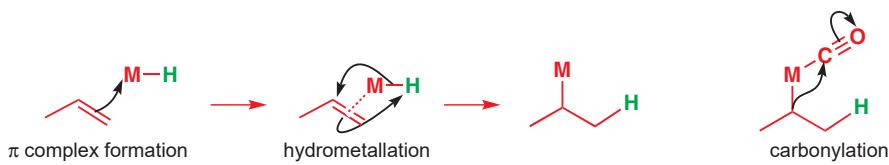


A catalytic cycle (going clockwise from the top) shows the various stages of alkene coordination, hydrometallation (migratory insertion) to produce an alkyl metal species, coordination of carbon monoxide followed by another migratory insertion, and finally reductive cleavage with hydrogen to produce the metal–hydride intermediate, which is then ready for another cycle. The steps leading to the other regioisomeric aldehyde and the ligands on the metal are omitted for clarity.



Interactive mechanism for the Oxo process

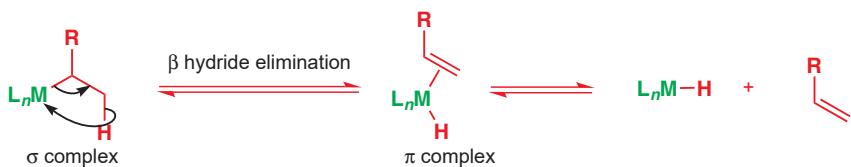
The mechanisms of the two key migratory insertion steps are worth discussion. **Hydrometallation** occurs by initial  $\pi$  complex formation followed by addition of the metal to one end of the alkene and hydrogen to the other. Both of the possible regiosomers are formed. The **carbonyl insertion reaction** is another migration from the metal to the carbon atom of a CO ligand.



## Insertion reactions are reversible

The reverse process, **decarbonylation**, is also fast but can be arrested by maintaining a pressure of carbon monoxide above the reaction mixture. The reverse of hydrometallation involves the elimination of a hydride from the adjacent carbon of a metal alkyl to form an alkene complex.

This process is known as  **$\beta$  hydride elimination** or simply  **$\beta$  elimination**. It requires a vacant site on the metal as the number of ligands increases in the process and so is favoured by the shortage of ligands in 16-electron complexes. In more complex structures, the metal and the hydride must be *syn* to each other on the carbon chain for the elimination to be possible. The product is an alkene complex that can lose the neutral alkene simply by ligand exchange.  $\beta$  elimination is an important final step in a number of transition-metal catalysed processes, but it can be a nuisance because Pd-Et (and other similar Pd-alkyl) complexes cannot be used as  $\beta$  elimination is too fast.



## Palladium is the most widely used metal in homogeneous catalysis

These elementary steps form the basis for most of organo-transition metal chemistry, and are the same regardless of the metal and the detailed structure of the ligands. Transition metal catalysis is an enormous and rapidly expanding field that we just do not have the space to discuss in comprehensive detail. Instead, we will concentrate on the chemistry of one important, and representative, transition metal: palladium. Pd-catalysed reactions are widely used in both industrial and academic laboratories, on both a minute and very large scale. The variety of reactions that can be catalysed by Pd together with the range of functional groups tolerated, and usually excellent chemo- and regioselectivity, means that most syntheses of organic molecules of any complexity will now involve palladium chemistry in one or more key steps.

### Choice of palladium complex

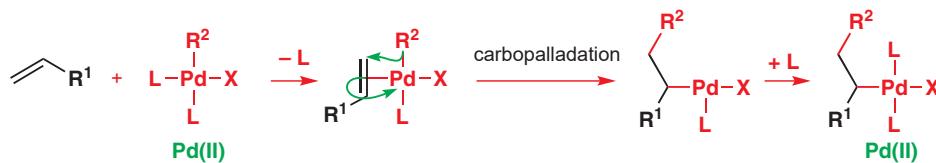
There are many available complexes of palladium(0) and palladium(II). Tetrakis(triphenylphosphine)palladium(0),  $\text{Pd}(\text{PPh}_3)_4$ , and tris(dibenzylidene-acetone)dipalladium(0),  $\text{Pd}_2(\text{dba})_3$ , or the chloroform complex,  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ , which is air-stable, are the most common sources of palladium(0). The detailed structures of some palladium complexes, particularly the dimers, are beyond the scope of this book but we will discuss the reactions in detail. Palladium(II) complexes are generally more stable than their palladium(0) counterparts. The dichloride  $\text{PdCl}_2$  exists as a polymer and is relatively insoluble in most organic solvents. However,  $(\text{PhCN})_2\text{PdCl}_2$  and  $(\text{MeCN})_2\text{PdCl}_2$  (both easily prepared from  $\text{PdCl}_2$ ) are soluble forms of  $\text{PdCl}_2$ , as the nitrile ligands are readily displaced in solution. Bis(phosphine)palladium(II) chloride complexes are also air-stable and readily prepared from  $\text{PdCl}_2$ . Palladium is, of course, an expensive metal—these complexes cost about £50–100 per gram—but very little is needed for a catalytic reaction.



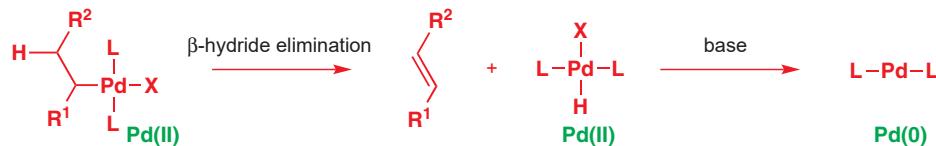
Let's start with a review of the basic chemistry of palladium, as you will be seeing many more examples of these steps in specialized situations. Palladium chemistry is dominated by two oxidation states. The lower, palladium(0), present in tetrakis(triphenylphosphine)palladium, for example, is nominally electron-rich, and will undergo oxidative addition with suitable substrates such as organic halides, resulting in a palladium(II) complex. Oxidative addition is thought to occur on the coordinatively unsaturated 14-electron species, formed by ligand dissociation in solution.



The resulting Pd–R σ bond in such complexes is very reactive, especially towards carbon–carbon π bonds. Thus an alkene in the reacting system will lead to coordination followed by migratory insertion into the palladium–carbon σ bond. Like hydrometallation this process is a migratory insertion and is called **carbopalladation** because carbon and palladium become attached to the ends of the alkene system. There is no change in oxidation state during this process, although the ligands (often phosphines) must dissociate to allow coordination of the alkene and associate to provide a stable final 16-electron product.



With some metals the process of olefin coordination and insertion may continue, leading to polymerization, but with palladium the metal is expelled from the molecule by a β-hydride elimination reaction and the product is an alkene, plus a Pd(II) complex. For the whole process to be catalytic, this Pd(II) product of β-hydride elimination must be converted to a Pd(0). This occurs in the presence of base, which removes HX from the palladium(II) species. This is another example of reductive elimination: one that forms a hydrogen halide rather than a carbon–carbon or carbon–hydrogen bond, as you saw earlier.



The speed of the β-hydride elimination (which is intramolecular and very fast) means that the original substrate for the oxidative addition reaction must be chosen with care—the presence of hydrogen at an  $\text{sp}^3$  carbon in the β position must be avoided. Thus, substrates for oxidative addition reactions in palladium chemistry are frequently vinylic, allylic, or aromatic and never ethyl or *n*-propyl.

## The Heck reaction couples together an organic halide or triflate and an alkene

All the individual steps outlined above combine to make up the catalytic pathway in the **Heck reaction** with which we started the chapter. The Heck reaction couples an alkene with an organic halide or triflate  $\text{R}^1-\text{X}$  to form a new alkene. The  $\text{R}^1$  group in  $\text{R}^1-\text{X}$  can be aryl, vinyl, or any alkyl group without β hydrogens on an  $\text{sp}^3$  carbon atom. The group X can be a halogen (Br or I) or triflate ( $\text{OSO}_2\text{CF}_3$ ). The alkene can be mono- or disubstituted and can be electron-rich, -poor, or -neutral. The base need not be at all strong and can be  $\text{Et}_3\text{N}$ ,  $\text{NaOAc}$ , or aqueous  $\text{Na}_2\text{CO}_3$ . The reaction is very accommodating!

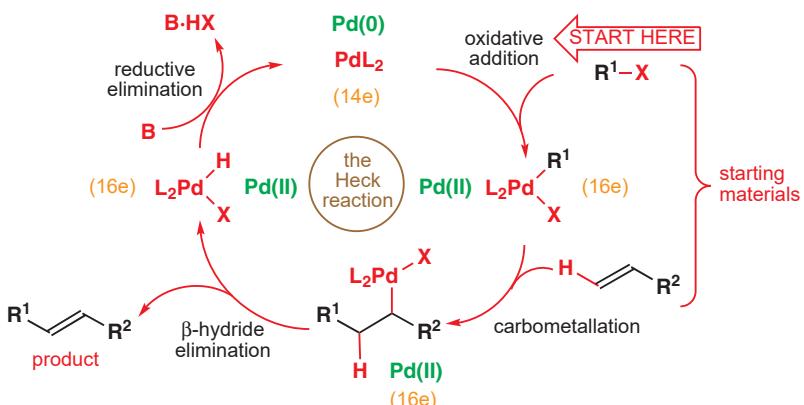
### Triflates

The triflate (trifluoromethanesulfonate) anion,  $\text{CF}_3\text{SO}_3^-$ , or  $\text{TfO}^-$ , is an excellent, non-basic leaving group. It is often used as an oxygen-based alternative to halides, and metals will insert into the  $\text{C}-\text{OSO}_2\text{CF}_3$  bond. Triflates, particularly aryl and vinyl triflates, can be made conveniently with Comins' reagent.

Comins' reagent

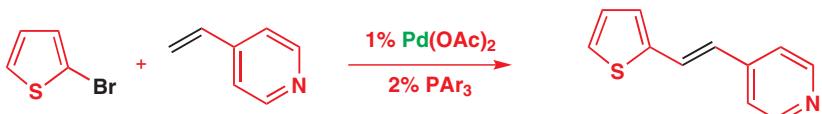


 Interactive mechanism for the Heck catalytic cycle



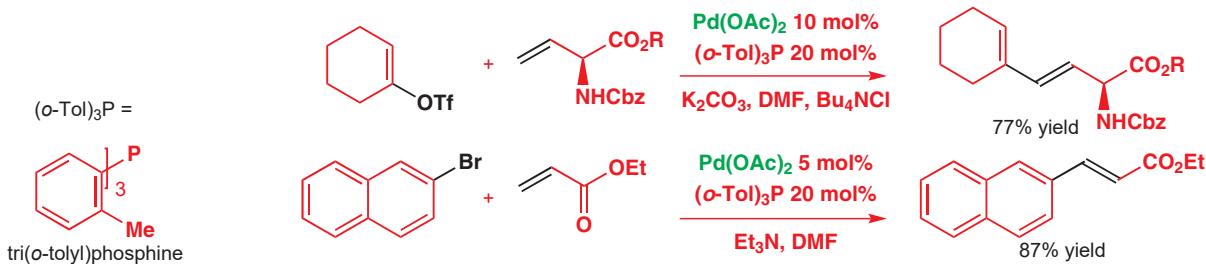
This palladium-catalysed addition of aryl, vinyl, or substituted vinyl groups to organic halides or triflates is one of the most synthetically useful palladium-catalysed reactions. The method is very efficient, and carries out a transformation that is difficult by more traditional techniques. The mechanism involves the oxidative addition of the halide, insertion of the olefin, and elimination of the product by a  $\beta$ -hydride elimination process. A base then regenerates the palladium(0) catalyst. The whole process is a catalytic cycle.

Here is the Heck reaction at work coupling two heterocyclic substrates. Easy chemistry to do, but impossible without a Pd catalyst.



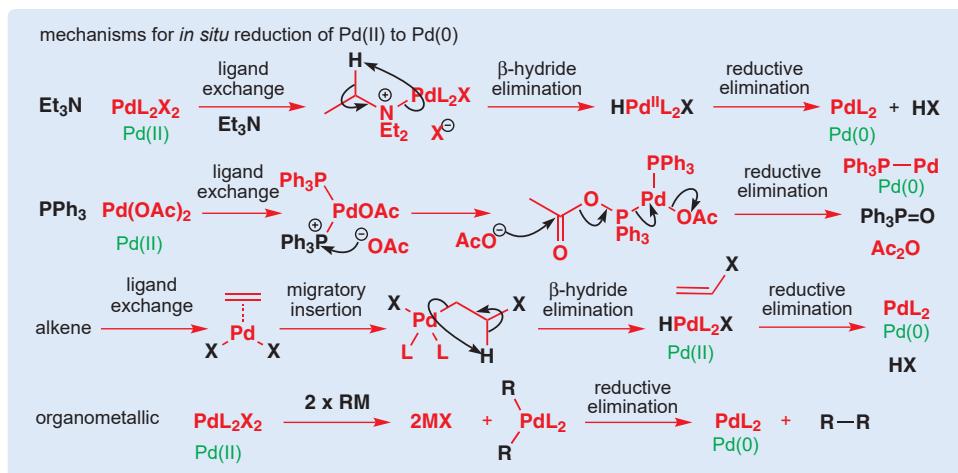
Notice the regioselectivity: unlike the carbonylation on p. 1077, the Heck reaction favours one isomer, and when the alkene is polarized by an electron-withdrawing group the new C–C bond forms at the other end of the alkene. Notice also in this example and those below that the Pd is added as Pd(II), not Pd(0): the box below explains how this works.

The mild conditions of the Heck reaction mean that protected amino acids can be made without any racemization. The two examples below use a more hindered analogue of triphenylphosphine, but the mechanism is the same.

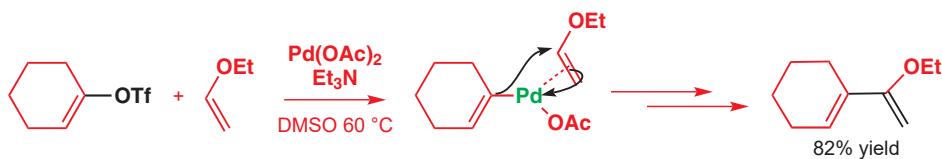


#### In situ formation of Pd(0) by reduction of Pd(II)

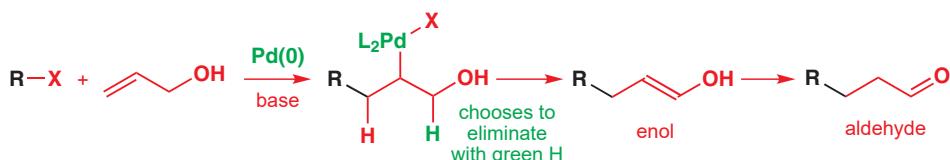
In reactions requiring palladium(0), formation of the active complex may be achieved more conveniently by reduction of a palladium(II) complex, for example  $\text{Pd(OAc)}_2$ . Any phosphine may then be used in the reaction, without the need to synthesize and isolate the corresponding palladium(0)–phosphine complex. The reduction of palladium(II) to palladium(0) can be achieved with amines, phosphines, alkenes, and organometallics such as DIBAL-H, butyllithium, or trialkylaluminium. The mechanisms are worth surveying as they illustrate the basic steps of organometallic chemistry.



In contrast, electron-donating groups such as ethers lead to attack at the end of the alkene substituted by oxygen to produce the 1,1-disubstituted product. These reactions must be dominated by the interaction of the filled  $\pi$  orbital of the alkene with an empty d orbital on Pd. In the example below, the Heck reaction works even in the absence of a phosphine ligand.

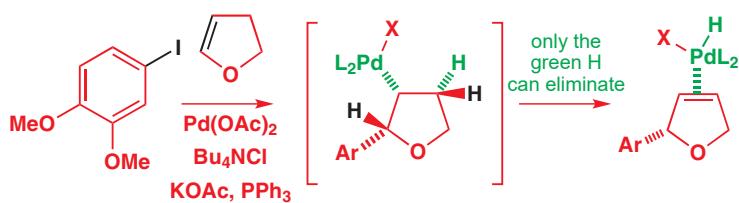


Because  $\beta$ -hydride elimination is reversible, when there is a choice the more stable of the possible alkenes usually results. The reaction of allylic alcohols is particularly important as the more stable of the two alkenes is the enol and a carbonyl compound is formed.

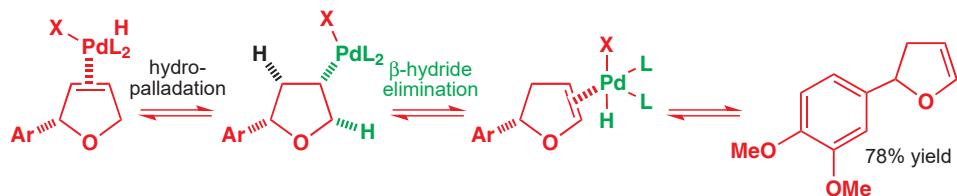


### Hydropalladation–dehydropalladation can lead to alkene isomerization

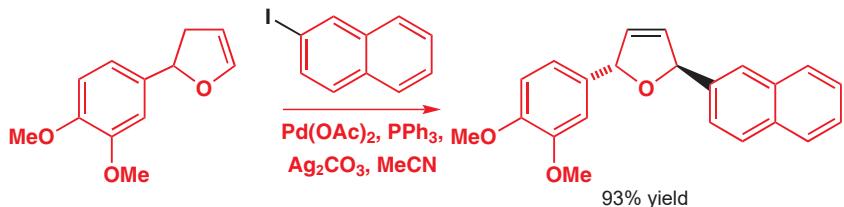
Reversible  $\beta$ -hydride eliminations provide a mechanism for interconverting regioisomers of an alkene, and the following reaction sequence also illustrates another point about the reductive elimination step: it is a *syn* elimination, and the C–Pd and C–H bonds have to eclipse one another for the Pd–H bond to form. Oxidative addition of the aryl iodide to a palladium(0) complex, formed from  $\text{Pd}(\text{OAc})_2$  by reduction, gives the active palladium(II) complex  $\text{ArPdOAc}_2$ . Carbopalladation occurs as expected on an electron-rich alkene to give the product of aryl addition to the oxygen end of the alkene in a *syn* fashion.  $\beta$ -Hydride elimination must occur away from the aryl group because there is only one C–H bond *syn* to the C–Pd bond. The alkene has moved one position round the ring.



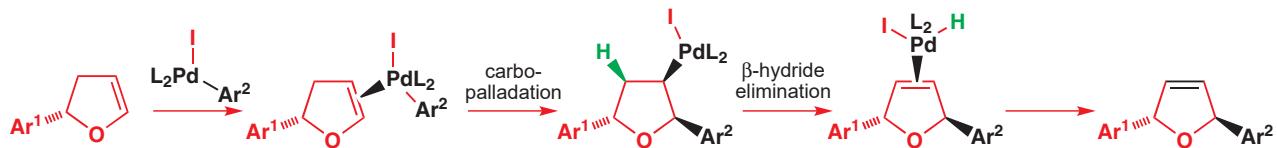
Hydropalladation in the reverse sense gives a new  $\sigma$  complex, which could eliminate either the black or the green hydrogens. Elimination of the green H gives the enol ether, which is the most stable alkene possible due to conjugation.



This product now undergoes a second Heck reaction involving naphthyl iodide:

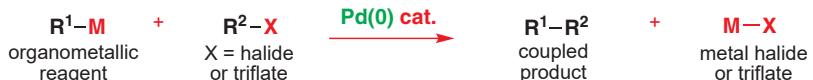


The initial mechanism is much the same. However, the enol ether has two diastereotopic faces: *syn* or *anti* to the aromatic substituent ( $\text{Ar}^1$ ) introduced in the first step. Palladium is very sensitive to steric effects and generally forms less hindered complexes where possible, so the palladium(II) complexes the face of the enol ether *anti* to  $\text{Ar}^1$ . This in turn controls all the subsequent steps, which must be *syn*, leading to a final product with *anti* stereochemistry. The requirement for *syn*  $\beta$ -hydride elimination also explains the regiochemical preference of the elimination. In the  $\sigma$ -bonded cyclic structure there is only one hydrogen (green) that is *syn* to the palladium; the one on the carbon bearing the naphthyl substituent is *anti* and cannot be eliminated. Further migrations of the alkene by hydropalladation are prevented by the silver carbonate, which rapidly removes iodide from the intermediate, preventing read-dition of Pd–H to the alkene.

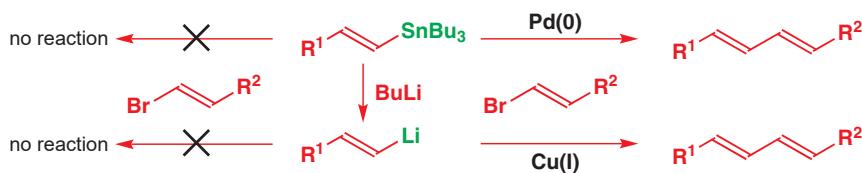


## Cross-coupling of organometallics and halides

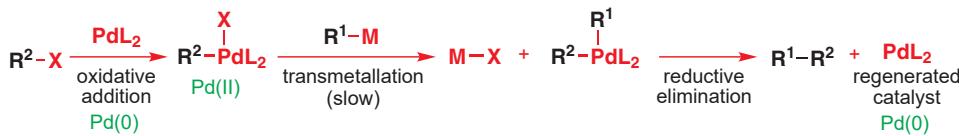
Other than  $\beta$ -hydride elimination, another important pathway by which palladium(II) intermediates can lead to neutral organic fragments is reductive elimination. This forms the basis of the mechanism for **cross-coupling reactions** between an organometallic reagent and an organic halide or triflate.



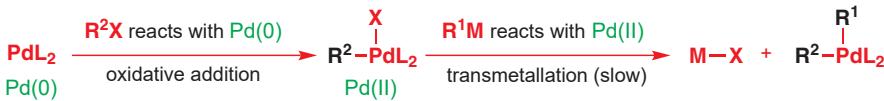
This is a reaction that seems very attractive for synthesis but, in the absence of a transition metal catalyst, the yields are very low. We showed in Chapter 27 how vinyl silanes can be made with control over stereochemistry and converted into lithium derivatives with retention. Neither of these vinyl metals couple with vinyl halides alone. But in the presence of a transition metal—Cu(I) for Li and Pd(0) for Sn—coupling occurs stereospecifically and in good yield.



The mechanism of palladium-catalysed cross-coupling starts, as in the Heck reaction, with oxidative addition of the halide or triflate to the initial palladium(0) phosphine complex to form a palladium(II) species. But the next step is new: it is a **transmetallation**, so-called because the nucleophile ( $R^1$ ) is transferred from the metal in the organometallic reagent to the palladium and the counterion ( $X=\text{halide or triflate}$ ) moves in the opposite direction. The new palladium(II) complex with two organic ligands undergoes reductive elimination to give the coupled product and the palladium(0) catalyst, ready for another cycle.



The reaction is important because it allows the coupling of two different components ( $R^1$  and  $R^2$ ), distinguished by being bonded either to the metal  $M$  or to the halide or triflate  $X$ . Both components form  $\sigma$  complexes with Pd but the halide partner ( $R^2X$ ) bonds first by oxidative addition and this  $R^2$ -Pd bond must survive while the metal partner ( $R^1M$ ) transfers  $R^1$  to Pd by transmetallation. Once the two components are joined to the palladium atom, only the cross-coupled product can be formed.  $R^2X$  combines with  $Pd(0)$  and  $R^1M$  with  $Pd(II)$ . There can then be no confusion. In contrast to the Heck reaction, here the metal defines the location of the new C–Pd bond.



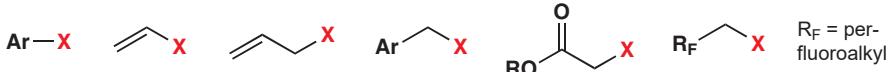
The halide partner ( $R^2X$ ) must be chosen with care, as  $\beta$ -hydride elimination would decompose the first intermediate during the slow transmetallation step. The choice for  $R^2$  is restricted to substituents without  $\beta$ -hydrogen atoms on  $sp^3$  carbon atoms: vinyl, allyl, benzyl, and polyfluoroalkyl halides, triflates, and phosphates have all been coupled successfully. The organometallic reagent ( $R^1M$ ) can be based on magnesium, zinc, copper, tin, silicon, zirconium, aluminium, or boron and the organic fragment can have a wide variety of structures as coupling is faster than  $\beta$ -hydride elimination.

$R^1-M$   $R^1$  = almost anything including examples with  $\beta$  H

$M = MgX, ZnX, Cu, SnR_3, SiR_3, ZrCp_2Cl, AlMe_2, B(OR)_2, BF_4^-$

Cp = cyclopentadienyl

$R^2-X$   $R^2$  must not have  $\beta$  Hs that can eliminate  $X = I, Br, (Cl), OTf, OPO(OR)_2$

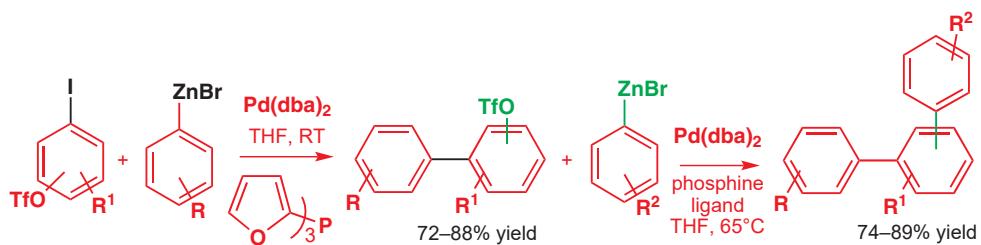


■ There is a problem in naming the two partners. The halide partner ( $R^2X$ ) is sometimes called the electrophile and the organometallic partner ( $R^1M$ ) the nucleophile. These names describe the nature of the reagents rather than the mechanism of the reaction and we will not use them.

### Named coupling reactions

Palladium-catalysed reactions involving organometallic partners based on B, Mg, Sn, and Zn are particularly important and are often referred to by the names of their discoverers: Suzuki coupling for B, Kumada coupling for Mg, Stille coupling for Sn, and Negishi coupling for Zn.

The difference in relative reactivity of aromatic iodides and triflates was exploited in this sequential synthesis of substituted terphenyls by repeated coupling with organozinc reagents. The more reactive iodide coupled at room temperature with palladium(0) and trifurylphosphine but warming to 65 °C was required for the triflate to participate in the second coupling.



### ■ Organometallic Nobels

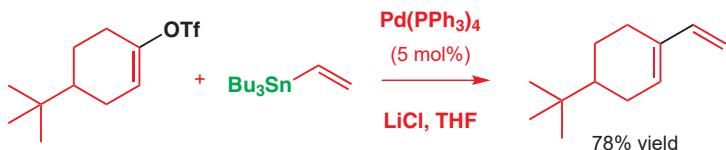
Organometallic chemistry has been a popular subject for the Nobel prize committee. In 1912 Grignard (Mg) won the award, in 1973 Wilkinson and Fischer for 'sandwich' compounds (such as ferrocene), in 2005 Chauvin, Grubbs, and Schrock for alkene metathesis, and in 2010 Heck, Negishi, and Suzuki (Stille had died in 1989) for transition-metal catalysed couplings.

In the reactions of triflates, a source of halide (typically LiCl) is generally required since triflate is a counterion and may not bind to the metal as a ligand: chloride can take its place.

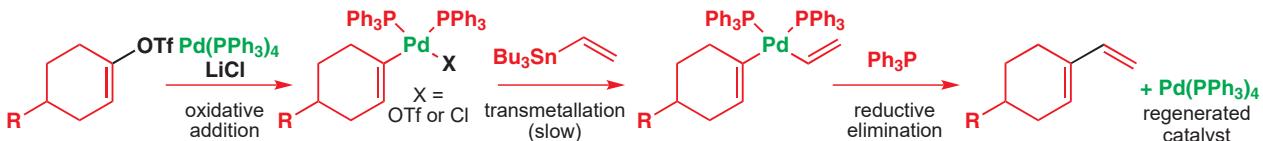
In spite of the wide range of organometallic reagents that can be used there are two classes that have proved particularly popular because they are stable intermediates in their own right and can be prepared and purified separately before the coupling reaction. These cross-couplings are known by the names of the two chemists whose work made the reactions so valuable. The Stille coupling employs a stannane as the organometallic component ( $R^1M$ ) while the Suzuki coupling relies on a boronic acid.

### The Stille coupling uses stannanes as the organometallic component

Since its discovery in the late 1970s, the Stille coupling has been widely used for the coupling of both aromatic and vinylic systems.

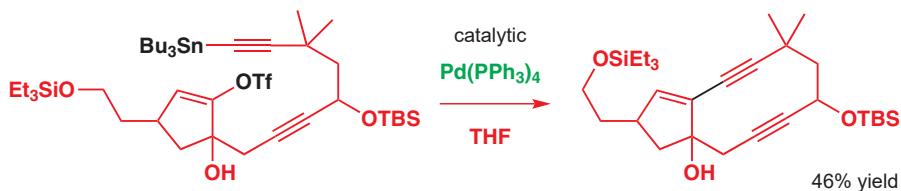


The mechanism involves the oxidative addition of the vinyl or aromatic triflate or halide to give an organopalladium intermediate. Transmetalation with the organostannane forms another organopalladium intermediate with two Pd–C  $\sigma$  bonds. A reductive elimination step releases the product and thereby regenerates the palladium(0) catalyst. Vinyl triflates can be made from enolizable aldehydes or ketones and aryl triflates from phenols, but the reaction also works with vinyl and aryl halides.

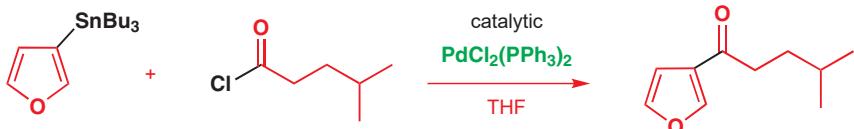


Interactive mechanism for the Stille coupling catalytic cycle

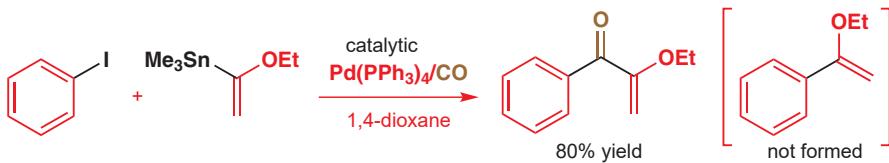
The Stille reaction is widely used to make bonds between  $sp^2$  carbon atoms, but it also works with  $sp$  carbons: the example below is a challenging formation of a 10-membered ring containing two alkynes.



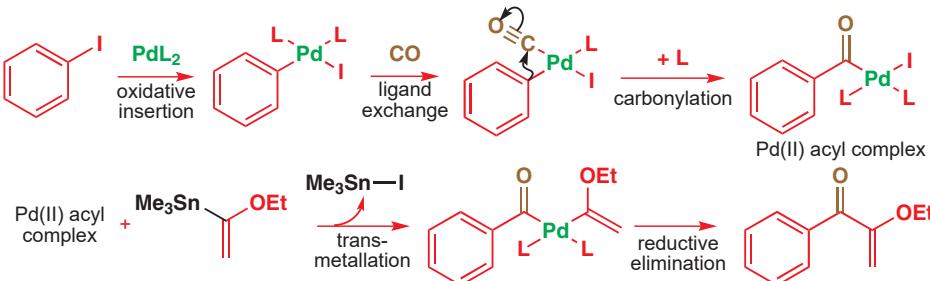
The Stille coupling may be combined with carbonylation in two ways. Acid chlorides may be used as substrates for the reaction with vinyl or aryl stannanes, although an atmosphere of carbon monoxide is frequently required to prevent decarbonylation after the oxidative addition step.



Simply performing a normal Stille reaction in the presence of carbon monoxide may also lead to carbonylated products. These reactions can take place in a CO saturated solution, under one atmosphere of pressure. Using these conditions, excellent yields of the carbonylated product can be obtained, without any of the normal coupling product being present.



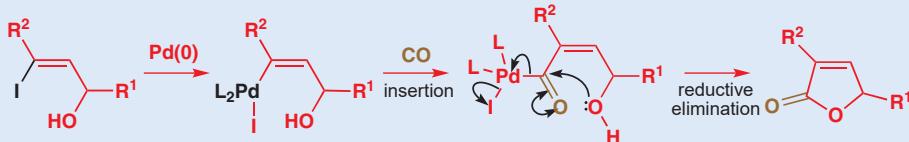
The mechanism follows that of a normal Stille coupling except that the carbon monoxide first exchanges for one of the phosphine ligands and then very rapidly inserts to produce an acyl palladium(II) complex. Transmetalation with the vinyl stannane in the usual way forms trimethylstannyl iodide and the key palladium complex carrying two carbon ligands. Transmetalation is always the slow step in these coupling reactions, allowing time for the carbon monoxide insertion. The final step—reductive elimination—releases the Pd(0) catalyst for the next cycle.



Interactive mechanism for the carbonylative Stille coupling catalytic cycle

### Acylic palladium species react like activated acid derivatives

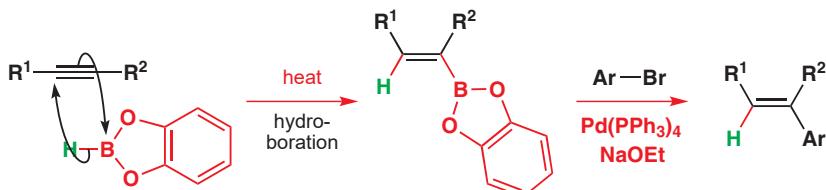
Carbonylation of a halide or triflate provides a direct route to a range of chain-extended acyl derivatives. A carbonyl group substituted with PdX (X = halide or triflate) is a reactive acylating agent, rather like an acid anhydride, as PdX is a good leaving group. Reaction with alcohols and amines gives esters and amides, while reduction with tributyltin hydride gives the aldehyde. Intramolecular attack by alcohols leads to lactones, as demonstrated in the conversion of a vinyl iodide into a 2H-furanone (butenolide). We will see more of these reactions later.



Interactive mechanism for palladium-catalysed carbonylative butenolide formation

### The Suzuki coupling couples boronic acids to halides

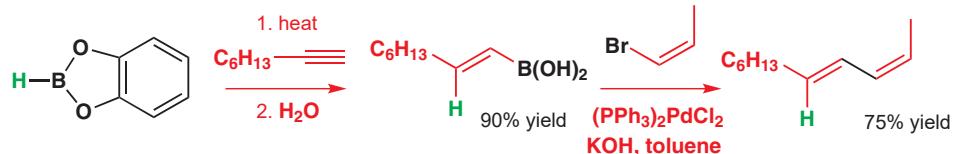
The Suzuki coupling of a boronic acid or ester with a vinyl or aryl halide or triflate is probably the most commonly used of all cross-coupling reactions. The original version, first reported in 1979, involved hydroboration of an alkyne with catecholborane, followed by palladium(0)-catalysed coupling of the resulting vinyl boronate with an aromatic iodide or bromide. The hydroboration is generally regioselective for the less hindered position and addition of boron and hydrogen occurs *cis* stereospecifically.



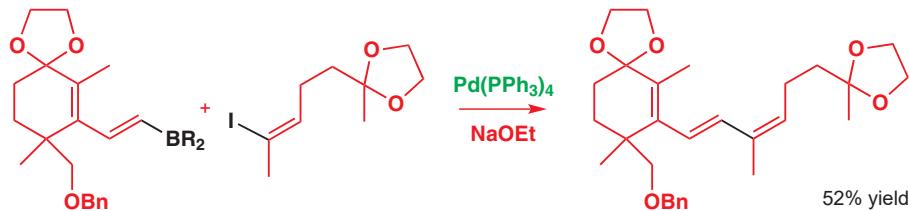
Hydroboration is covered in Chapter 19, p. 446.

Some methods for the synthesis of alkenes with control of double bond geometry were covered in Chapter 27.

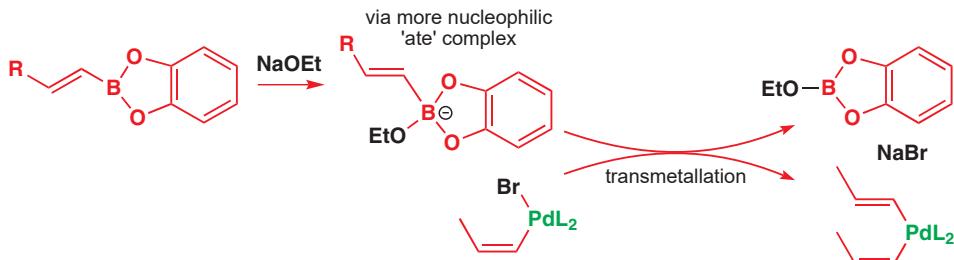
As in the Stille coupling, the geometry of both unsaturated components is preserved during the coupling so this is an excellent method for the stereoselective synthesis of dienes. Hydroboration of octyne followed by hydrolysis of the boronate gave exclusively the *E*-vinyl boronic acid. Coupling with the *Z*-vinyl bromide in toluene with palladium(0) catalysis with potassium hydroxide as the base gave the *E,Z*-diene in good yield. These dienes are very useful in the Diels–Alder reaction (Chapter 34).



This sort of reaction has been used in the synthesis of the unsaturated units of a range of natural products, including trisporol B. The key step is the stereocontrolled synthesis of an *E,Z*-diene. The geometry of both double bonds comes stereospecifically with retention of configuration from single geometrical isomers of the starting materials.

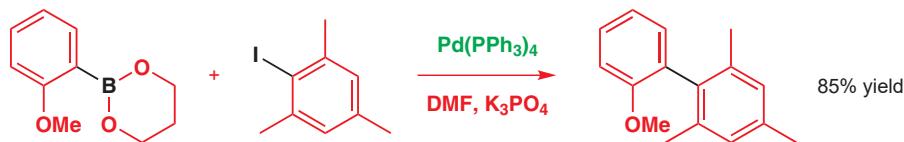


The mechanism of the Suzuki coupling is very similar to that of the Stille coupling. Oxidative addition of the vinylic or aromatic halide to the palladium(0) complex generates a palladium(II) intermediate. This then undergoes a transmetalation with the alkanyl boronate, from which the product is expelled by reductive elimination, regenerating the palladium(0) catalyst. The important difference is the transmetalation step, which explains the need for an additional base, usually sodium or potassium ethoxide or hydroxide, in the Suzuki coupling. The base accelerates the transmetalation step, leading to the borate directly, presumably via a more nucleophilic ‘ate’ complex.



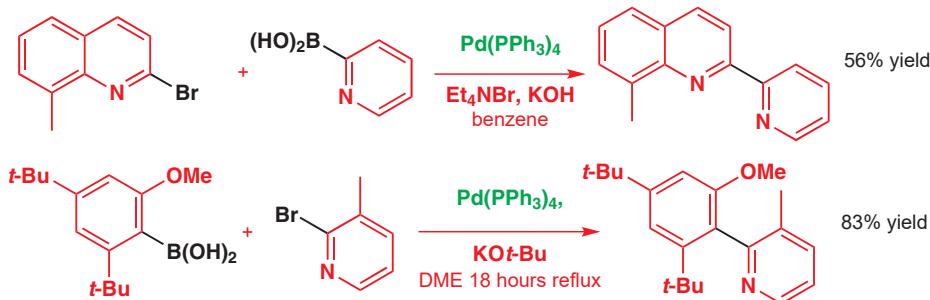
Interactive mechanism for the Suzuki coupling catalytic cycle

Sterically demanding substrates are tolerated well and Suzuki coupling is often used for aryl–aryl cross-couplings. This example has three *ortho* substituents around the newly formed bond (marked in black) and still goes in excellent yield.



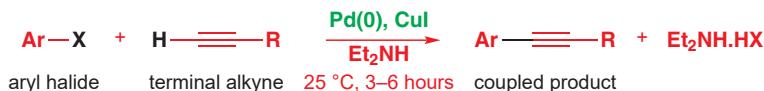
Aromatic heterocycles also couple well. The 2-position of a pyridine is very electrophilic and not at all nucleophilic (Chapter 29) but couplings at this position are fine with either the

halide or the boronic acid in that position. Clearly, it is a mistake to see either of these substituents as contributing a ‘nucleophilic carbon’. It is better to see the reaction as a coupling of two equal partners with the two substituents (the halide and the boronic acid) as control elements to ensure cross-coupling and prevent dimerization.

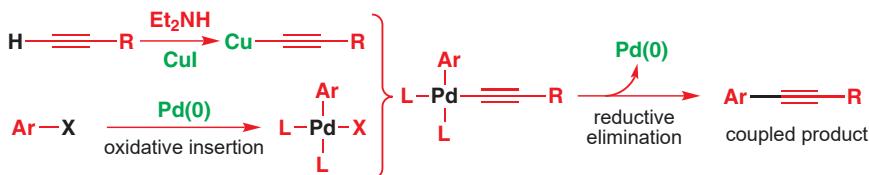


### Coupling to alkynes: the Sonogashira reaction

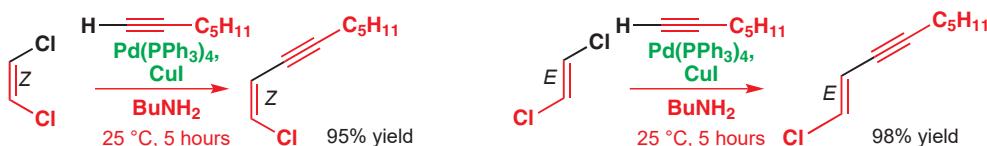
The coupling of terminal alkynes with aryl or vinyl halides under palladium catalysis is known as the **Sonogashira reaction** and is rather like the Heck reaction. It is a catalytic process, requiring a palladium(0) complex; it is performed in the presence of base, and generally uses copper iodide as a co-catalyst. One partner—the aryl or vinyl halide—is the same as in the Stille and Suzuki couplings but the alkyne needs no metal to activate it: the reaction works with the alkyne itself.



The mild conditions usually employed, frequently room temperature, mean that the reaction can be used with thermally sensitive substrates. By now, you should not be surprised by the mechanism! Oxidative addition of the organic halide gives a palladium(II) intermediate that undergoes transmetalation with the alkynyl copper (generated from the terminal alkyne, base, and copper iodide). Reductive elimination with coupling of the two organic ligands gives the product and regenerates the palladium(0) catalyst.

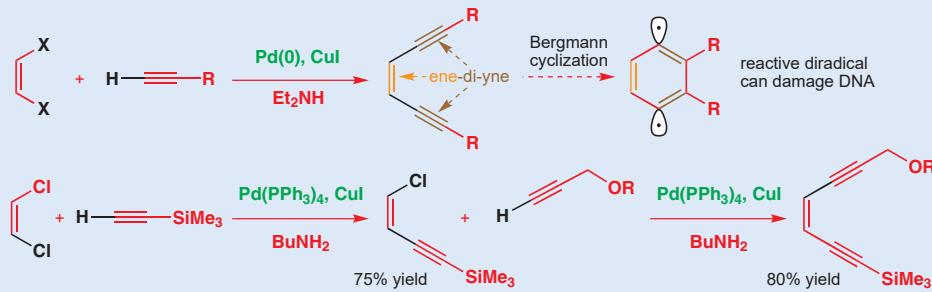


It is usually more convenient, as in the Heck reaction, to use a stable and soluble  $\text{Pd}(\text{II})$  derivative such as bis(triphenylphosphine)palladium(II) chloride instead of  $\text{Pd}(0)$ . This is rapidly reduced *in situ* to give a coordinatively unsaturated, catalytically active, palladium(0) species. The geometry of the alkyne is generally preserved so that *cis* (*Z*) and *trans* (*E*) dichloroethylene give the two different geometrical isomers of the enyne below in >99% stereochemical purity as well as excellent yield.



### Ene-diyne and the Bergmann cyclization

The Sonogashira reaction provides an important way to make the ene-diyne antibiotics. Symmetrical ene-diynes may be synthesized in one step from two molecules of a terminal alkyne and Z-dihaloethylene. The ene-diyne part of the molecule does the remarkable Bergmann cyclization to give a benzene diradical: the ene-diyne is able to penetrate DNA and the diradical is able to react with it, giving the compounds anticancer activity. To make the most biologically active compounds, however, the reaction is performed sequentially, allowing different functionality on each of the alkyne units.



### ● Palladium-catalysed coupling reactions: a summary

Coupling an aryl or vinyl halide with...	Typical example (X=I, Br, OTf)	See page	Name of reaction
an alkene	$\text{R}-\text{CH}=\text{CH}_2 + \text{Ar-X} \xrightarrow[\text{Pd cat. + ligands}]{} \begin{array}{l} \text{R}-\text{CH}=\text{CH-Ar} \\ \text{or} \\ \text{R}-\text{C}(=\text{CH}_2)-\text{Ar} \end{array}$	1079	Heck
an aryl or vinyl stannane	$\text{R}^1-\text{CH}=\text{CH-SnBu}_3 + \text{X}-\text{R}^2 \xrightarrow[\text{Pd cat. + ligands}]{} \text{R}^1-\text{CH}=\text{CH-CH=CH-R}^2$	1084	Stille
an aryl or vinylboronic acid or ester	$\text{R}^1-\text{C}_6\text{H}_4-\text{B}(\text{OR})_2 + \text{X}-\text{R}^2 \xrightarrow[\text{Pd cat. + ligands}]{} \text{R}^1-\text{C}_6\text{H}_4-\text{CH}_2-\text{R}^2$	1085	Suzuki
an alkyne	$\text{R}-\text{C}\equiv\text{H} + \text{Ar-X} \xrightarrow[\text{Pd cat. + ligands}]{} \text{R}-\text{C}\equiv\text{CH-Ar}$	1087	Sonogashira
an amine	$\text{R}^1-\text{NH}-\text{R}^2 + \text{X}-\text{C}_6\text{H}_4-\text{CH}_2-\text{R}^3 \xrightarrow[\text{Pd cat. + ligands}]{} \text{R}^1-\text{N}(\text{R}^2)-\text{C}_6\text{H}_4-\text{CH}_2-\text{R}^3$	1092 (later in Buchwald- this chapter)	Hartwig

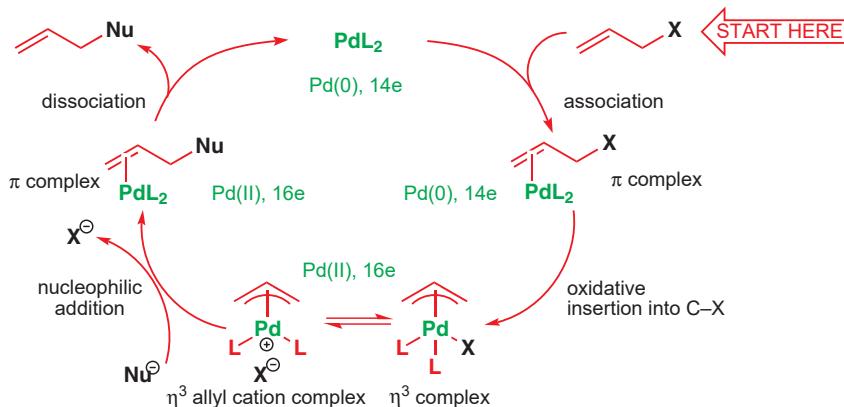
### Allylic electrophiles are activated by palladium(0)

Allylic compounds with good leaving groups, such as bromide and iodide, are excellent allylating agents but they suffer from loss of regiochemistry due to competition between the direct S<sub>N</sub>2 and S<sub>N</sub>2' reactions. This problem was described in Chapter 24. In contrast,  $\pi$ -allyl

cation complexes of palladium allow both the stereochemistry and regiochemistry of nucleophilic displacement reactions to be controlled.



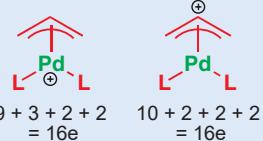
In addition, leaving groups ( $X$ ) that are usually regarded as rather unreactive still work, which makes the purification and handling of the starting materials easier. Acetate ( $X=OAc$ ) is the most commonly used leaving group, but a range of other functional groups ( $X=OCO_2R$ ,  $OPO_2(R)_2$ ,  $Cl$ ,  $Br$ ,  $OPh$ ) will perform a similar role. The full catalytic cycle is shown below, with the intermediate  $\pi$ -allyl complex in equilibrium between the neutral version, which has the leaving group coordinated to palladium, and the cationic  $\pi$ -allyl complex.



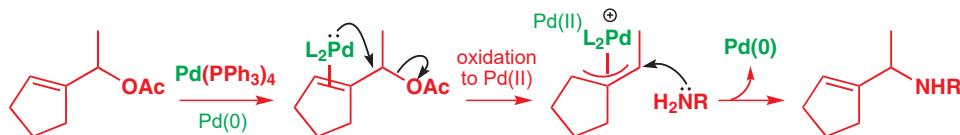
### The Pd $\pi$ -allyl cation complex

You can represent the palladium  $\pi$ -allyl cation complex in two ways. Either you draw a neutral allyl group complexed to  $Pd^+$  or you draw an allyl cation complexed to neutral  $Pd$ . Although the counting is different ( $Pd^+$  has only nine electrons: the neutral allyl has three, but the allyl cation only two), both come out as  $\eta^3$  16-electron species, which is just as well as they are merely different ways of drawing the same thing.

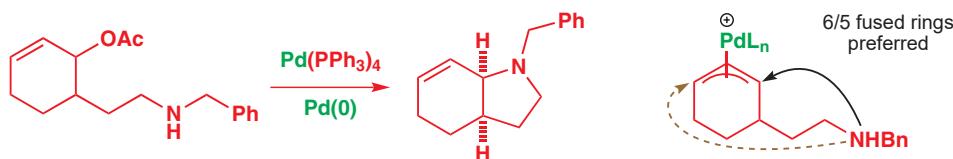
Pd  $\pi$ -allyl cation complex



Soft nucleophiles generally give the best results: stabilized enolates such as malonates, or cyanide, are best for carbon–carbon bond formation, but for C–X ( $X=O$ ,  $N$ ,  $S$ ) bond formation the reaction is successful with alkoxides, amines, and thiolates ( $RS^-$ ). In the example below an amine nucleophile attacks the allyl system to generate the more stable product with the double bond within the ring.



The intramolecular reaction works well to give heterocyclic rings—the regioselectivity is usually determined by the length of the chain and how far it can reach. Here a 6/5 fused product is preferred to a bridged product containing two seven-membered rings.

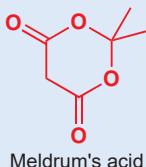


The reaction usually proceeds with *retention* of configuration at the reacting centre. As in  $S_N2$  substitution reactions going with retention (Chapter 36), this actually suggests a double inversion. Coordination of Pd to the double bond of the allylic acetate occurs on the less hindered face opposite the leaving group and we can think of the oxidative addition step as an invertive nucleophilic displacement of the leaving group by a pair of Pd electrons. The nucleophile then adds to the face of the  $\pi$ -allyl Pd cation complex opposite the Pd. The net result is displacement of the leaving group by the nucleophile with retention. Thereafter, the

Interactive mechanism for the  $\pi$ -allyl palladium-mediated coupling catalytic cycle

The arrows on the middle two diagrams are the best we can do to show how Pd(0) uses its electrons to get rid of the leaving group to become Pd(II), and how it accepts them back again when the nucleophile adds. They are not perfect: it is often difficult to draw precise arrows for organometallic mechanisms, but it is worth thinking about what is happening to the electrons in these steps, and curly arrows help us to do this.

**Meldrum's acid** has a very stable delocalized enolate: it is as acidic as a carboxylic acid ( $pK_a$  4.97) and the unusual stability of the enolate comes from the fixed conformation of the two carbonyl groups.

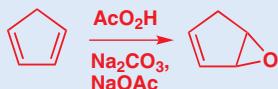


Meldrum's acid

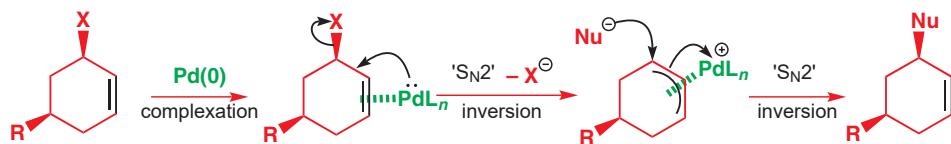
For many of the remaining schemes in the chapter we will ignore the additional ligands at palladium for simplicity's sake.

### Making vinyl epoxides

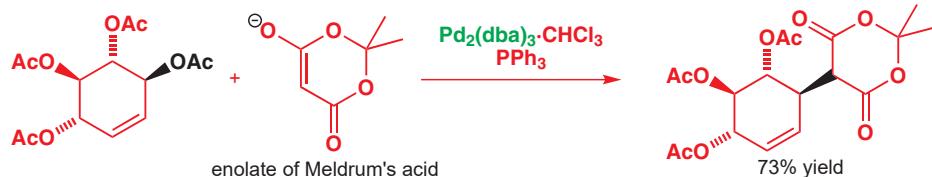
The synthesis of vinyl epoxides from dienes is mentioned in Chapter 19. The monoepoxide is formed first as the diene is more nucleophilic than the alkene in the monoepoxide. The main difficulty is that the monoepoxide rearranges with acid catalysis from the by-product, the carboxylic acid of the peroxyacid used in the epoxidation. The solution is simple: the mixture must be buffered to keep the acidity low.



nucleophile attacks from the less hindered face of the resulting  $\pi$ -allyl complex (that is, away from the metal), leading to overall retention of configuration.

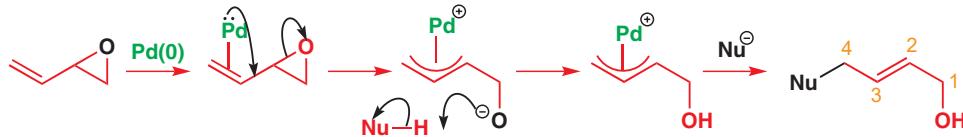


The reaction of this allylic acetate with the sodium salt of Meldrum's acid demonstrates the retention of configuration in the palladium(0)-catalysed process. The tetraacetate and the intermediate  $\pi$ -allyl complex are symmetrical, thus removing any ambiguity in the formation or reaction of the  $\pi$ -allyl complex and hence in the regiochemistry of the overall reaction.

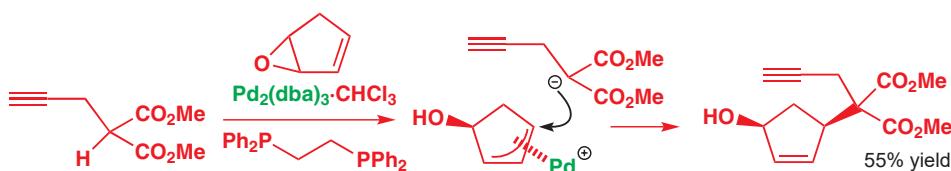


### Vinyl epoxides provide their own alkoxide base

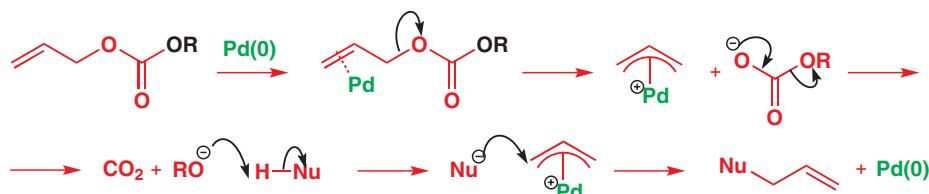
Vinyl epoxides and allylic carbonates are especially useful electrophiles because under the influence of palladium(0) they generate an alkoxide base, so no added base is required with these substrates. The overall reaction proceeds under almost neutral conditions—ideal with complex and sensitive substrates. The relief of strain in the three-membered ring drives the reaction with palladium(0) to produce the zwitterionic intermediate. Proton transfer activates the nucleophile, and attack at the less hindered end of the  $\pi$ -allyl palladium intermediate preferentially leads to overall 1,4-addition of NuH.



Retention of stereochemistry is demonstrated by the reaction of a substituted malonate with epoxycyclopentadiene. Palladium adds to the side opposite the epoxide so the nucleophile is forced to add from the same side as the OH group. This, no doubt, helps 1,4-regioselectivity.

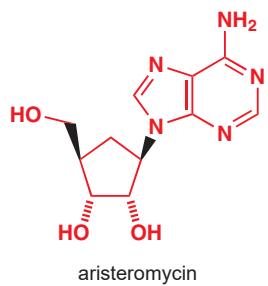
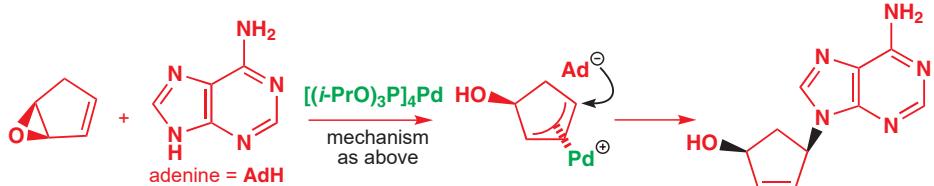


Allylic carbonates produce the required alkoxide by decarboxylation of the carbonate anion that is displaced in the formation of the  $\pi$ -allyl palladium intermediate. Deprotonation activates the nucleophile, which rapidly traps the  $\pi$ -allyl palladium complex to give the allylated product, regenerating the palladium(0) catalyst.

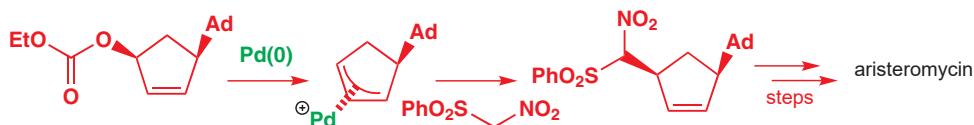


Trost and his group have used both of these palladium-catalysed alkylations in a synthesis of aristeromycin from epoxycyclopentadiene. The *cis* stereochemistry of this carbocyclic nucleotide analogue is of paramount importance and was completely controlled by retention of configuration in both substitutions.

The first reaction is between epoxycyclopentadiene and adenine, one of the heterocyclic building blocks of nucleic acids, and follows the mechanism we have just described to give a *cis*-1,4-disubstituted cyclopentene.

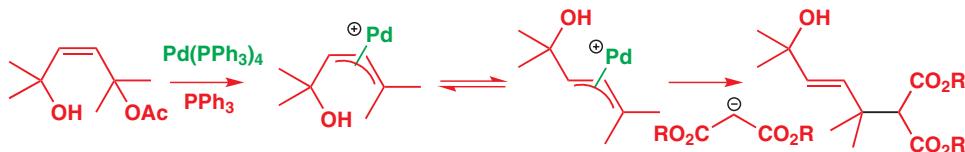


The alcohol is then activated by conversion into the carbonate, which reacts with phenylsulfonylnitromethane, and could later be converted into an alcohol. Once again, retention of stereochemistry during the palladium-catalysed substitution gives the *cis* product.

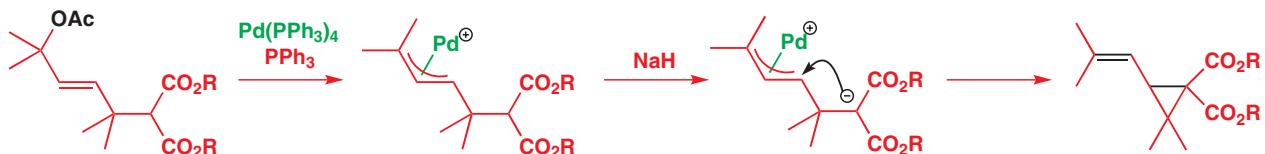


### Intramolecular alkylations make rings

$\pi$ -Allyl intermediates may also be used in cyclization reactions, including the synthesis of small and medium-sized rings using an intramolecular nucleophilic displacement. Three-membered rings form surprisingly easily, taking advantage of the fact that the leaving group can be remote from the nucleophile. The precursors can also be prepared by allylic alkylation. The sodium salts of malonate esters react with this monoacetate under palladium catalysis at the less hindered end to give the allylic alcohol.



Acetylation activates the second alcohol to displacement so that the combination of sodium hydride as base and palladium(0) catalyst leads to cyclization to the cyclopropane.

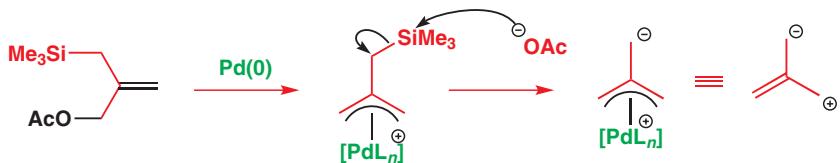


### Palladium can catalyse cycloaddition reactions

The presence of five-membered rings such as cyclopentanes, cyclopentenes, and dihydrofurans in a wide range of target molecules has led to a variety of methods for their preparation. One of the most successful of these is the use of trimethylenemethane [3 + 2] cycloaddition, catalysed by palladium(0) complexes. The trimethylenemethane unit in these reactions is derived from 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate, which is at the same time an allyl silane and an allylic acetate. This makes it both a weak nucleophile and an electrophile in the presence of palladium(0). Formation of the palladium  $\pi$ -allyl complex is followed by removal of the trimethylsilyl group by nucleophilic attack of the

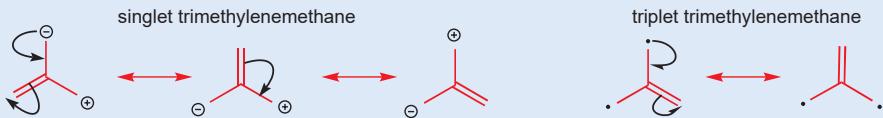
► Cycloadditions were described in Chapter 34.

resulting acetate ion, thus producing a zwitterionic palladium complex that can undergo cycloaddition reactions.

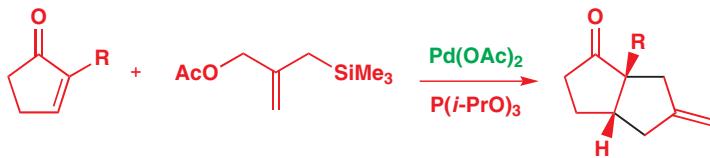


### Trimethylenemethane

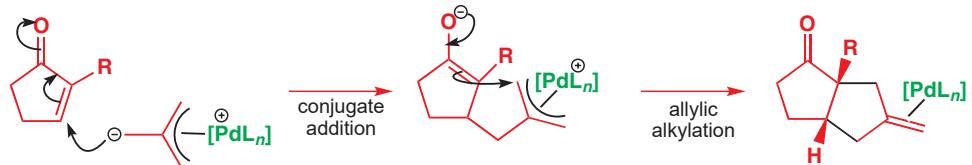
The symmetrical molecule with three  $\text{CH}_2$  groups arranged trigonally about a carbon atom is interesting theoretically. It could have a singlet structure with two charges, both of which can be delocalized, but no neutral form can be drawn. Alternatively, it could be a triplet with the two unpaired electrons equally delocalized over the three  $\text{CH}_2$  groups. This form is probably preferred and the singlet form is definitely known only as the palladium complex we are now describing. You might compare the singlet and triplet structures of trimethylenemethane with those of carbenes in Chapter 38.



The normal way to do the cycloadditions is to react the complex with an alkene bearing electron-withdrawing substituents that make the substrate prone to Michael-type conjugate addition. Cyclopentenones illustrate the reaction nicely.



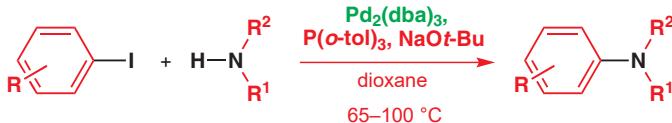
The mechanism is thought to be stepwise (in other words, not a real cycloaddition at all) with conjugate addition of the carbanion followed by attack of the resulting enolate on the  $\pi$ -allyl palladium unit to form a new five-membered ring having an *exo* methylene group.



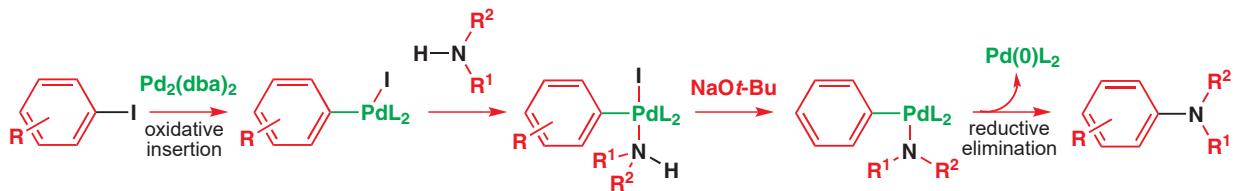
Interactive mechanism for the trimethylenemethane 'cycloaddition' catalytic cycle

### Palladium-catalysed amination of aromatic rings

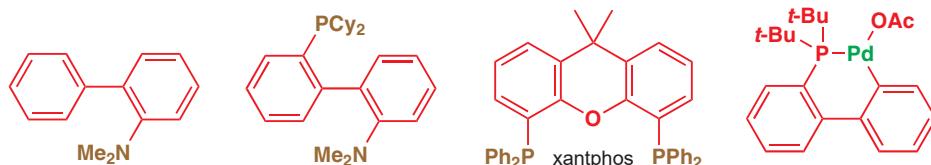
You've seen that palladium catalysis helps form carbon–carbon bonds that are difficult to make using conventional reactions. It can also help form carbon–heteroatom bonds that are difficult to make, and you have already seen some examples in the reactions of  $\pi$ -allyl complexes. Work starting in the 1990s by Buchwald and Hartwig has shown that Pd can be used to promote nucleophilic substitution at a vinylic or aromatic centre—a reaction which would not normally be possible. For example, aromatic amines can be prepared directly from the corresponding bromides, iodides, or triflates and the required amine in the presence of palladium(0) and a strong alkoxide base.



The mechanisms and catalysts used in this ‘Buchwald–Hartwig’ chemistry mirror those of coupling reactions involving oxidative addition, transmetalation, and reductive elimination. The first step, as usual, is oxidative insertion of Pd(0) into the aryl–halogen bond. The Pd(II) complex now adds the amine so that both coupling partners find themselves bonded to the same palladium atom. The base eliminates H–I from the complex and reductive elimination forms the Ar–N bond.

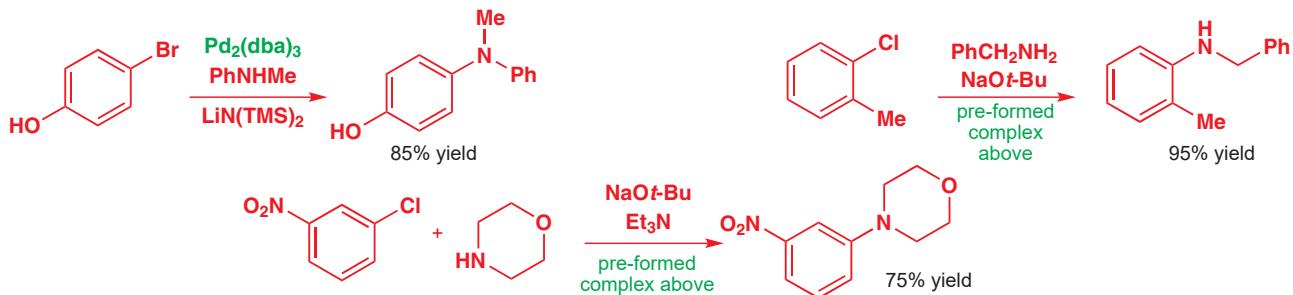


Various bases, such as *t*-BuONa, MeONa, LiN(TMS)<sub>2</sub>, or K<sub>2</sub>CO<sub>3</sub>, have been successful and some of the most successful ligands (coordinating groups shown in brown) are shown below. The fourth structure is a preformed complex used in catalytic amounts.

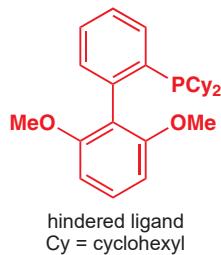
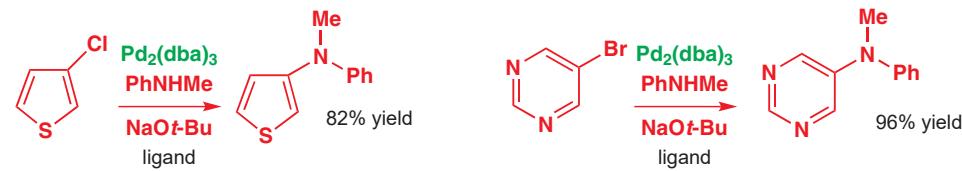


► If you are interested in reading more on the design and choice of these ligands, turn to the Further reading section at the end of the chapter.

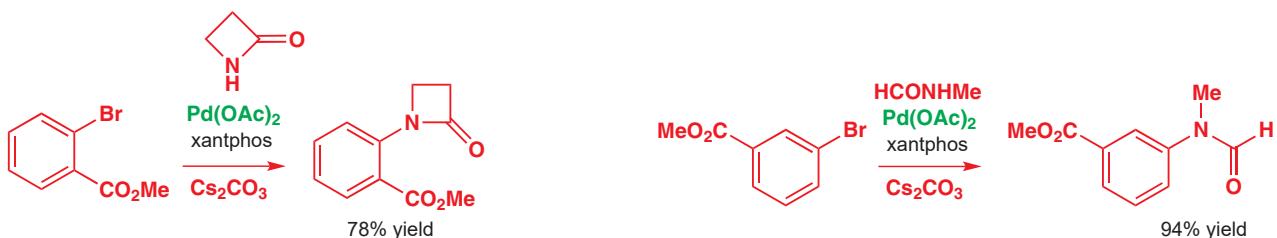
The range of compounds which can be made is very great: both electron-withdrawing and electron-donating substituents are acceptable; hindered compounds or those with acidic hydrogens such as phenols are tolerated. Even aryl chlorides, which are much cheaper than bromides or iodides, can also be successful.



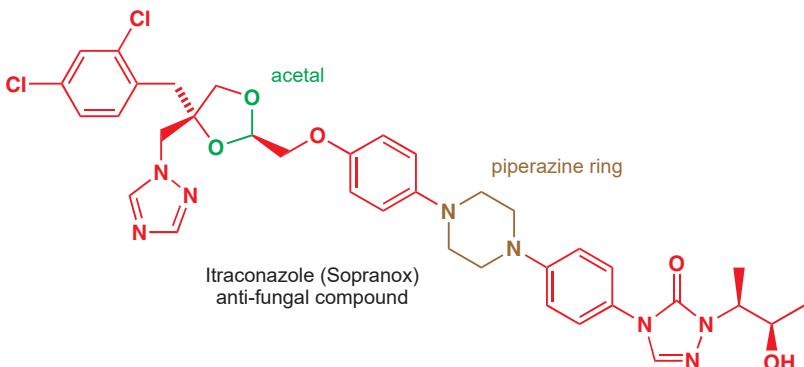
Aromatic heterocyclic halides also work well whether they are electron-deficient or electron-rich. These couplings use the more hindered ligand shown in the margin.



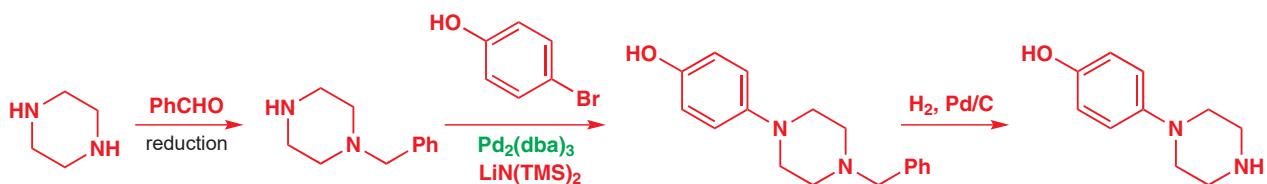
It is tempting to view the amine as the ‘nucleophile’ in these reactions but it is clear that nucleophilicity has little to do with it as amides also couple to aromatic rings under similar conditions. The ability to act as a ligand for palladium is the important thing. The ligand xantphos (see above) is used in these reactions and again the nature of the substituents on the benzene ring is of little account. Even strained azetidines react well.



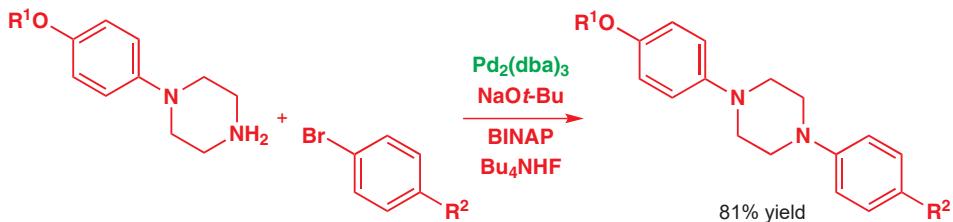
These reactions have been very widely used in the pharmaceutical industry in the making of medicinal compounds. When Sepracor wanted to make their anti-fungal compound itraconazole, it was obvious that they should make the two ends with stereochemistry and join them together with a central achiral section. Right in the middle is a piperazine ring joined to two different benzene rings, one connected through O and one through N. The C–N coupling chemistry of Buchwald and Hartwig could have been made for this problem.



We have already seen that *p*-bromophenol can be joined to an amine with palladium catalysis, so it should be easy to join it to piperazine. However, there is a potential problem of selectivity: we want to add this benzene ring just once, and the way to do this is to protect one nitrogen atom by reductive amination with benzaldehyde. The remaining NH group can then be coupled to the aromatic ring and the benzyl group removed by hydrogenation.



The workers at Sepracor then added the left-hand end of the molecule (we shall call this R<sup>1</sup>) to the free OH group. The other aromatic ring, already functionalized with the right-hand end of the molecule (we shall call this R<sup>2</sup>) was coupled as its bromide to the free NH group by a second Buchwald–Hartwig amination reaction process. It's easy to see how this chemistry simplifies the assembly of such a large and complex molecule.



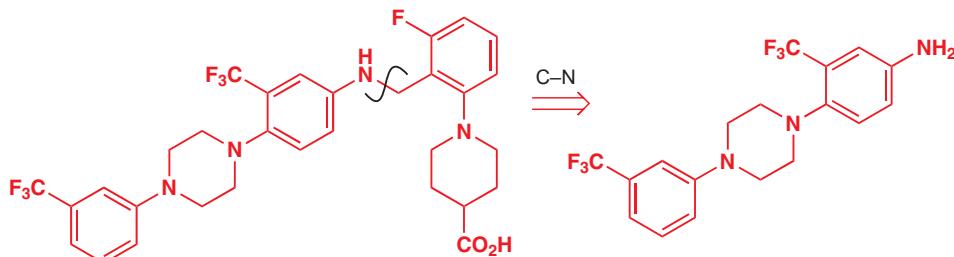
► The bisphosphine BINAP is shown on p. 319. It is a chiral compound, but that is irrelevant to its use here.

### Nucleophilic aromatic substitution and palladium catalysis compared

You will have noticed that Buchwald–Hartwig chemistry accomplishes the same as nucleophilic aromatic substitution ( $S_NAr$ , Chapter 22): the replacement of a halogen by a nucleophile. So what are the differences?

	$S_NAr$	Buchwald–Hartwig
the leaving group	$F > Cl > Br > I$ fluoride is not the best leaving group but it accelerates the addition	$I > Br > Cl >> F$ iodide is best at the oxidative addition step but chloride will do and aryl chlorides are cheaper
regiochemistry	there must be an electron-withdrawing group <i>ortho</i> or <i>para</i> to the halide	any substitution pattern acceptable

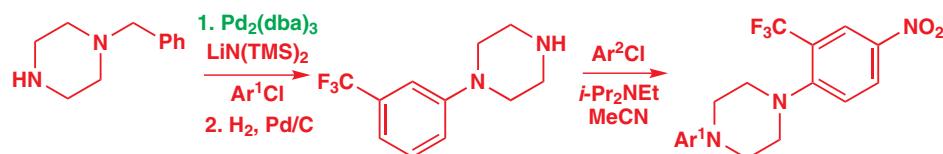
The synthesis of a drug to control blood clotting gives us the opportunity to review both methods. This compound also has a central piperazine ring and disconnection of the right-hand side chain reveals an amine that could be functionalized by alkylation with a suitable benzylic halide or reductive amination.



A standard way to make aromatic amines is by nitration and reduction (Chapter 21) so we can think of making this aminobenzene from the nitrobenzene below. Now we can disconnect the two  $\text{C}-\text{N}$  bonds with the idea of putting a halide ( $X$ ) at the point of substitution in each aromatic coupling partner.



The substituents on the right-hand ring are both electron withdrawing and are *ortho* and *para* to the leaving group. As you know from Chapter 22, this is perfect for ordinary nucleophilic aromatic substitution—so much so that chloride is a good enough choice and it is not necessary to use fluoride. The left-hand ring has again a good electron-withdrawing substituent but it is *meta* to the halide and so nucleophilic aromatic substitution will not work. Palladium catalysis is needed. Chemists at Berlex Biosciences chose to introduce the left-hand ring first.



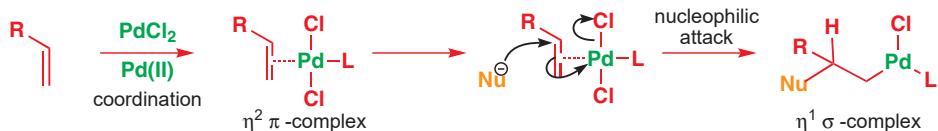
## Alkenes coordinated to palladium(II) are attacked by nucleophiles

Now for another case where a transition metal catalysis facilitates a reaction that would not occur under normal conditions: nucleophilic attack on an isolated double bond. Usually alkenes react with nucleophiles only when conjugated with an electron-withdrawing group. But coordination of an electron-rich alkene to a transition metal ion such as palladium(II) changes its reactivity dramatically: electron density is drawn towards the metal and away from the  $\pi$  orbitals of the alkene. This leads to activation towards attack by nucleophiles, just as in conjugate addition, and unusual chemistry follows. Unusual, that is, for the alkene; the palladium centre behaves exactly as expected.

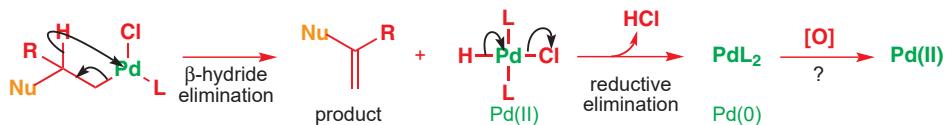


■ This regioselectivity is not the same as in the Heck reaction, where attack mostly occurs at the end of the alkene. Internal nucleophiles transferred from the palladium to the alkene usually prefer the terminal position of the alkene but external nucleophiles usually prefer the more substituted end.

Many nucleophiles, such as water, alcohols, and carboxylates, are compatible with an alkene–Pd(II) complex and can attack the complexed alkene from the side opposite the palladium. The attack of the nucleophile is regioselective for the more substituted position. This parallels attack on bromonium ions but is probably governed by the need for the bulky palladium to be in the less hindered position.



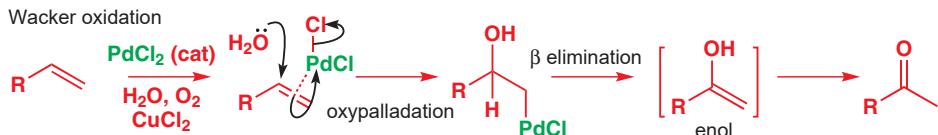
The resulting Pd(II)  $\sigma$ -alkyl species decomposes by  $\beta$ -hydride elimination to reveal the substituted alkene. Reductive elimination of a proton and the leaving group, usually chloride, leads to palladium(0). The weakness of this reaction is that the catalytic cycle is not complete: Pd(II), not Pd(0), is needed to complex the next alkene.



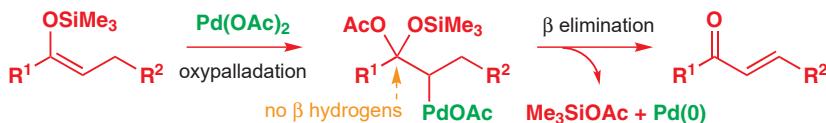
There are two solutions to this problem. We could use stoichiometric Pd(II) but this is acceptable only if the product is very valuable or the reaction is performed on a small scale. It is better to use an external oxidant to return the palladium to the Pd(II) oxidation state so that the cycle can continue. Air alone does not react fast enough (even though Pd(0) must be protected from air to avoid oxidation) but, in combination with copper(II) chloride, oxygen completes the catalytic cycle. CuCl<sub>2</sub> oxidizes Pd(0) to Pd(II) and is itself oxidized back to Cu(II) by oxygen, ready to oxidize more palladium.

### Oxypalladation and the Wacker oxidation

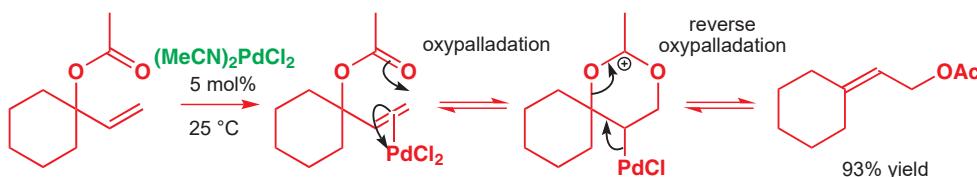
This combination of reagents has been used to oxidize terminal vinyl groups to methyl ketones and is known as the **Wacker oxidation**. The nucleophile is simply water, which attacks the activated alkene at the more substituted end in an *oxypalladation* step.  $\beta$ -Hydride elimination from the resulting  $\sigma$ -alkyl palladium complex releases the enol, which is rapidly converted into the more stable keto form. Overall, the reaction is a hydration of a terminal alkene that can tolerate a range of functional groups.



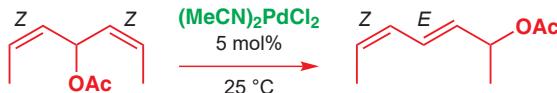
A related reaction is the oxidation of silyl enol ethers to enones. This requires stoichiometric palladium(II), although reoxidation of Pd(0) with benzoquinone can cut that down to about half an equivalent. The reaction provides a valuable way of turning regioselective methods for making silyl enol ethers (Chapter 20) into regioselective methods for oxidizing ketones to enones. The first step is again oxypalladation and  $\beta$  elimination puts the alkene in conjugation with the ketone: there are no  $\beta$  hydrogens on the other side.



An example of catalytic oxypalladation is the rearrangement of allylic acetates with Pd(II). The reaction starts with oxypalladation of the alkene and it is the acetate already present in the molecule that provides the nucleophile to attack the alkene. The intermediate can reverse the oxypalladation in either direction and the product is whichever allylic acetate has the more substituted alkene. In this case, trisubstituted beats monosubstituted easily.



The reaction is *E*-selective, which means that a simple synthesis of an *E,Z*-diene is possible from the symmetrical acetate with two *Z*-allylic alkenes. The one that rearranges goes *E* and the one that stays behind remains *Z*. The driving force for this rearrangement, from one disubstituted alkene to another, is establishment of conjugation.

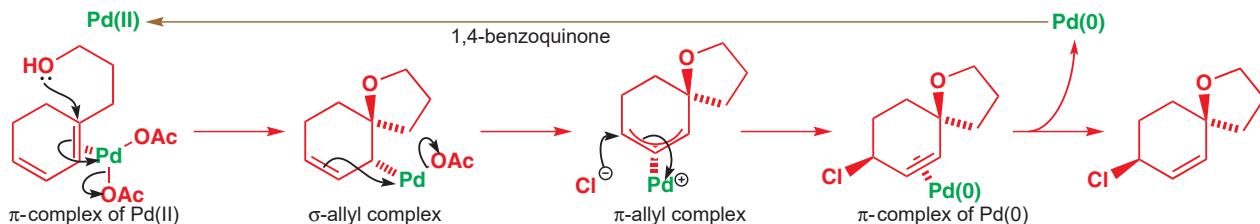


### Alcohols and amines as intramolecular nucleophiles

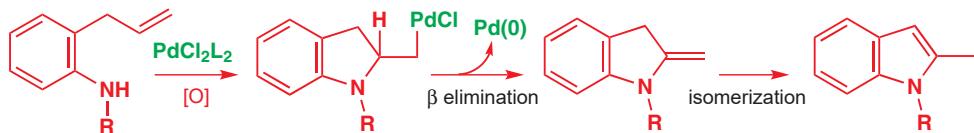
Cyclic ethers and amines can be formed with an intramolecular alcohol or amine nucleophile. Stoichiometric palladium can be avoided by using benzoquinone as the stoichiometric oxidant with a catalytic amount of palladium. In this example intramolecular oxypalladation of a diene is followed by attack of an external nucleophile on a  $\pi$ -allyl complex.



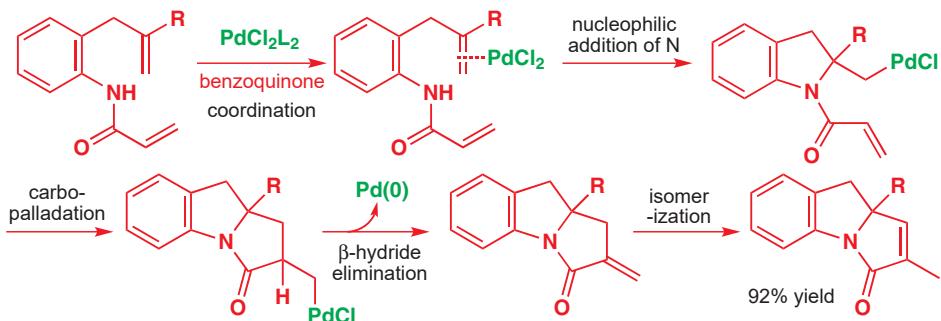
Palladium coordinates to one face of the diene, promoting intramolecular attack by the alcohol on the opposite face. The resulting  $\pi$ -allyl palladium can form a  $\pi$ -allyl complex with the palladium on the lower face simply by sliding along to interact with the double bond. Nucleophilic attack of chloride from the lithium salt then proceeds in the usual way on the face opposite palladium. The overall addition to the diene is therefore *cis*.



Nitrogen nucleophiles also attack alkenes activated by Pd(II), and benzoquinone can again act as a reoxidant, allowing the use of catalytic quantities of palladium. The mechanism follows the same pattern as for oxygen nucleophiles, and a final isomerization produces the most stable regioisomer of product. In this example the product is an aromatic indole, so the double bond migrates into the five-membered ring.



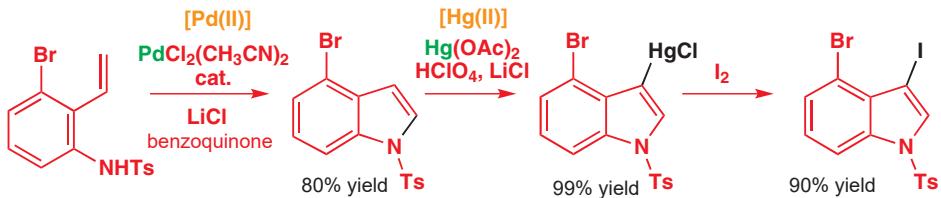
If the substrate lacks a hydrogen suitable for  $\beta$  elimination and there is another alkene present in the molecule, the  $\sigma$ -alkyl palladium intermediate can follow the Heck pathway to form a bicyclic structure in a tandem reaction sequence. Once again, the final step is a palladium-hydride-mediated isomerization to give the endocyclic alkene.



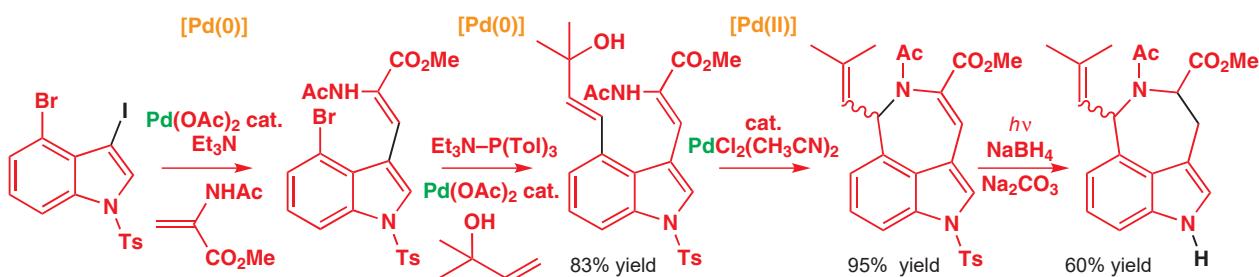
## Palladium catalysis in the total synthesis of a natural alkaloid

We take our leave of palladium by presenting a synthesis of an alkaloid, *N*-acetyl clavicipitic acid methyl ester, by Hegedus. The power of organometallic chemistry is illustrated in five of the steps in this seven-step process (the metals are highlighted in orange). Each of the organometallic steps catalysed by Pd(0) or Pd(II) has been described in this chapter. The overall yield is 18%, a remarkably good result for a molecule of such complexity.

The first step is to make an indole by Pd(II)-catalysed cyclization in the presence of benzoquinone as reoxidant. The nucleophilic nature of the 3-position of the indole (Chapter 30) was exploited to introduce the required iodide functionality. Rather than direct iodination, a high-yielding two-step procedure involving mercuration followed by iodination was employed.



Aryl iodides are more reactive towards oxidative addition than aryl bromides, and a selective Heck coupling (without phosphine ligands) with an unsaturated side chain left the bromide in place. A second Heck reaction of this bromide with an allylic alcohol was used to introduce a second side chain. Cyclization of the amide on to the allylic alcohol was achieved with palladium catalysis, not as might have been expected with palladium(0) but instead with palladium(II), to produce the seven-membered ring. Finally, the conjugated double bond was reduced and the sulfonamide removed under photolytic conditions.

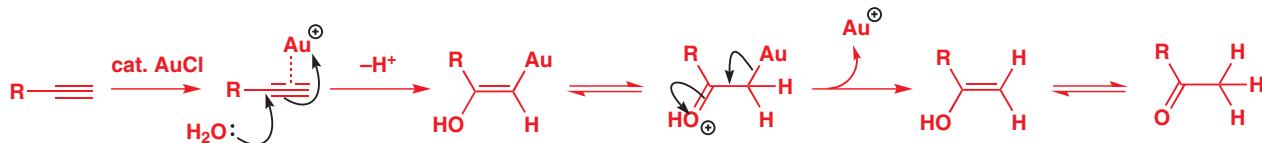


## An overview of some other transition metals

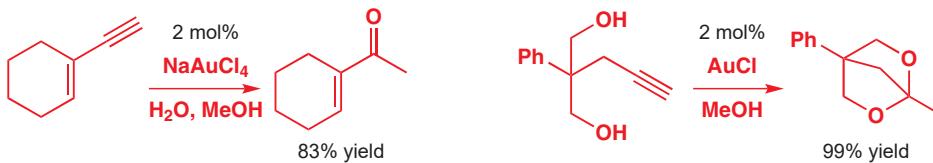
Some metals—palladium chief among them—see continual service in catalysis but others have their day and then fall out of favour when better alternatives become available. Tin is less popular now than it was 20 years ago because of its toxicity. A more serious case is mercury. Mercury(II) is an excellent catalyst for the addition of water to alkynes. But mercury is very toxic indeed, and the last ten years have seen its role largely superseded by gold. Do not recoil at the expense! Gold is expensive on the scale used to make rings, plates, medals, and coins, but here it is used in only catalytic quantities. Gold is in fact less expensive than palladium, rhodium, or ruthenium. Part of the age-old appeal of gold is its unreactivity as a metal: it is very stable but it does form Au(I) and Au(III) salts such as  $\text{AuCl}$  and  $\text{AuCl}_3$ . Both are available commercially and are generally used as their phosphine complexes.

### Gold: activating alkynes

$\text{Au(I)}$  and  $\text{Au(III)}$  form cationic  $\pi$  complexes with alkynes and these react with nucleophiles of many kinds. With water the result is simple: it adds to the more substituted end of the alkyne and the net result is hydration to give a ketone.



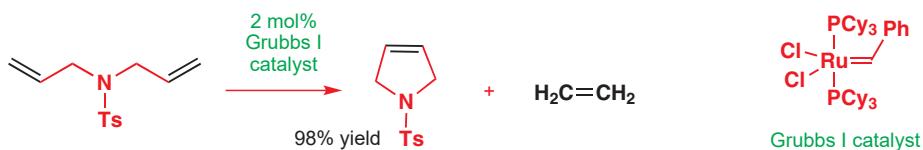
This simple reactivity can be developed in many more elaborate ways you can read about elsewhere, but simple examples include hydration of an enyne to form a conjugated ketone and the capture of the ketone by intramolecular acetal formation. The details give you an idea of reagents, solvents, and yields.



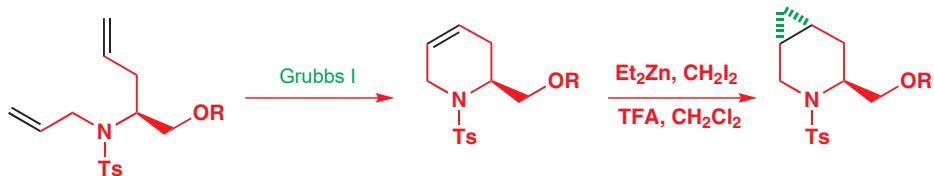
### Ruthenium: alkene (olefin) metathesis

The theme of this chapter is that transition metals let you do things to organic molecules which are unthinkable without them. Nowhere is this more true than in metathesis reactions, and we finish the chapter with a reminder of the power of the ruthenium catalysts we introduced in Chapter 38. There we discussed the carbene-based mechanism of the reaction, and we showed you some simple examples such as this cyclization of a symmetrical amine to give a five-membered heterocycle using a catalytic amount of the ruthenium complex known as Grubbs I catalyst.

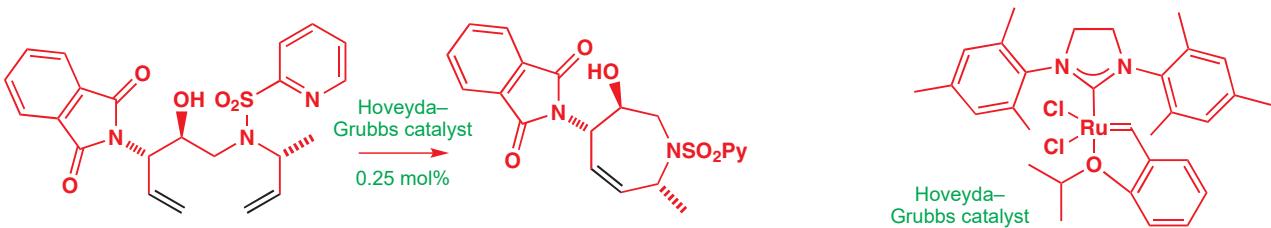
→ The structures of three important ruthenium complexes used as catalysts for metathesis are given on p. 1025.



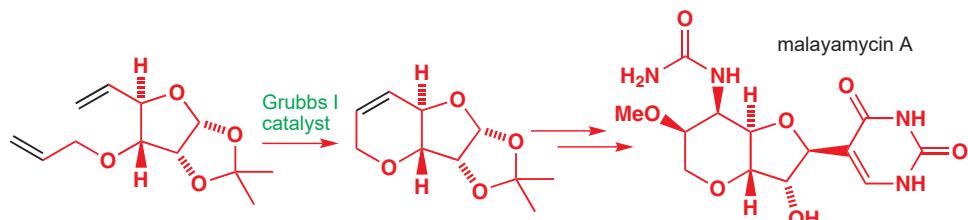
The synthesis of a sleep-inducing drug by GlaxoSmithKline in their laboratories at Verona used a very similar metathesis, although on an unsymmetrical amine and giving a six-membered heterocycle. The starting material is also a single enantiomer and the stereochemistry is important as the cyclopropane, introduced by a Simmons–Smith reaction (Chapter 38), must be on the opposite face of the six-membered ring to the side chain.



At another GlaxoSmithKline site, in the USA, the development of a drug for osteoporosis and osteoarthritis required a seven-membered heterocycle with two controlled chiral centres. This time the Hoveyda–Grubbs catalyst had to be used but the loading is very low indeed. Notice also that a free OH group does not interfere.



Our third example comes from Syngenta's crop protection laboratory in Basel. It is another cyclization but this time to form an oxygen heterocycle with four chiral centres. The final product of this synthesis is malayamycin A, a natural fungicide found in bacteria. The metathesis step is early in the synthesis and you will notice that the alkene formed in this cyclization is used to provide two more chiral centres in malayamycin.



In the next chapter you will see more ways in which ruthenium—along with osmium, titanium, rhodium, and others—can be used to solve the challenges of synthesis as we look at ways of making molecules as single enantiomers.

## Further reading

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Most textbooks of organometallic chemistry favour the inorganic approach of facts rather than explanation. There are usually plenty of structures and catalytic cycles but very few mechanisms. However, two brief introductions that might help you are: M. Bockmann, *Organometallics 1 and 2*: Oxford Primers, OUP, Oxford, 1994. A book that does contain mechanisms of a number of the reactions in this book, as well as others, is P. Wyatt and S. Warren, *Organic Synthesis: Strategy and Control*, Wiley, Chichester, 2007. Probably the best comprehensive account is J. Hartwig, *Organotransition Metal Chemistry*, University Science Books, New York, 2010.

The references to the examples of drug synthesis by metathesis are: W. M. Maton and GlaxoSmithKline group in Verona, *Organic Process Research and Development*, 2010, **14**, 1239; H. Wang and GlaxoSmithKline group in King of Prussia, Pennsylvania, *Organic*

*Process Research and Development*, 2008, **12**, 226; O. Loiseleur and Syngenta group at Basel, *Organic Process Research and Development*, 2006, **10**, 518.

*Organic Syntheses* are a good source of ways to make reagents and ways to carry out reactions. Comins' reagent is featured in *Organic Syntheses*, 1997, **74**, 77.

Leading references for the Buchwald and Hartwig chemistry: J. F. Hartwig and group, *Angew. Chem. Int. Ed.*, 2005, **44**, 1371; S. L. Buchwald and group, *Organic Letters*, 2005, **7**, 3965. Gold chemistry is reviewed by A. Fürstner and P. W. Davies, *Angew. Chem. Int. Ed.*, 2007, **46**, 3410. The drug syntheses are from C. H. Senanayake and group, *Tetrahedron: Asymmetry*, 2003, **14**, 3487; B. Ye and group, *Bioorg. and Med. Chem. Lett.*, 2004, **14**, 761.

The new gold chemistry of alkynes and alkenes is described in a long review H. C. Shen, *Tetrahedron*, 2008, **64**, 3885.

## Check your understanding

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To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 41 不对称合成

## 联系

### 基础

- Carbonyl group reactions ch6, ch9–ch11
- Stereochemistry and conformation ch14, ch16, & ch31
- Electrophilic addition to enolates and alkenes ch19 & ch20
- Aldol reactions ch26
- Diastereoselectivity ch32 & ch33
- Cycloadditions ch34

### 目标

- Why making pure enantiomers matters
- Chirality derives from nature
- The chiral pool provides starting materials, auxiliaries, and catalysts
- Chiral auxiliaries work well in asymmetric alkylation and aldol reactions
- Chiral catalysts for oxidation and reduction reactions
- Ligand-accelerated catalysis
- Catalysis with and without metals

### 展望

- Chemistry of life ch42
- Chemistry and the future ch43



'L'univers est dissymétrique'.  
Louis Pasteur, *Comptes Rendus Acad. Sci., Paris* June 1, 1874.

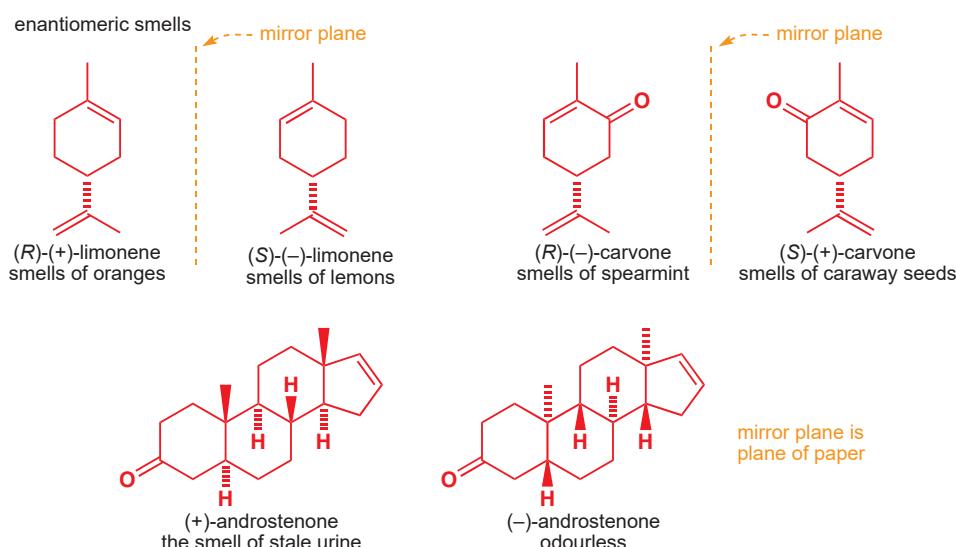
■ This chapter builds on the concepts introduced in Chapter 14: make sure you understand all the terms used to describe stereochemistry that are defined there. In particular make sure you are absolutely clear on the meanings of *chiral*, *achiral*, *enantiomer*, and *diastereoisomer*, along with what the designators *R*, *S*, *+*, *-*, *L*, and *D* refer to.

## Nature is asymmetric

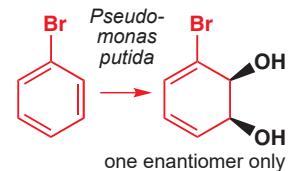
'How would you like to live in Looking-glass House, Kitty? I wonder if they'd give you milk in there? Perhaps looking-glass milk isn't good to drink...' Lewis Carroll, *Through the looking-glass and what Alice found there*, Macmillan, 1872.

You are chiral, and so are Alice, Kitty, and all living organisms. You may think you look fairly symmetrical in a looking-glass, but as you read this book you are probably turning the pages with your right hand and processing the information with the left side of your brain. Some organisms are rather more obviously chiral: snails, for example, carry shells that could spiral to the left or to the right. Not only is nature chiral, but by and large it exists as just one enantiomer—although some snail shells spiral to the left, the vast majority of marine snail shells spiral to the right; humans have their stomach on their left and their liver on their right; honeysuckle (*Lonicera*) climbs by spiralling to the left and all bindweed (*Convolvulus*) spirals to the right.

Nature has a left and a right, and it can tell the difference between them. You may think that human beings are sadly lacking in this respect, since as children we all had to learn, rather laboriously, which is which. Yet at an even earlier age, you could no doubt distinguish the smell of oranges from the smell of lemons, even though this is an achievement at least as remarkable as getting the right shoe on the right foot. The smells of orange and lemon differ in being the left- and right-handed versions of the same molecule, limonene. (*R*)-(+)-Limonene smells rounded and orangey; (*S*)-(−)-limonene is sharp and lemony. Similarly, spearmint and caraway seeds smell quite different, although again this pair of aromas differs only in being the enantiomeric forms of the ketone carvone. Evolution has left many of us regrettably sensitive to (+)-androstenone, the smell of stale human urine. (−)-Androstenone is essentially odourless.



(+)-Androstenone is also a pig pheromone. You may not wish to know that it is the active component of DuPont's Boarmate, used by pig farmers to prepare sows for artificial insemination.

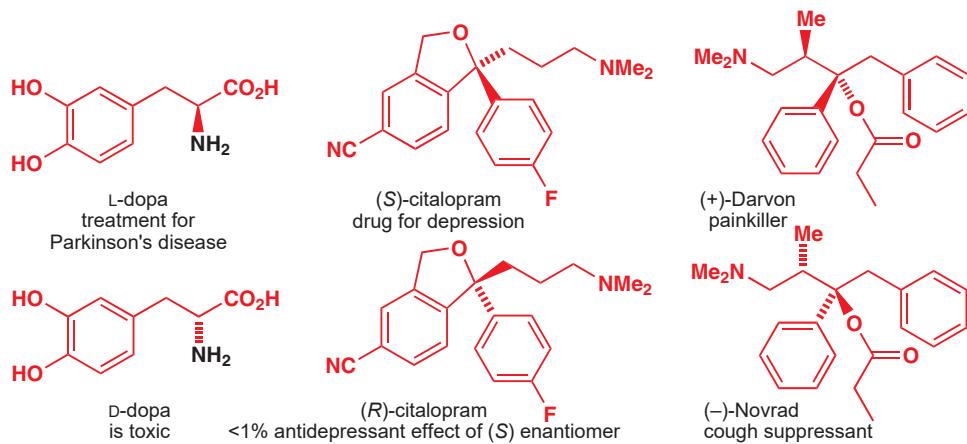


Even bacteria know their right from their left: *Pseudomonas putida* can use aromatic hydrocarbons as a foodstuff, degrading them to diols. The diol produced from bromobenzene is formed as one enantiomer only.

How can this be? We said in Chapter 14 that enantiomers are chemically identical, so how is it that we can distinguish them with our noses and bacteria can produce them selectively? Well, the answer lies in a proviso to our assumption about the identity of enantiomers: they are identical *until they are placed in a chiral environment*. This concept will underlie all we say in this chapter about how to make single enantiomers in the laboratory. We take our lead from nature: all life is chiral, so all living systems are chiral environments.

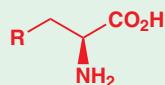
The sheer complexity of life means that nature has to build its living structures from molecules that are chiral, principally amino acids and sugars. For all of those chiral molecules, evolution has forced the use of a single enantiomeric form, for example every amino acid in your body has the same configuration (usually labelled *S*). From this fact derives the larger-scale chirality of all living structures, from the right-handed double helix of DNA to the location of a blue whale's internal organs. The answer to the question posed by Alice at the start of the chapter is most certainly *no*—her kitten's digestive system will be able to hydrolyse the achiral fats in the looking-glass milk quite easily (achiral compounds are superimposable on their mirror image), but looking-glass proteins (which will be made of *D*-amino acids) and *L*-lactose will be quite indigestible.

For a perfumer or flavour and fragrance manufacturer, the distinction between the differently scented enantiomers of the same molecule is clearly of great importance. Nonetheless, we could all get by with caraway-flavoured toothpaste. Yet when it comes to drug molecules, making the right enantiomer can be a matter of life and death. Parkinson's disease sufferers are treated with the non-proteinogenic amino acid dopa (3-(3,4-dihydroxyphenyl)alanine). Dopa is chiral, and only (*S*)-dopa (known as *L*-dopa) is effective in restoring nerve function. (*R*)-Dopa is not only ineffective, it is quite toxic, so the drug must be marketed as a single enantiomer.



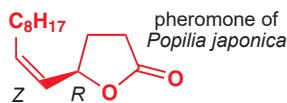
► The molecules of life are examined in detail in the next chapter.

■ Natural *L*-amino acids all look like this:



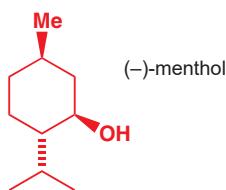
All have *S* stereochemistry except cysteine (*R*=SH), where the priority rules mean the chiral centre is *R*. Some bacteria make their cell walls from 'unnatural' *R*-amino acids to make them unassailable by the (*S*-amino acid-derived) enzymes used by higher organisms to hydrolyse peptides (see p. 1141).

In other cases, only one of the two enantiomers of a drug molecule possesses activity: the antidepressant citalopram and the painkiller naproxen are both marketed only as their *S* enantiomer because the *R* enantiomers are essentially inactive. In a few cases, the enantiomers both have activity, but in different ways: (+)-Darvon and (-)-Novrad are a painkiller and a cough suppressant, respectively.



It is not only drugs that have to be manufactured enantiomerically pure. This simple lactone is the pheromone released by the Japanese beetle *Popilia japonica* as a means of communication. The beetles, whose larvae are serious crop pests, are attracted by the pheromone, and synthetic pheromone is marketed as 'Japonilure' to bait beetle traps. Provided the synthetic pheromone is the stereoisomer shown, with the *Z* double bond and the *R* configuration at the stereogenic centre, only 25 µg per trap catches thousands of beetles. You met this compound in Chapter 27, where we pointed out that double bond stereocontrol is important since the *E* isomer of the pheromone is virtually useless as a bait (it retains only about 10% of the activity). Even more important is control over the configuration at the chiral centre because the *S* enantiomer of the pheromone is not only inactive in attracting the beetles, but acts as a powerful inhibitor of the *R* enantiomer—even 1% of *S* enantiomer in a sample of pheromone destroys the activity.

So you see why chemists need to be able to make compounds as single enantiomers. In Chapters 32 and 33 we looked at *relative stereochemistry* and how to control it; this chapter is about how to control *absolute stereochemistry*. We call this asymmetric synthesis.

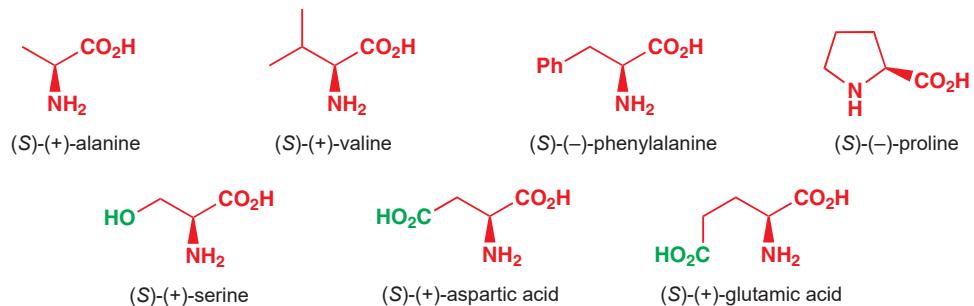


In the last 25 years or so, this subject has occupied more organic chemists than possibly any other, and we are now at a point where it is not only possible (and in fact essential because of strict regulatory rules) to make many drug molecules as single enantiomers, but it is also even possible to make many chiral molecules that are indigenous to nature more cheaply in the laboratory. By 2007, for example, at least 30% of the world's supply of menthol was not extracted from plants but made synthetically. A thousand tonnes of (*-*)-menthol a year is made by the company Takasago in Japan using the techniques of asymmetric synthesis that you will meet later in this chapter.

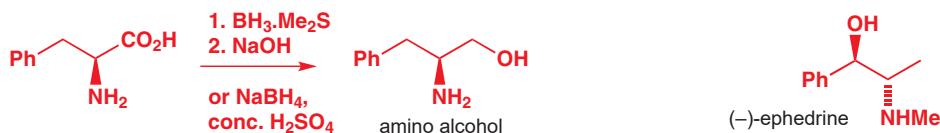
## The chiral pool: Nature's chiral centres 'off the shelf'

When we first introduced you to enantiomers and chirality in Chapter 14, we stressed that any imbalance in enantiomers always derives ultimately from nature. A laboratory synthesis of a chiral compound from achiral or racemic starting materials alone always gives a racemic mixture of enantiomers. If you want to make just one enantiomer, you have to use a starting material or reagent which is also just one enantiomer. This seems like a chicken-and-egg situation, until you realize that nature provides a collection of 'off the shelf' enantiomerically pure compounds that we can exploit in various ways. This collection of natural, enantiomerically pure compounds is called the **chiral pool**. The principal groups of compounds in the chiral pool are:

1. The amino acids. There is a full list of the natural amino acids found in proteins on p. 554, but for the purposes of this chapter you should make sure you are familiar with the structures below. They all have simple side chains that are simple alkyl groups or functionalized chains with plenty of versatile chemistry, and can be obtained by hydrolysis of protein.



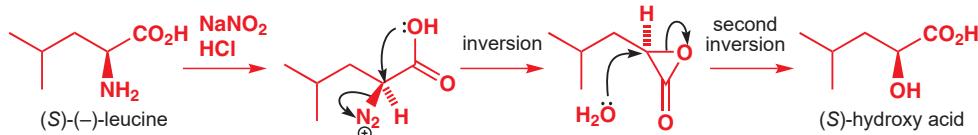
2. Simple derivatives of the amino acids: amino alcohols and hydroxy acids. It's easy to reduce amino acids to amino alcohols with borane ( $\text{BH}_3$ ), usually generated in the reaction mixture by treating sodium borohydride with concentrated sulfuric acid. We will use a number of naturally derived amino alcohols as starting materials in this chapter.



Ephedrine is an amino alcohol which is itself a useful member of the chiral pool—it's a plant extract readily available as either diastereoisomer (see p. 314), each, unusually, also available as either enantiomer.

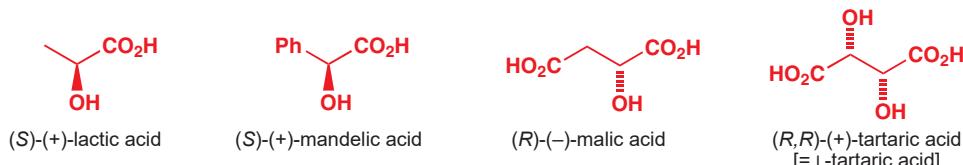
It's also easy to make hydroxy acids from amino acids by diazotization. You saw this being done in Chapter 33, but as a reminder nitrous acid generates a diazonium salt, which undergoes substitution by water via an intermediate  $\alpha$ -lactone. Two configurational inversions are involved, so the product alcohol retains *S* stereochemistry.

diazotization–hydrolysis of amino acids to give hydroxy acids proceeds with overall retention



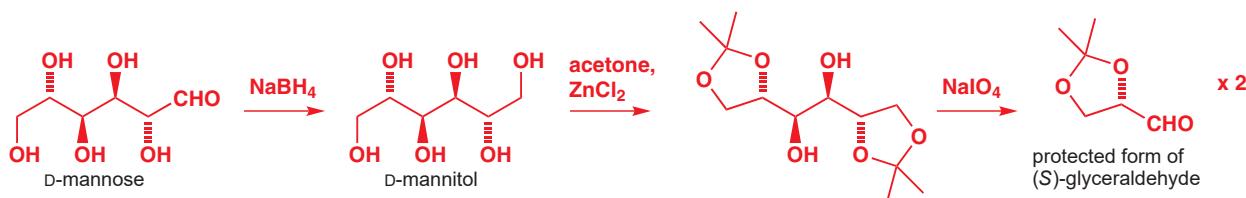
Look back at p. 875 for more on the mechanism of this transformation—it's very important that the reaction goes with overall *retention* of stereochemistry.

Some hydroxy acids are themselves available from nature, and are therefore also members of the chiral pool: both (*R*)- and (*S*)-lactic acid, for example, can be made by bacterial fermentation; mandelic, malic, and tartaric acids are extracted from almonds, apples, and grapes, respectively.



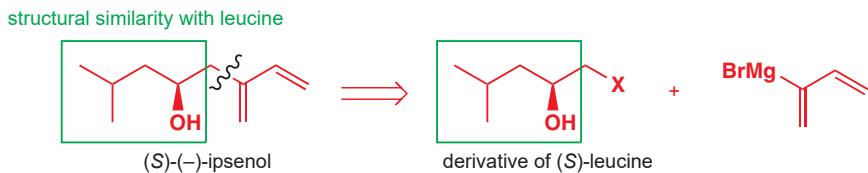
3. Carbohydrates and their derivatives. There are a great many simple carbohydrates available, but one of the most useful is mannose. Reduction to the alcohol gives the  $C_2$ -symmetric compound mannitol, which can be converted to a useful aldehyde by selective protection as a bis-acetal with acetone and a Lewis acid. Cleavage of the remaining diol with sodium periodate gives two equivalents of a useful protected form of glyceraldehyde.

The concept of  $C_2$  rotational symmetry is discussed on p. 320.  $C_2$  symmetry is compatible with chirality. For the oxidative cleavage of diols to aldehydes, see p. 443.

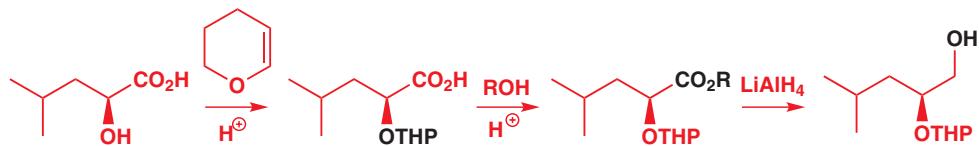


In this chapter we will show you the many and varied ways in which members of the chiral pool can be put to work in asymmetric synthesis, but the most straightforward application is simply to spot that a target molecule has a close structural similarity with, say, an amino

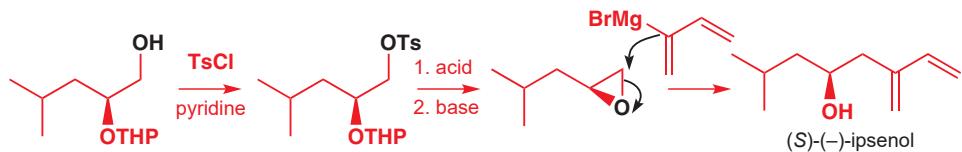
acid. This is what Mori did when he made another important insect pheromone, ipsenol. The left-hand half of the molecule has the same structure as the side chain of leucine, and the S chiral centre can also come from (*S*)-leucine.



Mori used (*S*)-leucine as the starting material and converted it to the (*S*)-hydroxy acid by the method on p. 875. The hydroxyl group was protected as the THP derivative (Chapter 23).



Reduction of the acid, via the ester, then allowed introduction of the tosylate leaving group, which was displaced to make an epoxide. The epoxide was opened by a Grignard reagent to introduce the diene portion and give the target molecule.

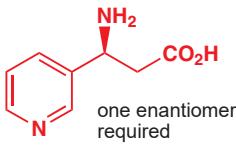


→ This drawback is highlighted in the synthesis of oseltamivir in Chapter 43 (p. 1174).

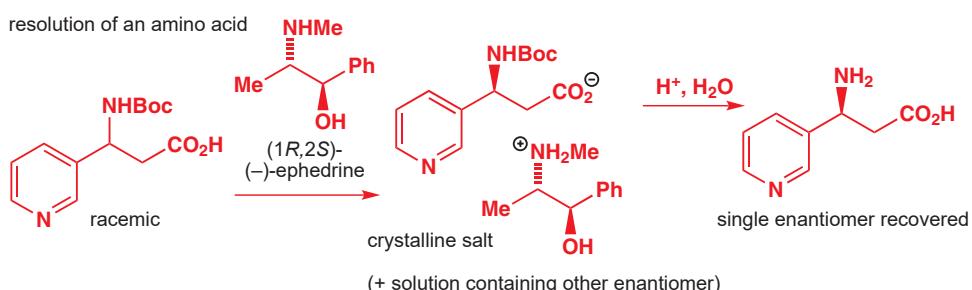
This might seem rather long-winded, and long-windedness can be a drawback of syntheses starting from the chiral pool: you have to shoe-horn your synthetic route into the available starting materials. Another drawback of syntheses starting from the chiral pool is the fact that many natural compounds are only available as one enantiomer or, if both enantiomers are available, one is much more expensive than the other. You will see some ingenious ways of circumventing this problem later in the chapter, but we deal with a very simple one in the next section.

**Resolution can be used to separate enantiomers**

→ We will not explain resolution again here: turn to p. 322 for the details.



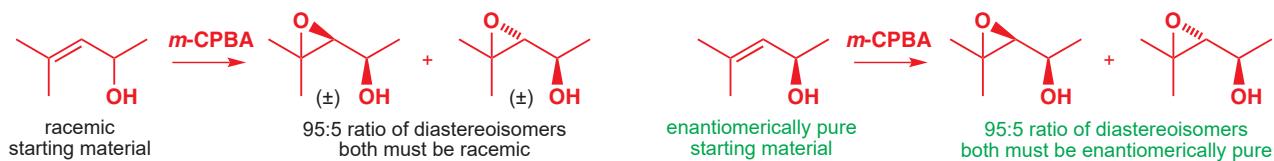
In Chapter 14 we introduced you to resolution as a means of separating enantiomers. Resolution requires an enantiomerically pure resolving agent, which must be a compound from the chiral pool or a simple derivative of that compound. When the Swiss company Cilag wanted one enantiomer of the unusual chiral amino acid in the margin in order to make some potential drug candidates, the chemists there decided the easiest way to get hold of it quickly and in large quantities was to make it in racemic form and then resolve it. It turned out that one of the two enantiomers of the protected derivative below forms a crystalline salt with cheap, readily available  $(-)$ -ephedrine, while the other remains in solution. Filtration and treatment with acid to remove the protecting group and protonate the acid gave them a single enantiomer of their target amino acid.



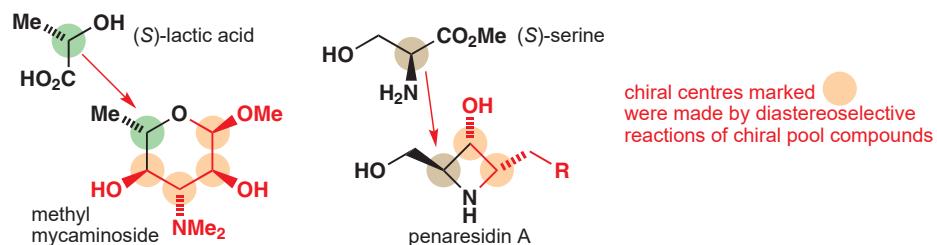
Of course, with resolution, there is a maximum yield of 50% because if you only want one enantiomer, the other is wasted. But there are many cases where you might want *both* enantiomers. You may need to test them both for biological activity, for example. In that case, resolution is ideal—in the example above the chemists at Cilag could get hold of the other enantiomer of the amino acid just by evaporating the mother liquors from the recrystallization. This is a big advantage of resolution: it lets you get both enantiomers using just one compound from the chiral pool.

## Chiral auxiliaries

In Chapter 33 we showed you methods for making single diastereoisomers using diastereoselective reactions. Diastereoselective reactions work just as well whether the starting material is racemic or enantiomerically pure—you get the same diastereoisomeric outcome in each case, but if you start with racemic material you get racemic product and if you start with enantiomerically pure material you get enantiomerically pure product. Here's an example, from p. 867:



So if you use a starting material from the chiral pool, you can build new chiral centres in enantiomerically pure form just by using diastereoselective reactions. We showed you two syntheses at the end of Chapter 33 using this idea: the chiral pool starting materials (*S*)-lactic acid and (*S*)-serine were converted to two natural products using a series of diastereoselective reactions to introduce further chiral centres into the molecules.



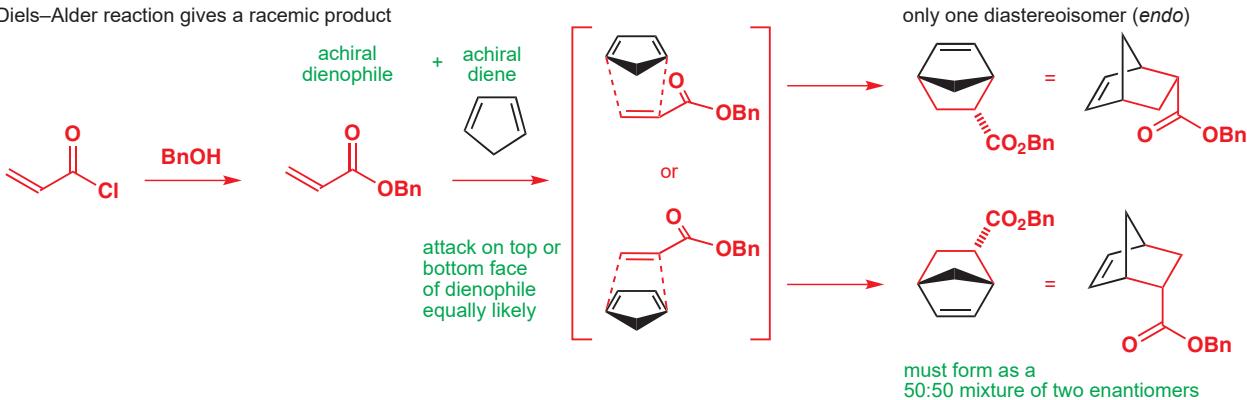
These syntheses are on pp. 872–875.

The syntheses rely on the fact that the structure of the chiral pool starting material is still there in the product. But the same idea can work even if the starting chiral compound is no longer part of the target you are making. In this case the chiral starting material is called a *chiral auxiliary*. Chiral auxiliaries are extremely versatile because they can be used to make a whole variety of target molecules in enantiomerically pure form. We will explain how they work with two examples.

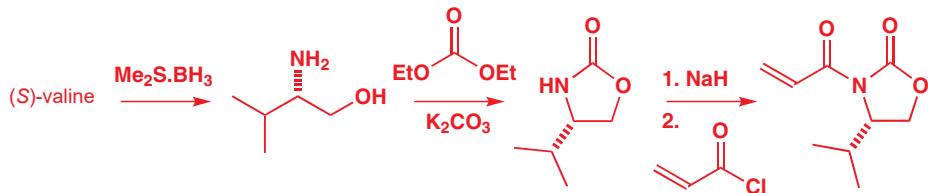
► Diels–Alder reactions of cyclopentadiene appear on p. 880.

The product of a Diels–Alder reaction between cyclopentadiene and benzyl acrylate must necessarily be racemic as both reagents are achiral. Although only one *diastereoisomer*—the *endo* product—is formed, it must be formed as an exactly 50:50 mixture of *enantiomers*. There is nothing to tell the diene whether to attack the top or the bottom face of the dienophile so it does both, each 50% of the time.

Diels–Alder reaction gives a racemic product

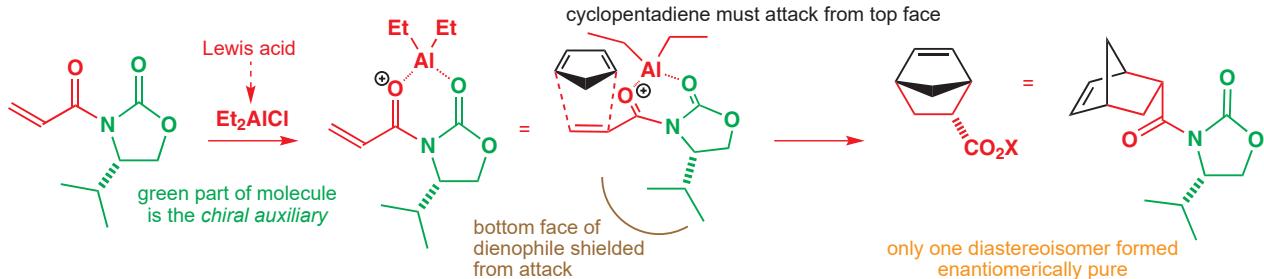


Now see what happens if we replace the achiral benzyl ester group of the dienophile with an amide derived from the amino acid valine. Here's the synthesis of such a dienophile using the amino acid reduction you saw on p. 1105.



As we discussed in Chapter 34, the presence of a Lewis acid increases the rate of Diels–Alder reactions, and in this case is also vital for high stereoselectivity.

The two faces of the double bond of the dienophile are now different because of the chiral centre: they are diastereotopic, and the diene can distinguish between them. If we now do the Diels–Alder reaction in the presence of a Lewis acid, Et<sub>2</sub>AlCl, the aluminium chelates the oxygen atoms of the dienophile to form the rigid and reactive structure shown below. The isopropyl group is held in such a way that its steric bulk prevents the diene attacking that face of the prochiral alkene. The diene has no choice but to attack from above, and only one of the possible diastereoisomeric products is formed.

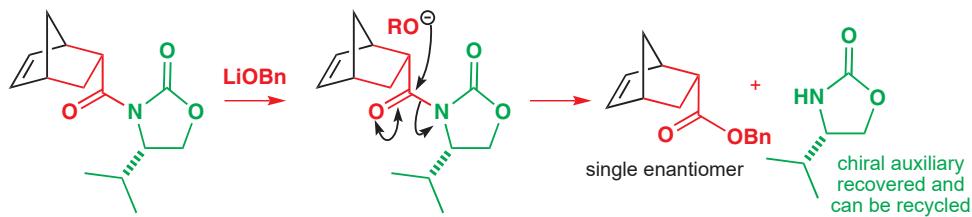


Interactive chiral auxiliary-controlled Diels–Alder reaction

We call the green valine-derived part of this molecule the *chiral auxiliary*—it assists the substrate to react in a diastereoselective way such that only one of the two possible products is allowed to form. The chiral auxiliary was enantiomerically pure to start with, so the product must be diastereoisomerically *and* enantiomerically pure.

Finally comes the step which shows the power of chiral auxiliary strategy: we just remove the chiral auxiliary from the product by treating with a nucleophile. The auxiliary can in principle be used again, but most importantly of all, the product obtained is just one of the two enantiomers we made in the racemic version of this reaction. This isn't a resolution—all

of these steps go in high yield—it is truly an enantioselective synthesis of the Diels–Alder product, using a chiral auxiliary to help us.



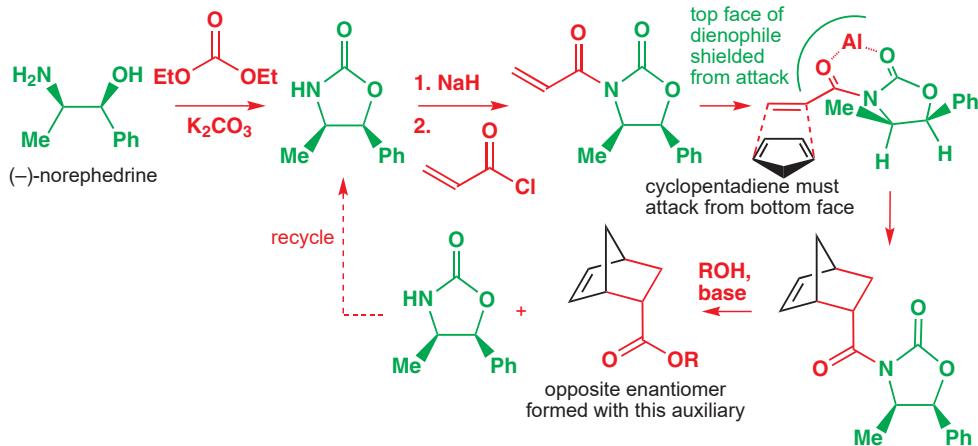
Overall, by sequential attachment of the auxiliary, diastereoselective reaction, and removal of the auxiliary we have made the same product but as a single enantiomer.

### • This is what we mean by a chiral auxiliary strategy

- 1 An enantiomerically pure compound (usually derived from a simple natural product like an amino acid), called a chiral auxiliary, is attached to the starting material.
- 2 A diastereoselective reaction is carried out, which, because of the enantiomeric purity of the chiral auxiliary, gives only one enantiomer of the product.
- 3 The chiral auxiliary is removed by, for example, hydrolysis, leaving the product of the reaction as a single enantiomer. The best chiral auxiliaries (of which the example above is one) can be recycled, so although stoichiometric quantities are needed, there is no waste.

We have introduced you to this chiral auxiliary before any other because it is more commonly used than any other. It is a member of the oxazolidinone (the name of the heterocyclic ring) family of auxiliaries developed by David Evans at Harvard University, and is easily and cheaply made from the amino acid (*S*)-valine. Even though it is cheap, it can be recycled. The last step of the route above regenerates the auxiliary ready for re-use.

The most versatile chiral auxiliaries should also be available as both enantiomers. For the valine-derived one here, this is not the case—(*R*)-valine is quite expensive since it is not found in nature. However, by starting with the naturally occurring (and cheap) compound nor-ephedrine, we can make an auxiliary that, although not enantiomeric with the one derived from (*S*)-valine, acts as though it were.



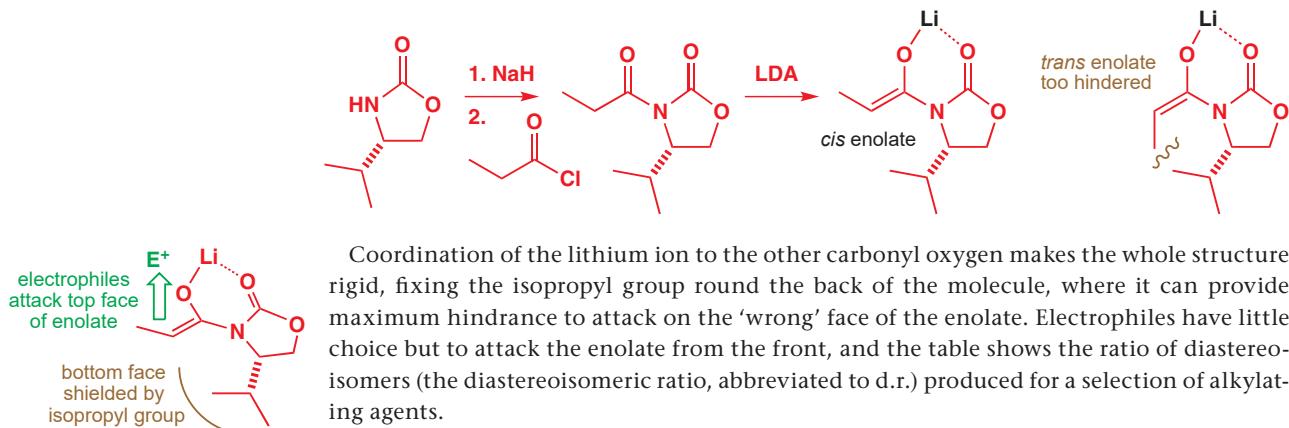
As the diagram shows, the two substituents of the auxiliary lie on the top face of the dienophile and force the cyclopentadiene this time to attack the bottom face. Now when the auxiliary is cleaved from the product the opposite enantiomer is formed. We can choose which enantiomer we want simply by choosing the right auxiliary for the job.

### Alkylation of enolates

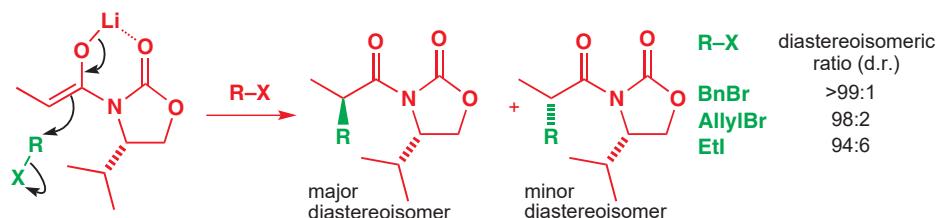
Chiral auxiliaries can be used in plenty of other reactions, and some of the most common are reactions of enolates. Evans's oxazolidinone auxiliaries are particularly appropriate here

► Enolates are a sort of alkene and can form as *cis* or *trans* geometrical isomers. One of the consequences of this is discussed in Chapter 33.

because they are readily turned into enolizable carboxylic acid derivatives. Treatment with base (usually LDA) at low temperature produces an enolate, the bulky auxiliary means that only the *cis* enolate forms: the *trans* enolate is too hindered.



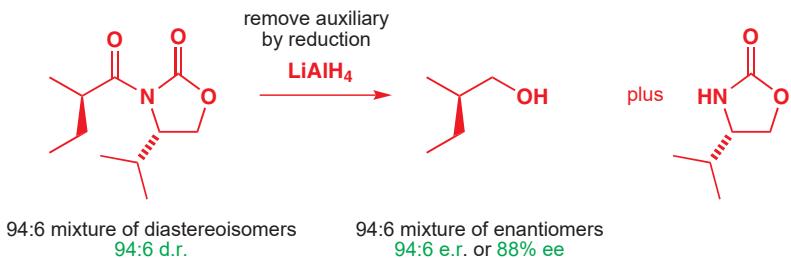
Coordination of the lithium ion to the other carbonyl oxygen makes the whole structure rigid, fixing the isopropyl group round the back of the molecule, where it can provide maximum hindrance to attack on the ‘wrong’ face of the enolate. Electrophiles have little choice but to attack the enolate from the front, and the table shows the ratio of diastereoisomers (the diastereoisomeric ratio, abbreviated to d.r.) produced for a selection of alkylating agents.



As you can see, none of these reactions is truly 100% diastereoselective and, indeed, only the best chiral auxiliaries (of which this is certainly one) give >98% of a single diastereoisomer. The problem with less than perfect diastereoselectivity is that, when the chiral auxiliary is removed, the final product is contaminated with some of the other enantiomer. A 94:6 ratio of diastereoisomers will result in a 94:6 ratio of enantiomers, or a sample of 94:6 e.r. (e.r. for enantiomeric ratio).

### Enantiomeric excess

Compounds that are neither racemic nor enantiomerically pure are usually called *enantiomerically enriched*. Chemists have two ways of referring to the ratio of enantiomers in an enantiomerically enriched sample. The first is the simple one we have just used: e.r. or enantiomeric ratio, expressed as two numbers adding to 100. More common, however, is to express this ratio as an *enantiomeric excess*. Enantiomeric excess (or ee) is defined as the excess of one enantiomer over the other, expressed as a percentage of the whole. So a 94:6 mixture of enantiomers consists of one enantiomer in 88% excess over the other, and we call it an enantiomerically enriched mixture with 88% ee. Why not just say that we have 94% of one enantiomer? Enantiomers are not like other isomers because they are simply mirror images. The 6% of the minor enantiomer can be paired with 6% of the major isomer to form a racemic mixture amounting to 12% of the total. The mixture contains 12% racemate and 88% of one enantiomer, hence 88% ee.



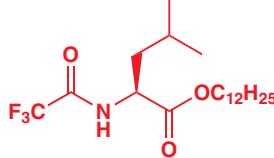
We will see shortly how we can make further use of the chiral auxiliary to increase the ee of the reaction products. But first, we should consider how to measure ee. One way is simply to measure the angle through which the sample rotates plane-polarized light. The angle of rotation is approximately proportional to the enantiomeric excess of the sample (see box). The problem with this method is that to measure an actual value for ee you need to know what rotation a sample of 100% ee gives, and that is not always possible. Also, polarimeter measurements are notoriously unreliable—they depend on temperature, solvent, and concentration, and are subject to massive error due to small amounts of highly optically active impurities.

### Is optical rotation proportional to enantiomeric excess?

Imagine you have a sample, A, of an enantiomerically pure compound—a natural product perhaps—and, using a polarimeter, you find that it has an  $[\alpha]_D$  of +10.0. Another sample, B, of the same compound, which you know to be *chemically* pure (perhaps it is a synthetic sample), shows an  $[\alpha]_D$  of +8.0. What is its enantiomeric excess? Well, you would have got the same value of 8.0 for the  $[\alpha]_D$  of B if you had mixed 80% of your enantiomerically pure sample A with 20% of a racemic (or achiral) compound with no optical rotation. Since you know that sample B is chemically pure, and is the same compound as A, it must therefore indeed consist of 80% enantiomerically pure material plus 20% racemic material, or 80% of one enantiomer plus 20% of a 1:1 mixture of the two enantiomers—which is the same as 90% of one enantiomer and 10% of the other, or 80% enantiomeric excess. Optical rotations can give a guide to enantiomeric excess—sometimes called *optical purity* in this context—but slight impurities of compounds with large rotations can distort the result and there are some examples where the linear relationship between ee and optical rotation fails because of what is known as the Horeau effect. You can read more about this in Eiel and Wilen, *Stereochemistry of organic compounds*, Wiley, 1994.

Chemists now usually use chromatography, or occasionally spectroscopy, to quantify ratios of enantiomers. You may think that this should be impossible—since enantiomers are chemically identical and have identical NMR spectra, how can chromatography or spectroscopy tell them apart? Well, again, they are identical *unless they are in a chiral environment*. We introduced HPLC on a chiral stationary phase as a way of separating enantiomers preparatively in Chapter 14. The same method can be used analytically—less than a milligram of chiral compound can be passed down a narrow column containing silica modified with a chiral additive. One enantiomer passes through the silica faster than the other; the two enantiomers are separated and the quantity of each can be measured (usually by UV absorption or by refractive index changes) and an ee derived. Gas chromatography can be used in the same way—the columns are packed with a chiral stationary phase such as the isoleucine derivative shown in the margin.

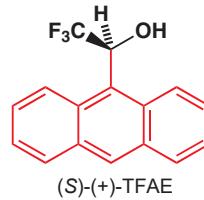
► This is the principle on which resolution relies: see p. 322.



gas chromatography with this chiral stationary phase allows enantiomers to be separated

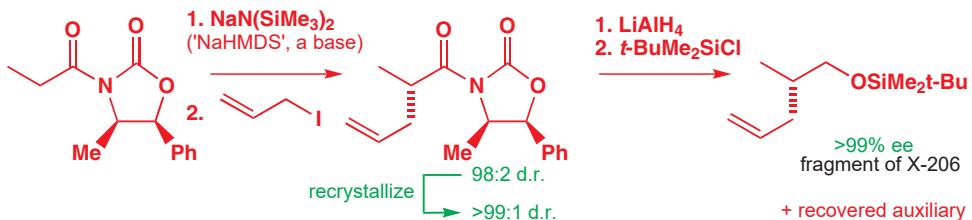


Another powerful method of discriminating between enantiomers is to add an enantiomerically pure compound to the NMR sample that simply forms a complex with the compound under investigation. The complexes formed from the two opposite enantiomers are diastereoisomeric, and therefore have different chemical shifts and, by integrating the NMR signals, the ratio of enantiomers can be determined. Among the most commonly used is this alcohol, 2,2,2-trifluoro-1-(9-anthryl)ethanol, or TFAE, which can both hydrogen-bond to and form



$\pi$ -stacked complexes with a range of functionalized compounds, and often splits NMR signals due to enantiomeric compounds very cleanly.

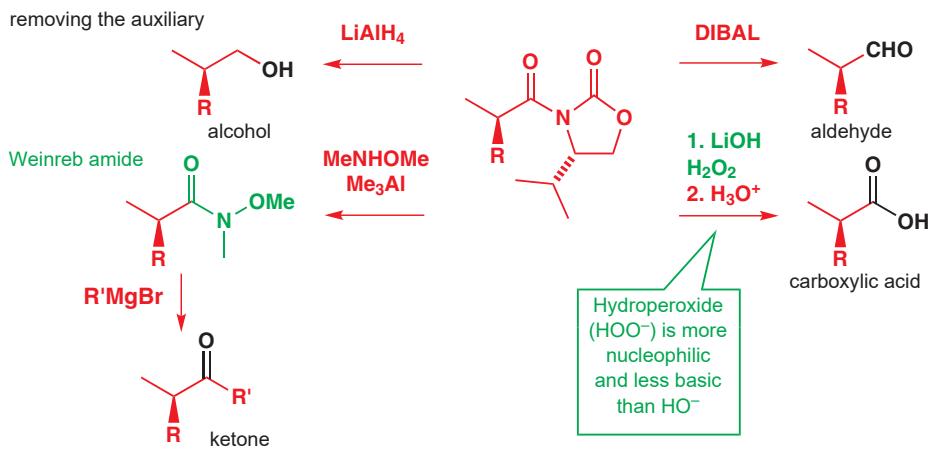
Time to go back to chiral auxiliaries. We pointed out that, although we want to get maximum levels of stereoselectivity in our chiral-auxiliary-controlled reaction, we may still have a small percentage of a minor diastereoisomer, which, once we have removed our chiral auxiliary, will compromise the ee of our final product. It is at this point that we can use a trick that essentially employs the chiral auxiliary in a secondary role as a resolving agent. Provided the products are crystalline, it will usually be possible to recrystallize our 94:6 mixture of diastereoisomers to give essentially a single diastereoisomer, rather like carrying out a resolution with an enormous head start. Once this has been done, the chiral auxiliary can be removed and the product may be very close to 100% ee. Of course, the recrystallization sacrifices a few percentage points of yield, but these are invariably much less valuable than the few percentage points of ee gained! Here is an example from the work of Evans himself. During his synthesis of the complex antibiotic X-206 he needed large quantities of the small molecule below. He decided to make it by a chiral-auxiliary-controlled allylation, followed by reduction to give the alcohol. The auxiliary needed is the one derived from norephedrine, and the reaction of the enolate with allyl iodide gives a 98:2 mixture of diastereoisomers. However, recrystallization converts this into an 83% yield of a single diastereoisomer in >99% purity, giving material of essentially 100% ee after removal of the auxiliary.



At this point we should also come clean about the asymmetric Diels–Alder reaction we introduced on p. 1108: it is not quite as selective as we implied—a minor diastereoisomer is formed in a 7% yield, with the major isomer accounting for 93%. But just one recrystallization gives >99% diastereoisomerically pure material in 81% yield.

This is one big bonus of using a chiral auxiliary—it's much easier to purify diastereoisomers than enantiomers and a chiral auxiliary-controlled reaction necessarily produces diastereoisomeric products.

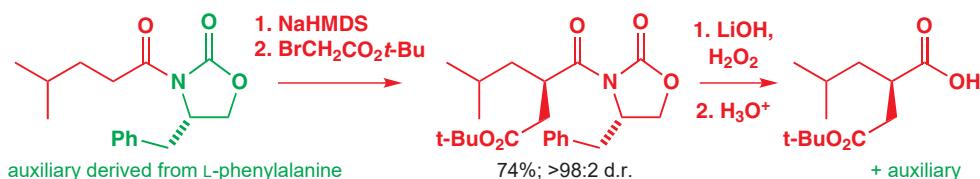
Both these examples of auxiliary-controlled alkylation make use of  $\text{LiAlH}_4$  reduction to the alcohol in the step which removes the auxiliary. You saw attack with an alkoxide above, and several other alternative methods are possible as well, summarized below. DIBAL ( $i\text{-Bu}_2\text{AlH}$ , p. 533) reduces the product to an aldehyde, while converting the product to a Weinreb amide (p. 219) makes formation of a ketone possible.



**Epimers** are pairs of diastereoisomers differing in configuration at just one chiral centre.

**Epimerization** is the interconversion of such diastereoisomers just as racemization is the interconversion of enantiomers.

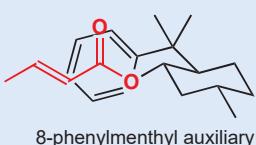
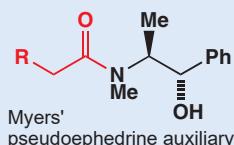
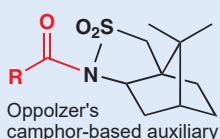
Simple hydrolysis under acid or basic conditions risks epimerizing the newly created chiral centre, and a good solution is to use the less basic, more nucleophilic hydroperoxide anion. This was the approach taken by chemists making this component of a collagenase inhibitor. Notice that this auxiliary is a variant based on L-phenylalanine.



These various ways of removing auxiliaries illustrate the ways in which it is possible to make a virtue out of one of their big disadvantages: chiral auxiliaries must first be attached to the compound under construction, and after they have done their job they must be removed. The best auxiliaries can be recycled, but even then there are still at least two ‘unproductive’ steps in the synthesis.

### Oxazolidinones are not the only auxiliaries

Other auxiliaries are also used, and the choice of auxiliary may depend not only on the selectivity of the reaction under investigation but also on the physical properties of the products. The camphor-based auxiliary of Oppolzer is reputed to confer crystallinity on its derivatives, while the pseudoephedrine auxiliary of Myers is cheap, readily available, and very easy to introduce. More bulky auxiliaries such as 8-phenylmenthol work well where control over long-range interactions, such as conjugate additions, are required.



 Interactive mechanism for  
Oppolzer's sultam in conjugate  
addition



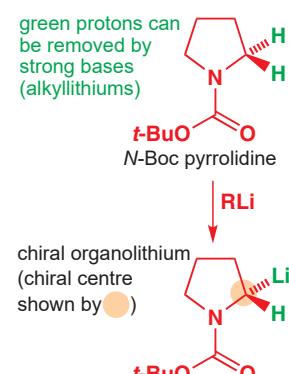
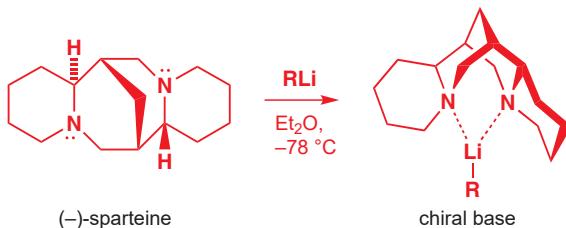
## Interactive mechanism for 8-phenylmenthol in Diels–Alder reaction

## Chiral reagents

A chiral auxiliary is a chiral molecule attached to the starting material of the reaction; diastereoselective reactions of compounds from the chiral pool are likewise controlled by chirality in the starting material, and we call this type of stereocontrol *substrate control*. But is it also possible for enantioselective reactions to be controlled by chiral *reagents*? For example, a typical achiral base will just remove a proton from a substrate, but an enantiomerically pure chiral base can select one of two enantiotopic protons and form a product enantioselectively. The product of course has to be chiral, so we can't use a chiral base to make planar enolates enantioselectively, for example, but we can use a chiral base to make chiral organolithiums.

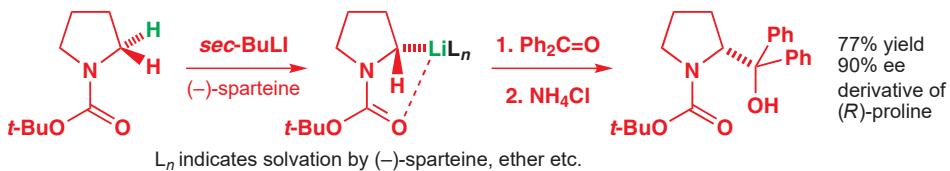
Alkylolithiums are sufficiently strong as bases to remove the protons adjacent to the nitrogen atom of *N*-Boc pyrrolidine, shown in the margin. The product of deprotonation is an organolithium which is a chiral molecule; the lithium-bearing carbon is chiral.

Alkyllithiums can be turned into chiral bases in quite a simple way—by complexation with a chiral ligand. A widely used example is the tetracyclic diamine ( $-$ )-sparteine. Sparteine's structure looks complex, but it is a relatively widely available natural product which folds around the lithium atom of an alkyllithium and places the base in a chiral environment.



This chiral base can now choose to remove from the pyrrolidine substrate just one of the enantiotopic protons adjacent to nitrogen, and form a chiral, enantiomerically enriched organolithium. The stereochemistry of the organolithium is preserved through its reactions with electrophiles such as the ketone shown here.

## Interactive mechanism for sparteine-mediated lithiation



One of the reasons this reaction is so useful is that the products happen to be derivatives of the less readily available (*R*)-proline. But, as with chiral auxiliaries, if you use a chiral reagent you need a full equivalent of the source of enantiomeric purity (here, (*-*)-sparteine) which can get prohibitively expensive on a large scale. It is for this reason that the real pinnacles of achievement in asymmetric synthesis make use of *asymmetric catalysis*, which we turn to next.

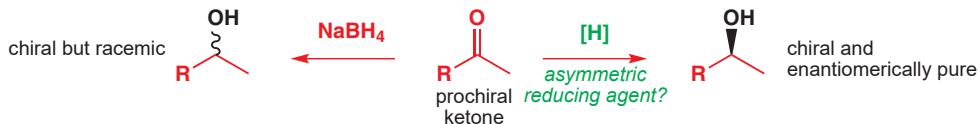
## Asymmetric catalysis

→ Look back at Chapters 31 and 33 (p. 820) if you need reminding about the terms prochiral, enantiotopic, and diastereotopic.

If we want to create a new chiral centre in a molecule, our starting material must have **pro-chirality**—the ability to become chiral in one simple transformation. The most common prochiral units that give rise to new chiral centres are the trigonal carbon atoms of alkenes and carbonyl groups, which become tetrahedral by addition reactions. In the last section you saw a prochiral, tetrahedral  $\text{CH}_2$  group becoming a chiral organolithium by enantioselective removal of one enantiotopic proton. Much more common are the reactions you saw in the section before that, where in every case a prochiral alkene (we can count enolates as alkenes for this purpose) reacted selectively on one face because of the influence of the chiral auxiliary, which made the faces of the alkene diastereotopic.

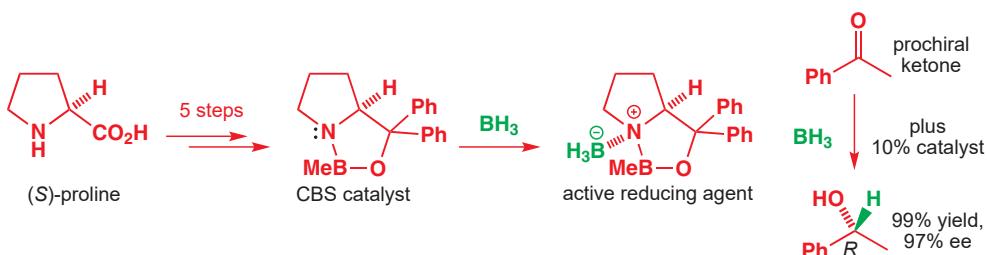
## Catalytic asymmetric reduction of ketones

One of the simplest transformations you could imagine of a prochiral unit into a chiral one is the reduction of a ketone. Although chiral auxiliary strategies have been used to make this type of reaction asymmetric, conceptually the simplest way of getting the product as a single enantiomer would be to use a chiral reducing agent—in other words, to attach the chiral influence not to the *substrate* (as we did with chiral auxiliaries) but to the *reagent*. We need an asymmetric version of  $\text{NaBH}_4$ .



One of the more widely used solutions to this challenge is the chiral borohydride analogue invented by Itsuno in Japan and developed by Corey, Bakshi, and Shibata. It is based on a stable boron heterocycle made from an amino alcohol derived from proline (see the box below for the synthesis), and is known as the CBS catalyst after its developers. The active reducing agent is generated when the heterocycle forms a complex with borane. Only catalytic amounts (usually about 10%) of the boron heterocycle are needed because borane is sufficiently reactive to reduce ketones only when complexed with the nitrogen atom. The rest of the borane just waits until a molecule of catalyst becomes free.

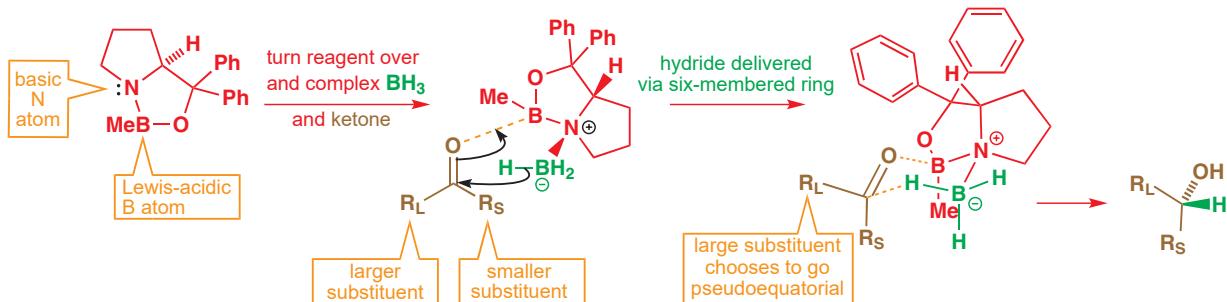
■ The fact that the reactions are catalytic in the heterocycle means that relatively little is needed. Note the distinction from chiral auxiliaries here: although auxiliaries are recoverable, they always have to be used in stoichiometric quantities and recovery is usually a separate step. Later in the chapter you will see catalytic reactions that use 1000 times less catalyst than this one.



CBS reductions are best when the ketone's two substituents are well-differentiated sterically—just as Ph and Me are in the example above. The reaction works because the heterocyclic

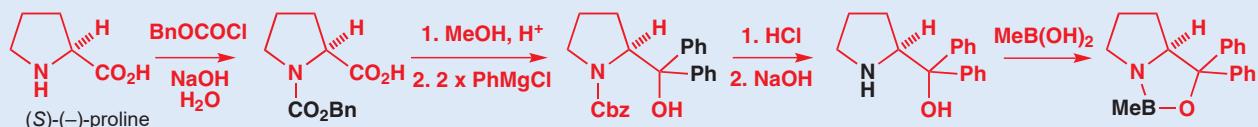
catalyst brings together the borane (which complexes to its basic nitrogen atom) and the carbonyl compound (which complexes to its Lewis-acidic boron atom). Complexation activates both partners towards reaction: donating electron density to the borane is essential to persuade it to transfer hydride, and withdrawing electron density from the carbonyl group makes it electrophilic enough to react with a weak hydride source. The hydride is delivered via a six-membered cyclic transition state, with the enantioselectivity arising from the preference of the larger of the ketone's two substituents ( $R_L$ ) for the pseudoequatorial position on this ring.

Interactive asymmetric reduction of ketone with CBS catalyst



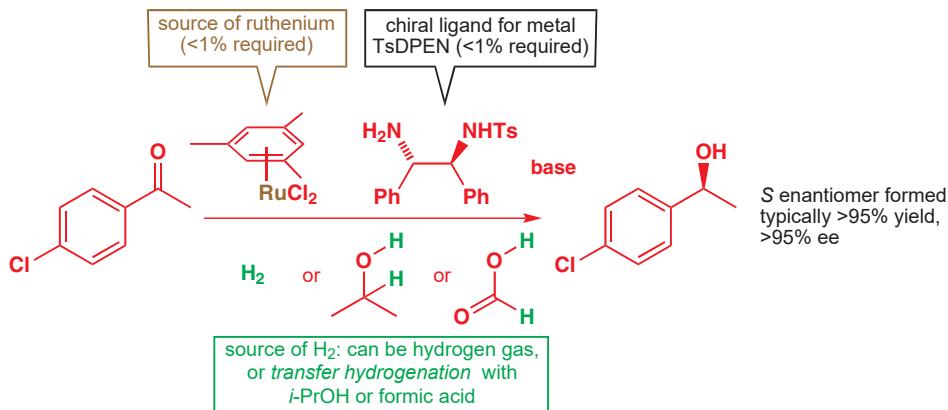
### Making the CBS catalyst

To make the CBS heterocycle,  $(S)$ -proline has to be protected as its  $N$ -Cbz derivative (Chapter 23) and converted to its methyl ester. Esters react with Grignard twice to give tertiary alcohols (Chapter 10), so  $\text{PhMgBr}$  followed by deprotection gives the amino alcohol needed. Condensation with methylboronic acid ( $\text{MeB(OH)}_2$ ) gives the stable catalyst.



To make the other enantiomer, you would need the rather more expensive 'unnatural'  $(R)$ -proline, which you can make by the method of p. 1114, but in such a case you might consider using one of the alternative reduction methods described below.

Until recently, the CBS reagent was one of the most commonly used asymmetric reducing agents for ketones. But in the early years of the 21st century a new reaction has taken over that role—one in which the job of bringing together the ketone and the reducing agent is taken by an atom of ruthenium. The ruthenium is added as  $\text{Ru(II)}$  in a 16-electron complex (see p. 1116) with an aromatic compound such as 1,3,5-trimethylbenzene (known as mesitylene). A chiral ligand is needed—the diamine derivative shown here is best. Only very small amounts (often  $\ll 1\%$ ) of the catalyst and ligand are required, which is a good thing as both are much more expensive than the reagents in the CBS reduction. The reducing agent itself can be hydrogen or, more conveniently, a more easily handled source of hydrogen atoms such as isopropanol (which gets oxidized to acetone) or formic acid (which gets oxidized to carbon dioxide). Here's a typical example; we will explain how it works shortly.



This revolution in asymmetric catalysis using chiral complexes of transition metals was made possible principally by the work of Ryoji Noyori (who developed the Ru- and Rh-catalysed reductions we describe in this chapter) and of K. Barry Sharpless (who developed the Os- and Ti-catalysed oxidations). This work won Noyori and Sharpless the Nobel Prize for Chemistry in 2001, along with William Knowles (who was the first to apply metal-catalysed asymmetric reactions to industrial targets).

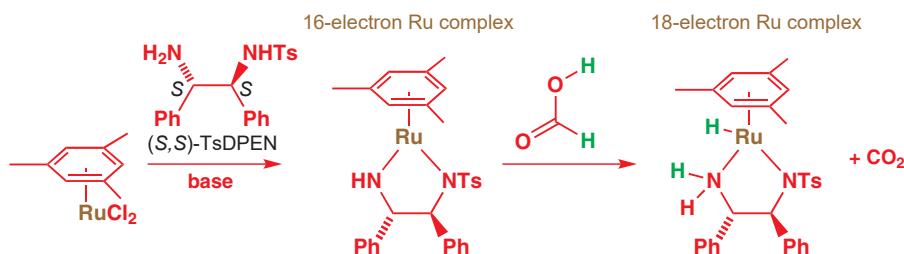
■ This section discusses several reactions of organometallic compounds. In order to understand their mechanisms you must be familiar with the terminology associated with organometallic complexes, such as how to 'count electrons', described in Chapter 40.

 Interactive mechanism for ruthenium-catalysed ketone hydrogenation

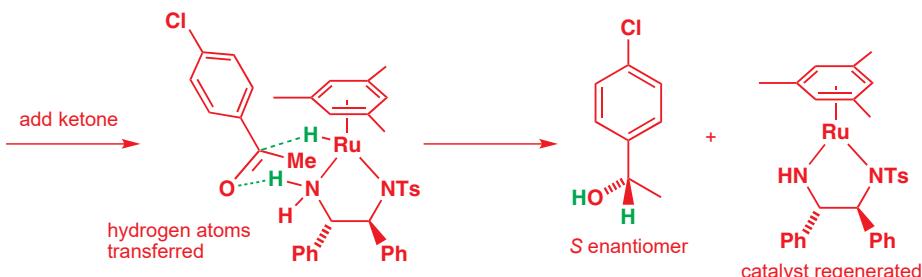
■ To show how fast this area is moving, we can quote from the first edition of this textbook, published in 2001: 'You would not normally choose catalytic hydrogenation for reducing a carbonyl group to an alcohol and, indeed, carbonyl reductions using hydrogenation with a chiral catalyst are not usually very enantioselective.' A lot has changed in little more than a decade.

You have met several reactions of ruthenium complexes, especially in Chapters 38 and 40, where you saw ruthenium carbenes catalysing the metathesis of alkenes. Ruthenium is one of a select group of transition metals (Pd, Ru, Rh, Cu, Os, and Ti being the others) which play an important role in asymmetric catalysis. The key to their success is the transition metal coordination chemistry we looked at in the last chapter: the metals can act as coordination sites for substrates, and by using other ligands which are chiral and enantioERICALLY pure, the reactions they catalyse can be made to take place in an asymmetric environment.

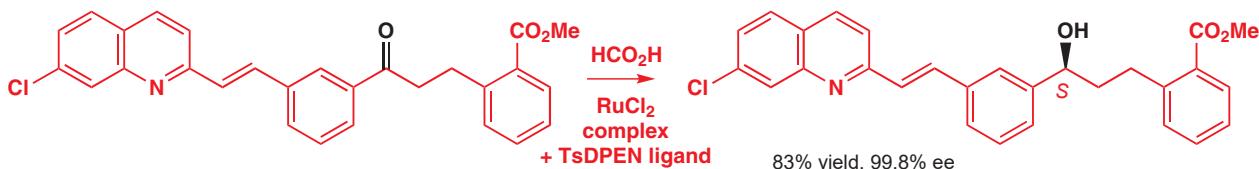
The ruthenium-catalysed reduction of ketones starts with coordination of the tosyl-diamine ligand ((S,S)-N-toluenesulfonyl 1,2-phenylenediamine, or 'TsDPEN') to the ruthenium metal. This is a 16-electron complex, and can be reduced by formic acid to an 18-electron ruthenium hydride.



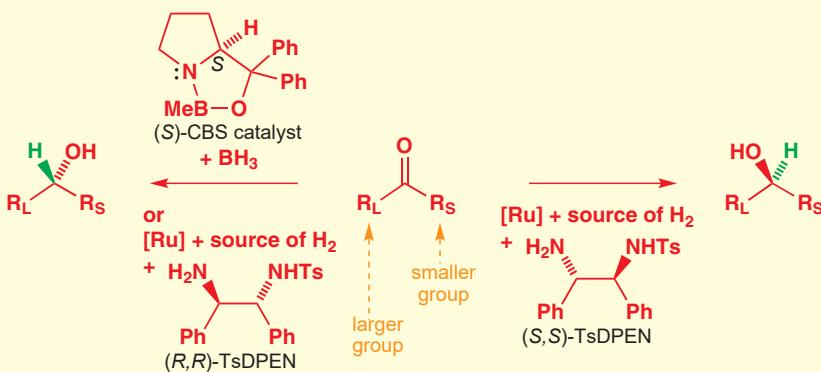
Now comes the reduction. Provided the ketone approaches the ruthenium complex in the right orientation, with the smaller methyl group tucked in under the ruthenium and the larger aryl group pointing away from the bulky ligands, the 18e complex can transfer to the carbonyl group simultaneously  $\text{H}^-$  from Ru and  $\text{H}^+$  from the protonated nitrogen. The chiral ligand means that the alcohol is formed as a single enantiomer, and the ruthenium catalyst is regenerated.



The reduction shown below is particularly important because it generates a late intermediate in the industrial synthesis of the anti-asthma drug montelukast (Singulair). Several methods have been used, but in 2008 chemists at the Croatian pharmaceutical company Pliva patented a method using the ruthenium catalyst with a derivative of TsDPEN as a ligand to give the product in 83% yield and 99.8% ee on a scale of several kilograms.

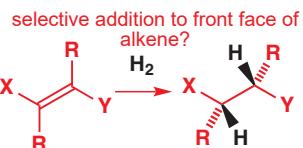
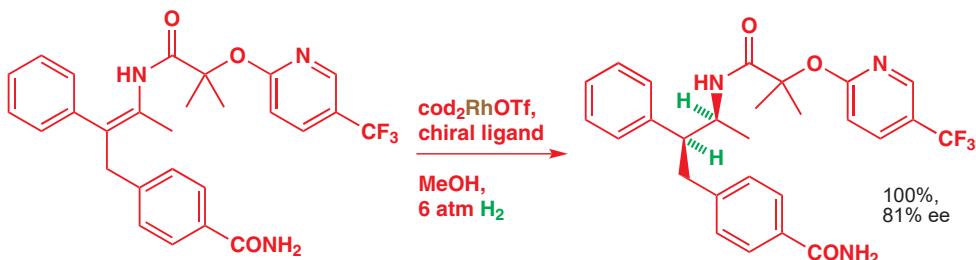


● Two methods for reducing carbonyl compounds enantioselectively



### Catalytic asymmetric hydrogenation of alkenes

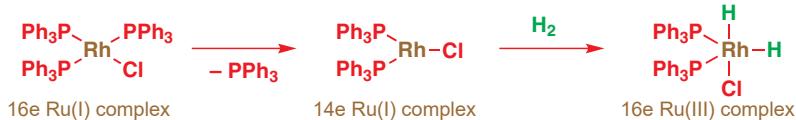
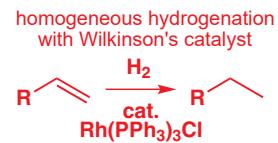
Reduction of a ketone can give a chiral secondary alcohol, but reduction of an alkene by addition of hydrogen to one of its two enantiotopic faces can give all sorts of products, creating either one or two chiral centres, depending on the substituents on the alkene. By way of illustration (and explanation will follow soon) the alkene hydrogenation below creates, in one step, the two chiral centres of a precursor to the anti-obesity drug taranabant. A single diastereoisomer is formed by *syn* addition of hydrogen, and a chiral ligand ensures that one enantiomer is formed preferentially.



■ cod is the ligand cyclooctadiene, and 6 atmospheres pressure of H<sub>2</sub> is used.

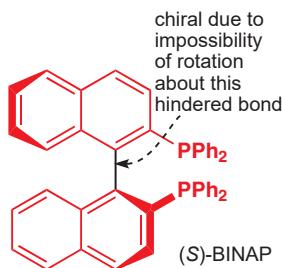
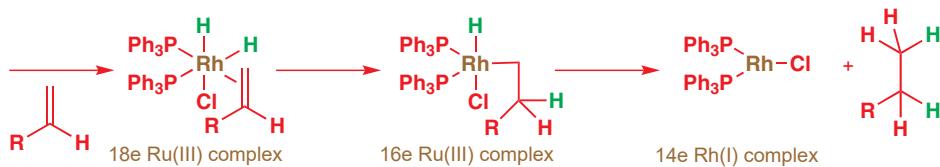
You have seen numerous hydrogenations of alkenes using hydrogen over a solid catalyst of palladium supported on charcoal ('heterogeneous hydrogenation'), but catalytic asymmetric hydrogenation of alkenes uses a different type of catalyst—a soluble complex, often of Ru or Rh with phosphine-containing ligands. The substrates for asymmetric alkene hydrogenation are also more limited than those for hydrogenation with Pd/C because they must carry a functional group close to the alkene, allowing coordination to the transition metal catalyst. In the example above, that functional group is the amide directly adjacent to the alkene.

The inspiration for these catalysts came from the work of Wilkinson in London in the 1960s, who showed that RhCl(PPh<sub>3</sub>)<sub>3</sub> (known as Wilkinson's catalyst) promoted *homogeneous* hydrogenation of alkenes (i.e. during the reaction there is only one, solution, phase). Wilkinson's catalyst is a 16-electron complex of Rh(I), and it works as a catalyst because it can easily lose one of the phosphine ligands to form a 14-electron complex. This undergoes addition of H<sub>2</sub>, giving a 16-electron Ru(III) complex.



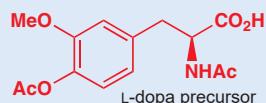
▶ See p. 1074 for more on Wilkinson's catalyst.

The complex is still coordinatively unsaturated, so an alkene can form a  $\pi$  complex with a full complement of 18 electrons. Migratory insertion of one of the hydrogen atoms, followed by reductive elimination, gives back the 14-electron Rh complex and the reduced alkane.



■ The detailed mechanism of this reaction is too complicated for us to examine here. Unusually, it involves two diastereoisomeric complexes, of which the more reactive is the one which is less favoured.

### Industrial synthesis of L-dopa



A related hydrogenation to give the product above, using a different catalyst, was developed by William Knowles at Monsanto. This hydrogenation was the first demonstration of the use of asymmetric catalysis in the synthesis of a chiral drug, and Knowles shared the Nobel Prize in 2001 with Noyori and Sharpless.

The conceptual advance which allows this sort of hydrogenation to become asymmetric is the replacement of the two achiral triphenylphosphine ligands of Wilkinson's catalyst with chiral phosphine ligands. Notice that two of the triphenylphosphines remain coordinated through the whole reaction mechanism, so by doing this we can ensure that the Rh always remains in a chiral environment.

The usual solution is to use one chiral molecule containing two phosphorus atoms, and the most important of these is BINAP. BINAP is a chelating diphosphine: the metal sits between the two phosphorus atoms, firmly anchored in a chiral environment. The chirality here is of an unusual sort, since BINAP, which you met in Chapter 14 (p. 319), has no chiral centres. It is one of the class of chiral molecules, known as *atropisomers*, whose chirality arises from the inability of the bond between the two naphthalene rings to rotate.

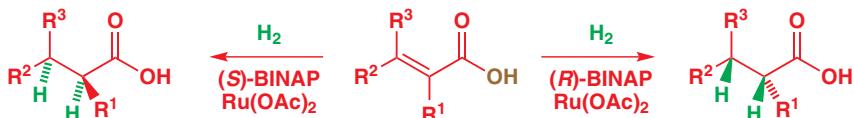
Incorporating (S)- or (R)-BINAP into a hydrogenation with Rh can lead to high enantiomeric excesses in the products because during the migratory insertion step the complex is forced to transfer hydrogen to only one of the two possible enantiotopic faces of the alkene. As we remarked before, asymmetric hydrogenations require a functional group which can coordinate to the metal, and with Rh the best substrates are *N*-acyl enamines. Those of the type shown below give excellent results, and usefully with (S)-BINAP the products are protected amino acids of the opposite enantiomeric series to those found in nature.



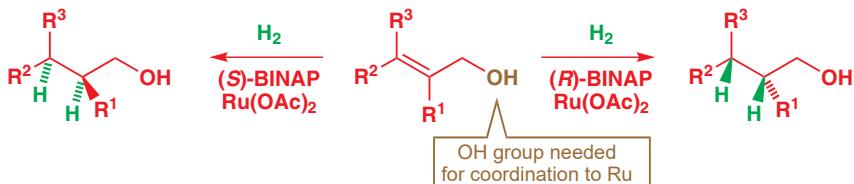
It is even economical for the more expensive of the natural amino acids to be made synthetically by this type of reaction rather than isolated from natural sources—phenylalanine, which is of industrial importance as a component of the artificial sweetener aspartame (NutraSweet), is manufactured using enantioselective hydrogenation.

Noyori found that using ruthenium instead of rhodium broadens greatly the scope of the substrates that will undergo asymmetric hydrogenation. They still need a functional group—usually the OH group of an alcohol or a carboxylic acid—to allow coordination to the metal, but the alkene itself can be a simple allylic alcohol or unsaturated acid derivative. BINAP is again a good ligand, and of course by choosing which enantiomer of BINAP you use you can choose which enantiomer of the product you get.

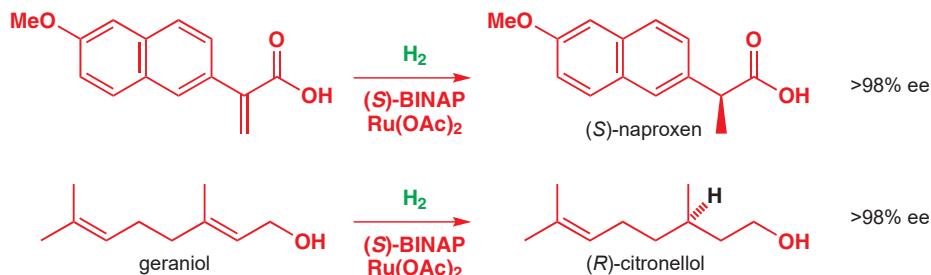
Ru-catalysed asymmetric hydrogenation of unsaturated carboxylic acids



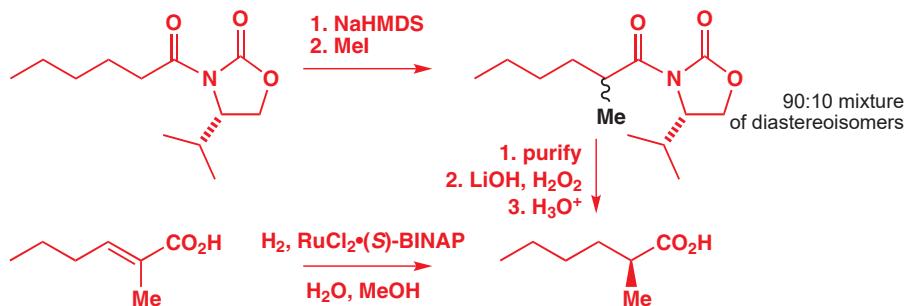
Ru-catalysed asymmetric hydrogenation of allylic alcohols



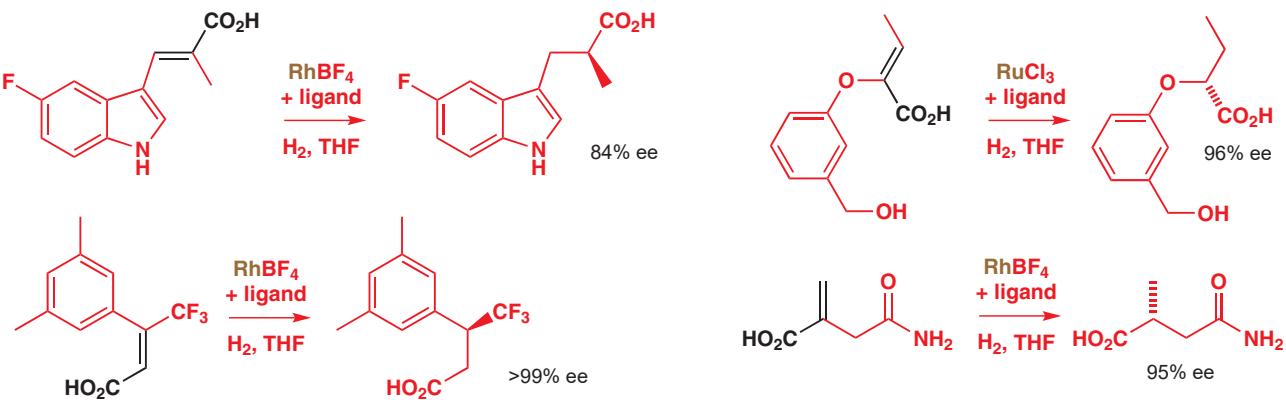
Two important industrial asymmetric syntheses which routinely use this chemistry are the production of the painkiller (*S*)-naproxen and the synthetic intermediate and perfumery compound (*R*)-citronellol. It is gratifying to note that this chemistry, using <1% of Ru, gives citronellol in higher enantiomeric purity than many natural sources of the same compound!



Reduction of unsaturated carboxylic acids gives products that you might alternatively think of making by auxiliary-controlled alkylation methods. When the NutraSweet company needed this chiral branched carboxylic acid as a single enantiomer, they initially used the auxiliary methods of p. 1110 to make a small amount, but they found that ruthenium-catalysed hydrogenation was greatly to be preferred on a large scale: just 22 g of the ruthenium-(*S*)-BINAP complex is needed to produce 50 kg of product with 90% ee.

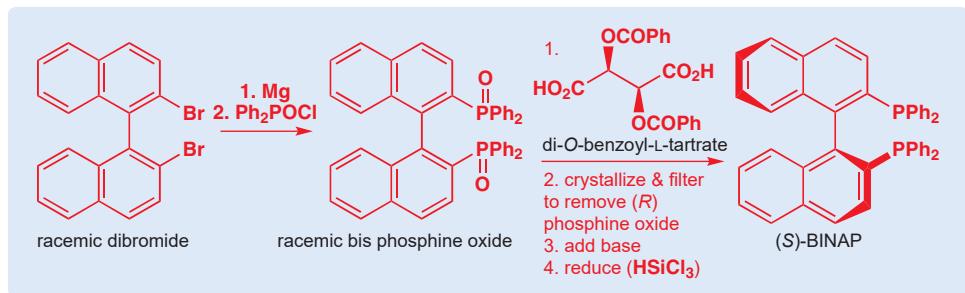


In the last 20 years, the variety of ligands available for rhodium and ruthenium-catalysed hydrogenations has increased to the point where the right combination of metal and ligand will reduce almost any unsaturated carboxylic acid derivative in high enantiomeric excess. Details are beyond the scope of this book, but we leave you with four examples, all from industrial drug syntheses, to illustrate how versatile the method can be.



### Resolution of BINAP

BINAP is not derived from a natural product, and has to be synthesized in the laboratory and resolved using a naturally derived resolving agent. The scheme shows one method by which enantiomerically pure BINAP may be made—the resolution step is unusual because it relies on formation of a molecular complex, not a salt. The bis phosphine oxide of (*S*)-BINAP co-crystallizes with di-*O*-benzoyl-L-tartrate, leaving the (*R*)-phosphine oxide in solution. Base releases the pure (*R*)-phosphine oxide that is resolved, which is then reduced to the phosphine with trichlorosilane.

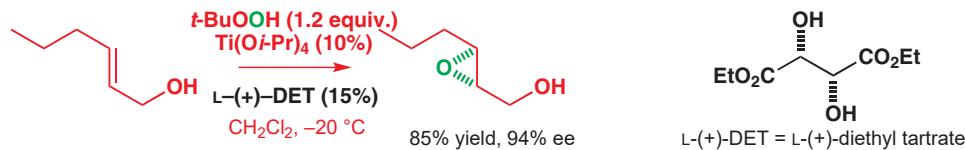


### Asymmetric epoxidation

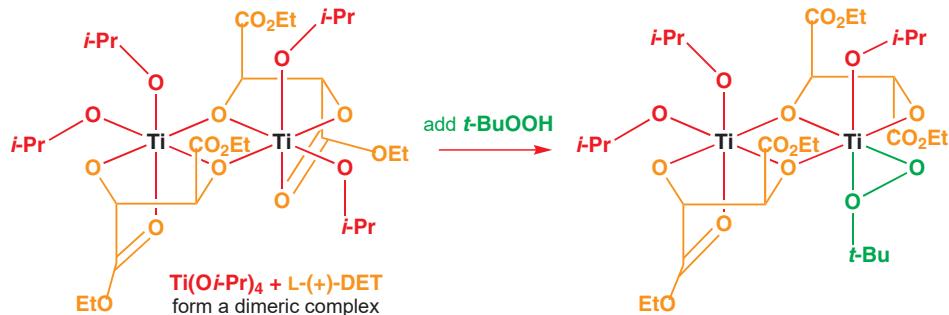
K. B. Sharpless (1941–) studied at Stanford and was first appointed at MIT but is now at the Scripps Institute in California. His undoubted claim to fame rests on the invention of no fewer than three reactions of immense significance: asymmetric epoxidation (AE) and asymmetric dihydroxylation (AD) are discussed in this chapter. The third reaction, asymmetric aminohydroxylation (AA), has still to reach the perfection of the first two.

Asymmetric *hydrogenation* of an alkene can create two new chiral centres, but introduces no new functionality as it does so. Asymmetric *oxidation* of an alkene is different: it can create two new chiral centres and two new functional groups at the same time. We will now look at two examples of asymmetric oxidation, both products of the laboratories of Professor Barry Sharpless.

The first of Sharpless's reactions is an oxidation of alkenes by asymmetric epoxidation. You met vanadium as a transition-metal catalyst for epoxidation with *t*-butyl hydroperoxide in Chapter 32, and this new reaction makes use of titanium, as titanium tetrakisopropoxide, Ti(O*i*-Pr)<sub>4</sub>, to do the same thing. Sharpless and his co-worker Tsutomu Katsuki surmised that by adding a chiral ligand to the titanium catalyst they might be able to make the reaction asymmetric. The ligand that works best is diethyl tartrate, and one example of the reaction is shown below.

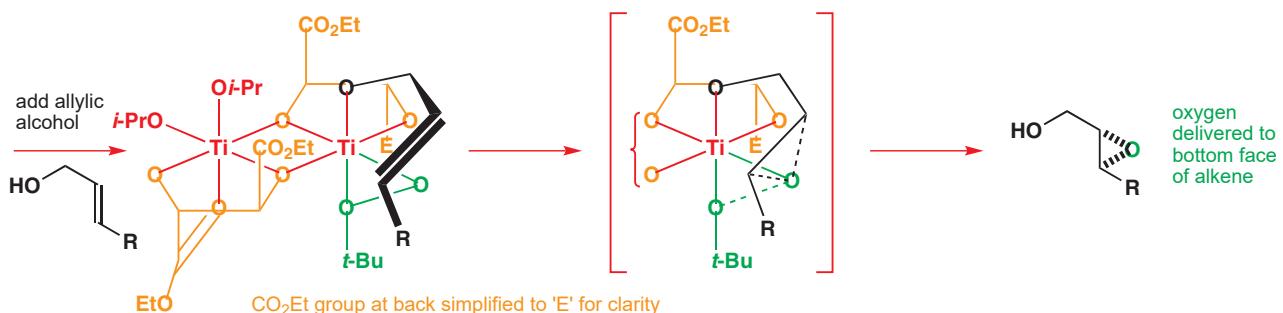


Transition-metal-catalysed epoxidations work only on allylic alcohols, so this is a limitation of the method, but otherwise there are few restrictions on what can be epoxidized enantioselectively, and when this reaction was discovered in 1981 it was by far the best asymmetric reaction known. Because of its importance, a lot of work went into discovering exactly how the reaction worked, and the scheme below shows what is believed to be the active complex, formed from two titanium atoms bridged by two tartrate ligands (shown in orange). Each titanium atom retains two of its isopropoxide ligands and is coordinated to one of the carbonyl groups of the tartrate ligand. The reaction works best if the titanium and tartrate are left to stir for a while so that these dimers can form cleanly. When the oxidizing agent (*t*-BuOOH, shown in green) is added to the mixture, it displaces one of the remaining isopropoxide ligands and one of the tartrate carbonyl groups.



For this oxidizing complex to react with an allylic alcohol, the alcohol must become coordinated to the titanium too, displacing a further isopropoxide ligand. Because of the shape

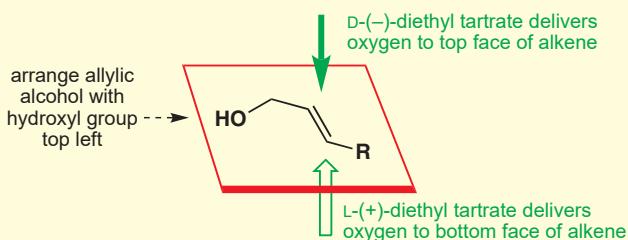
of the complex the reactive oxygen atom of the bound hydroperoxide has to be delivered to the lower face of the alkene (as drawn), and the epoxide is formed in high enantiomeric excess. Displacement of the product by another molecule of hydroperoxide starts the cycle again.



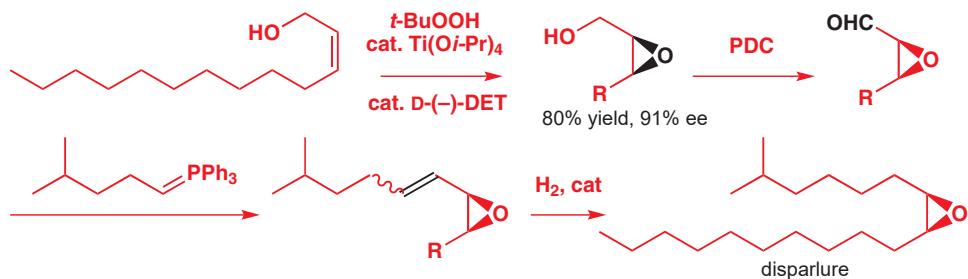
Different allylic alcohols coordinate in the same way to the titanium and reliably present the same enantiotopic face to the bound oxidizing agent, and the preference for oxidation with L-(+)-DET is shown in the schematic diagram below. Tartrate is ideal as a chiral ligand because it is available relatively cheaply as either enantiomer. L-tartrate is extracted from grapes; D-(-)-tartrate is rarer and more expensive, but still cheap by the standards of some of the bisphosphine ligands used in the last section. By using D-(-)-tartrate it is, of course, possible to produce the other enantiomer of the epoxide equally selectively.

Interactive mechanism for the Sharpless epoxidation of allylic alcohols

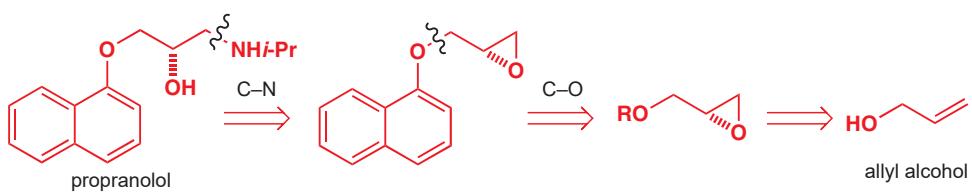
### ● Enantioselectivity in the Sharpless asymmetric epoxidation



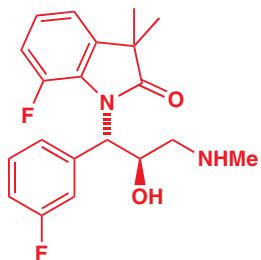
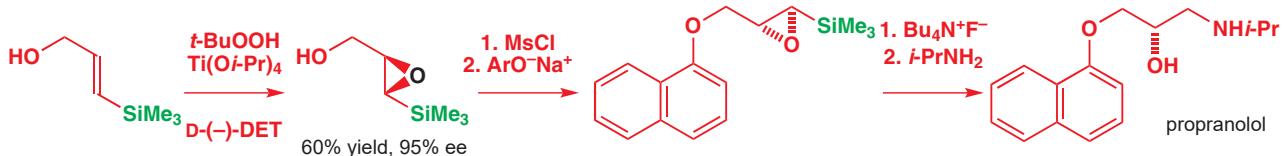
Sharpless also found that this reaction works with only a catalytic amount of titanium-tartrate complex because the reaction products can be displaced from the metal centre by more of the two reagents. The catalytic version of the asymmetric epoxidation is well suited to industrial exploitation, and the American company J. T. Baker has employed it to make synthetic disparlure, the pheromone of the gypsy moth, by oxidation of the epoxy alcohol to an aldehyde with pyridinium dichromate (PDC) (p. 543), Wittig reaction (p. 689), and hydrogenation.



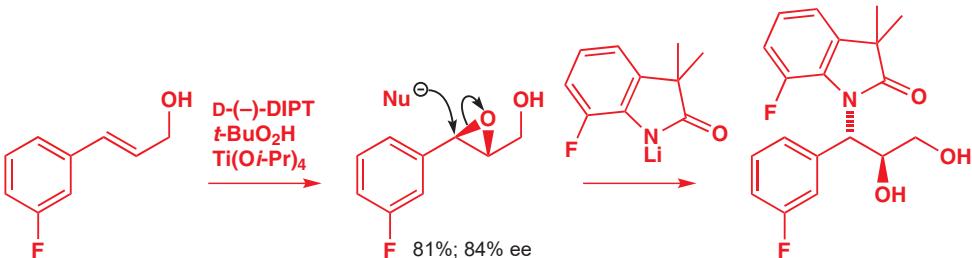
Not many target molecules are themselves epoxides, but the great thing about the epoxide products is that they are highly versatile—they react with many types of nucleophiles to give 1,2-disubstituted products. You met the chiral beta-blocker drug propranolol in Chapter 28, and its 1,2,3-substitution pattern makes it a good candidate for synthesis using asymmetric epoxidation.



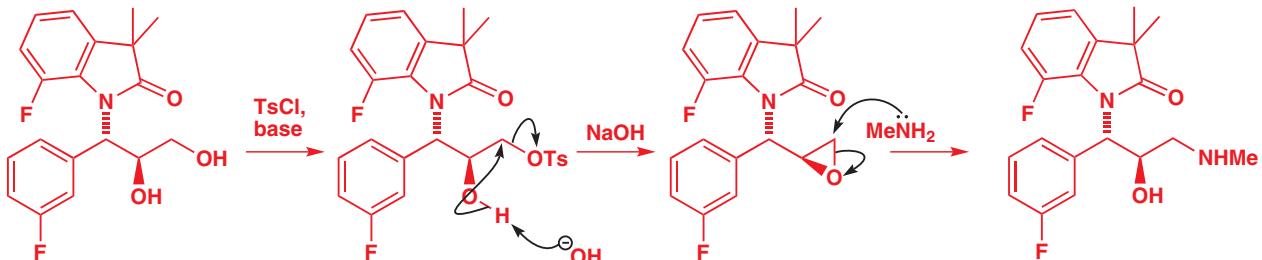
Unfortunately, the obvious starting material, allyl alcohol itself, gives an epoxide that is hard to handle, so Sharpless, who carried out this synthesis of propranolol, used this silicon-substituted allylic alcohol instead. The hydroxyl group was mesylated and displaced with 1-naphthoxide and, after treatment with fluoride to remove the silicon, the epoxide was opened with isopropylamine.



Chemists at the drug company Wyeth needed the amine shown in the margin. The 1,2,3-functional group pattern led them to think of using the Sharpless asymmetric epoxidation, and epoxidation of a fluorinated allylic alcohol using D-(-)-diisopropyl tartrate (DIPT) gave them the enantiomer they wanted with slightly better selectivity than diethyl tartrate. The benzylic end of the epoxide is more reactive towards nucleophilic substitution, and in the presence of  $\text{Ti}(\text{O}-\text{i-Pr})_4$ , this time simply acting as a Lewis acid, the lithiated heterocycle opens the epoxide with inversion of configuration.

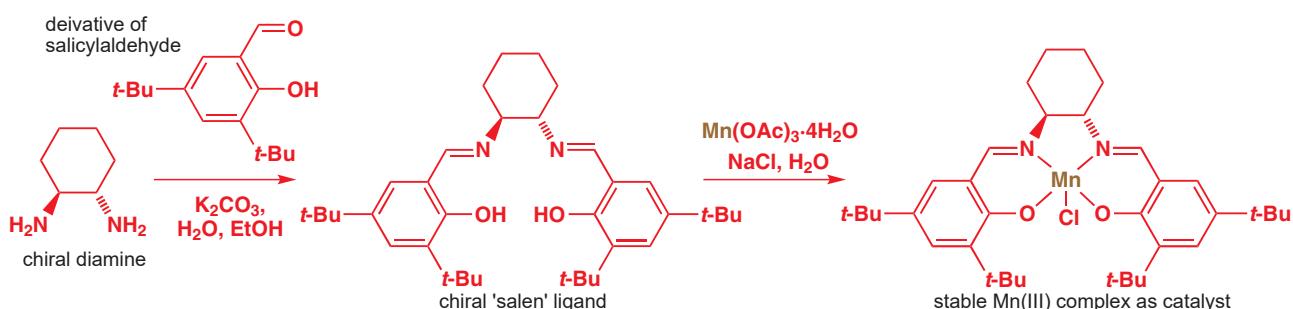


Finally, it's necessary to bring in the amino group, and this can be done by tosylating the less hindered primary hydroxyl group selectively, closing to an epoxide in base, and then reopening the epoxide at the less hindered terminal position with methylamine.

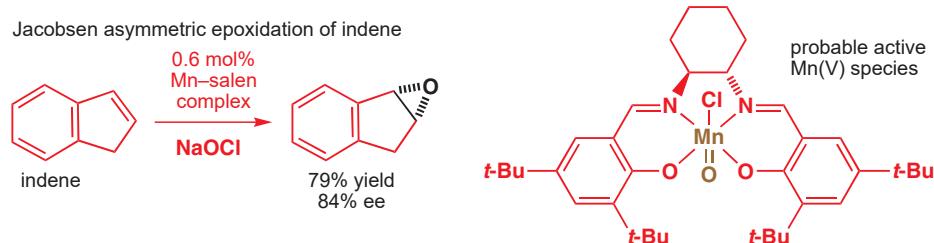


The Sharpless asymmetric epoxidation is reliable, but it works only for allylic alcohols. There is an alternative, however, which works with simple alkenes. The method was developed by Eric Jacobsen and employs a manganese catalyst with a chiral ligand built from a simple diamine. The diamine is not a natural compound and has to be made in enantiomeric form by resolution, but at least that means that both enantiomers are readily available. The diamine is condensed with a derivative of salicylaldehyde to make a bis-imine known as a 'salen'.

■ 'Salen' is an abbreviation of salicylidenediamine and simpler salens had long been used as tetradentate ligands for coordination chemistry.



Mn(III) sits neatly in a tetracoordinate pocket in the ligand, and catalyses the epoxidation of simple alkenes by sodium hypochlorite, NaOCl, ordinary domestic bleach. Best results are obtained when the alkenes are *cis* (although an alternative range of ligands, developed by Tsutomu Katsuki, work well with *trans* alkenes), and one of the most significant applications of the Jacobsen epoxidation is with indene, which gives an epoxide in 84% ee with <1% of the catalyst. The mechanism of the reaction is complex and not fully understood, although it probably involves a Mn(V) oxo species and may involve radical intermediates.

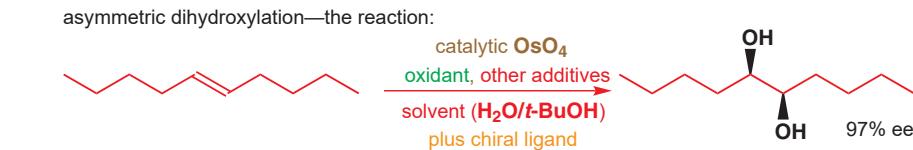


This epoxide plays a starring role in the synthesis of the anti-HIV compound indinavir: see Chapter 43.

Together, the epoxidations of Sharpless, Jacobsen, and Katsuki, plus others we do not have space to cover, provide valuable solutions to many synthetic problems—in particular because epoxides are such useful reactive synthetic intermediates. But no epoxidation reaction is as general as the oxidation reaction we cover next.

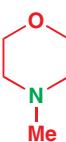
## Asymmetric dihydroxylation

This alternative asymmetric oxidation really is probably the best asymmetric reaction of all. It is an asymmetric version of the *syn* dihydroxylation of alkenes by osmium tetroxide. Here is an example—although the concept is quite simple, the recipe for the reactions is complicated so we need to approach it step by step.

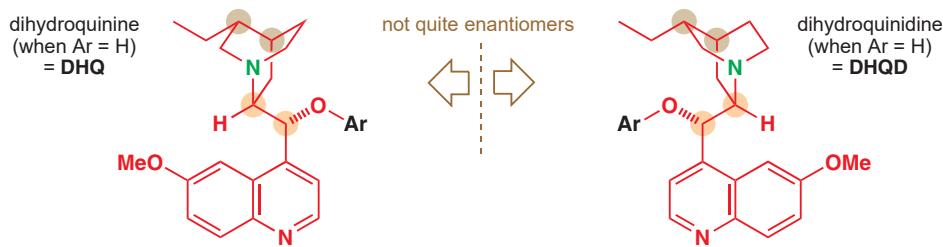


The active reagent is based on osmium(VIII) and is used in just catalytic amounts. This means that there has to be a stoichiometric quantity of another oxidant to reoxidize the osmium after each catalytic cycle— $K_3Fe(CN)_6$  is most commonly used. Because  $\text{OsO}_4$  is volatile and toxic, the osmium is usually added as  $K_2\text{OsO}_2(\text{OH})_4$ , which forms  $\text{OsO}_4$  in the reaction mixture. The ‘other additives’ include  $K_2\text{CO}_3$  and methanesulfonamide ( $\text{MeSO}_2\text{NH}_2$ ), which increases the rate of the reaction by regenerating the catalyst at the end of each catalytic cycle.

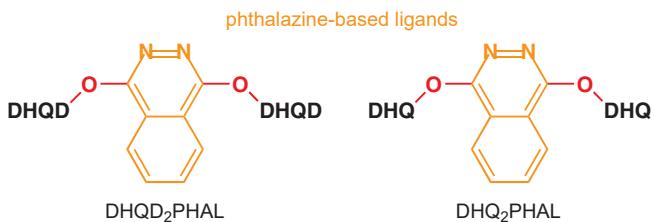
Now for the chiral ligand. Tertiary amines are good ligands for osmium and increase the rate of dihydroxylations: one of the reasons that NMO is used in the racemic version of the reaction (see p. 442) is that the by-product, *N*-methylmorpholine, accelerates the reaction. Sharpless chose some available chiral tertiary amines as ligands, and it turned out that the best ones are based on the alkaloids dihydroquinidine and dihydroquinine, whose structures are shown below. They coordinate to the osmium through the green nitrogen atom.



tertiary amines, such as *N*-methylmorpholine, accelerate the rate of osmium-catalysed dihydroxylations

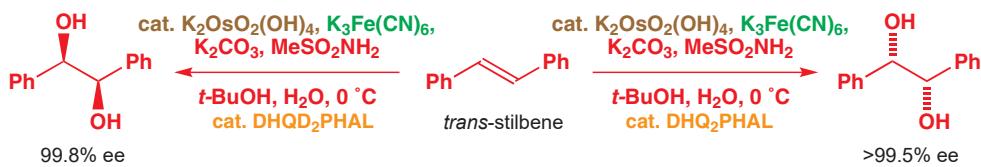


The alkaloids (usually abbreviated to DHQD and DHQ, respectively) must be attached to an aromatic group Ar, the choice of which varies according to the substrate. The most generally applicable ligands are these two phthalazines in which each aromatic group Ar carries two alkaloid ligands, either DHQ or DHQD.



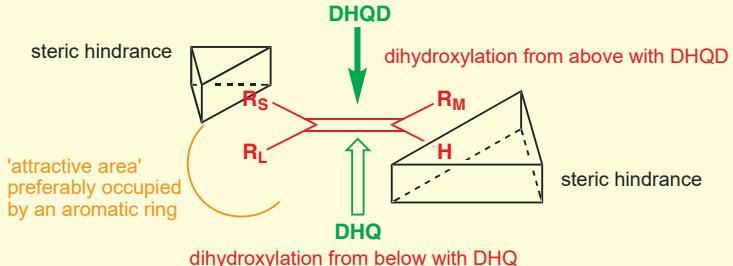
Dihydroquinine and dihydroquinidine are not enantiomeric (although the chiral centres ringed in orange are of opposite configuration in each of the pairs, those ringed in brown remain the same in both), but they act on the dihydroxylation as though they were.

Here, after all that introduction, is a real example, and probably the most remarkable of any in this chapter. *trans*-Stilbene dihydroxylates more selectively than any other alkene, and this particular example is one of the most enantioselective catalytic reactions ever invented.



We can sum up the usual selectivity of the AD reaction with the diagram shown below. With the substrate arranged as shown, with the largest ( $R_L$ ) and next largest ( $R_M$ ) groups bottom left and top right, respectively, DHQD-based ligands will direct OsO<sub>4</sub> to dihydroxylate from the top face of the alkene and DHQ-based ligands the bottom face.

#### ● Enantioselectivity in the Sharpless asymmetric dihydroxylation



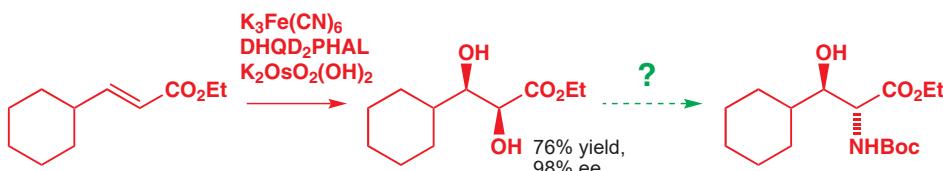
The reason for this must come from the way in which the substrate interacts with the osmium-ligand complex. However, the detailed mechanism of the asymmetric dihydroxylation is still far from clear-cut. What is known is that the ligand forms some sort of 'chiral pocket', like an enzyme active site, with the osmium sitting at the bottom of it. Alkenes can only approach the osmium if they are correctly aligned in the chiral pocket, and steric hindrance forces the alignment shown in the scheme above. The analogy with an enzyme active

#### AD-mix

A mixture of all the reagents except MeSO<sub>2</sub>NH<sub>2</sub> can be purchased commercially as AD-mix. AD-mix- $\alpha$  contains DHQ<sub>2</sub>PHAL, while AD-mix- $\beta$  contains DHQD<sub>2</sub>PHAL.

site goes even further, since it appears that part of the pocket is ‘attractive’ to aromatic or strongly hydrophobic groups. This part appears to accommodate R<sub>L</sub>, part of the reason why the selectivity in the dihydroxylation of *trans*-stilbene is so high.

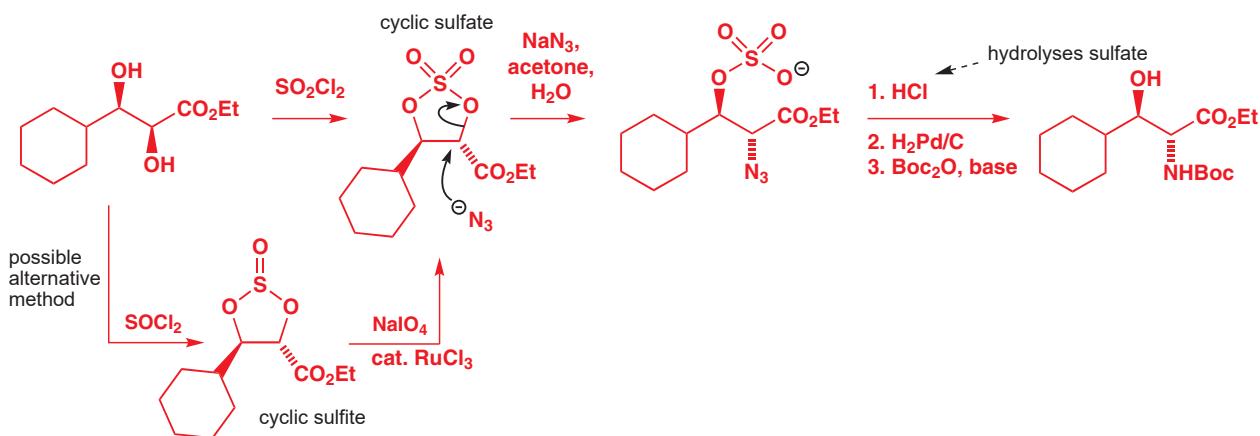
The asymmetric dihydroxylation is much less fussy about the alkenes it will oxidize than Sharpless’ asymmetric epoxidation. Osmium tetroxide itself is a remarkable reagent, since it oxidizes more or less any sort of alkene, electron-rich or electron-poor, and the same is true of the asymmetric dihydroxylation reagent. The following example illustrates both this and a synthetic use for the diol product.



The chemists at Lilly in Spain who made this diol wanted to turn it into the protected amino acid shown after the dotted arrow as part of the synthesis of an anti-HIV compound. The ease with which diols can be made means that there are a number of reliable methods for transforming them into derivatives which undergo the sort of substitution needed. The one used here was to make the diol into a cyclic sulfate using sulfonyl chloride, SO<sub>2</sub>Cl<sub>2</sub>. Cyclic sulfates behave like epoxides, and this one opens easily with azide at the more reactive position adjacent to the carbonyl group. Hydrolysis of the remaining sulfate ester, hydrogenation of the azide to the amine, and protection with Boc gave the target compound.

You can account for this by considering the mechanism of the dihydroxylation reaction (p. 905): it’s a cycloaddition, so either the LUMO or the HOMO of the alkene can be involved.

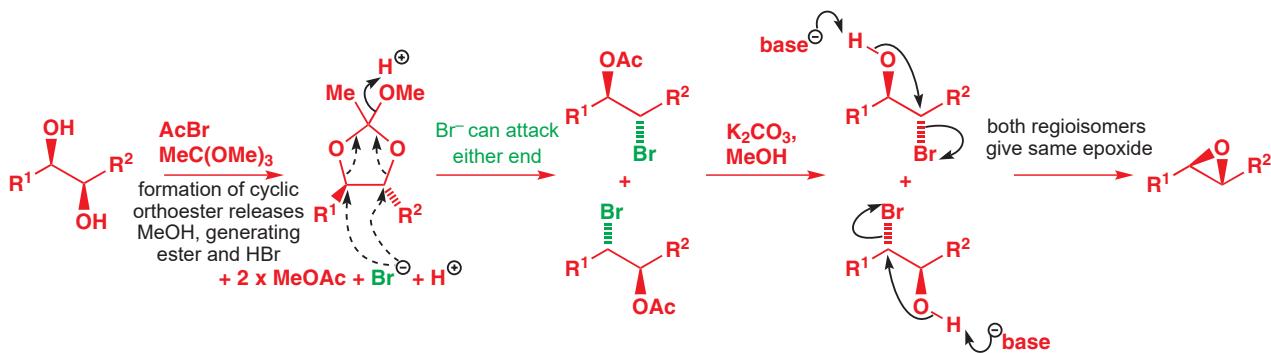
We explained in Chapter 15 that S<sub>N</sub>2 reactions adjacent to carbonyl groups are very fast. The regioselectivity of the ring opening of a cyclic sulfate, like that of an epoxide, is directed by the competition between relative rates of two nucleophilic substitution reactions. Benzylic and carbonyl-substituted positions usually open faster. There is more discussion of the regioselectivity of epoxide opening on p. 351.



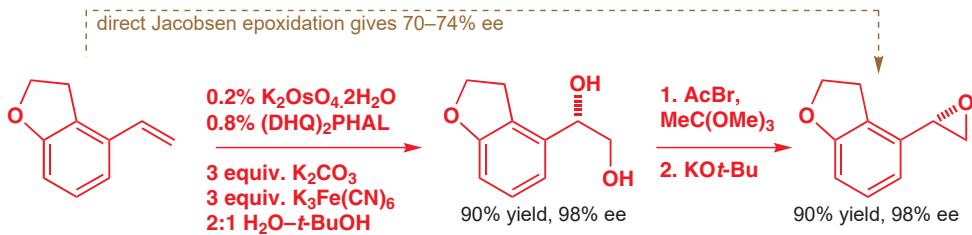
An alternative way of achieving the same transformation to the cyclic sulfate is to use thionyl chloride (SOCl<sub>2</sub>) to give a sulfite, followed by ruthenium-catalysed oxidation to the sulfate.

Diols can even be converted with retention of stereochemistry directly to epoxides. Treatment of a diol with trimethyl orthoacetate and acetyl bromide gives firstly the cyclic orthoester, which opens with bromide to a regioisomeric mixture of the bromoacetates. The regiochemistry is irrelevant because treatment with base hydrolyses the ester and closes both of the resulting bromoalcohols to the same epoxide.

→ See Chapter 39, p. 1059, for more on orthoesters.

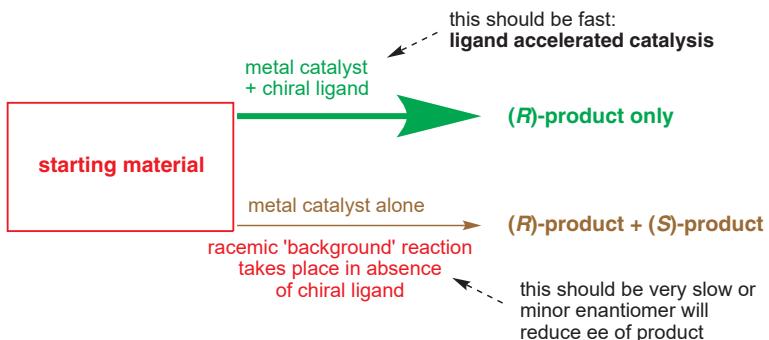


It's no surprise that when chemists from Bristol Myers Squibb needed the epoxide below, they turned to asymmetric dihydroxylation rather than either of the epoxidation methods we have shown you. Sharpless epoxidation works only with allylic alcohols, and Jacobsen epoxidation performs poorly here, giving only 70–74% ee (mainly because the substrate is not a *cis* alkene). However, asymmetric dihydroxylation saves the day with 98% ee and around 90% yield, and a variant of the reaction we have just shown you gives the epoxide, also in 90% yield—well worth the extra step.



### Ligand-accelerated catalysis

Asymmetric dihydroxylation is such a good reaction not just because of the careful way in which the ligands have been designed. It is a good reaction for a more fundamental reason: the reaction on which it is based (osmium-catalysed dihydroxylation) works only very poorly in the absence of the amine ligand. The chiral amine ligands don't just provide a chiral environment, they accelerate the reaction at the same time. This is what we mean by 'ligand accelerated catalysis'.



In any asymmetric reaction, we want the reagents to combine with one another only in the presence of the asymmetric influence provided by the chiral ligands. If the reaction works anyway, even without the chiral ligands, we have an uphill struggle because the reagents are quite capable of producing racemic product on their own. Racemic 'background' reactions are the reason why many of the reactions you are familiar with because they work so well racemically—addition of Grignard reagents to aldehydes, for example—don't really have good asymmetric versions. In the next section you will meet some more examples of reactions which are significantly accelerated by the presence of a chiral ligand.

■ In this section we will not consider the detailed mechanisms by which the stereochemistry of the ligand controls the stereochemistry of the product: in many cases this is not known anyway. We simply want to show you how the idea of ligand-accelerated catalysis has led to the discovery of new asymmetric reactions.

### Asymmetric formation of carbon–carbon bonds

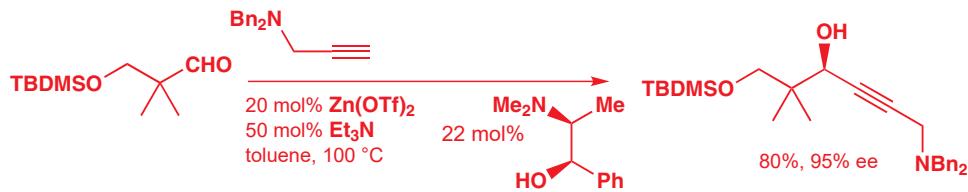
One of the first reactions you met in this book (Chapters 6 and 9) was the addition of an organometallic reagent to an aldehyde or a ketone. If the products of such an addition are chiral they are of course racemic. How might we make such a reaction enantioselective? One way would be to exploit the idea of ligand-accelerated catalysis and use a reaction which really doesn't work very well in the racemic series.

This is the case when the organometallic reagent is a dialkylzinc. Diethylzinc is commercially available as a solution in toluene or hexane, but it reacts only very slowly with an aldehyde

if the two are just left to stir together. However, if a chiral amino alcohol is added, the reaction becomes much faster. The amino alcohol forms a zinc alkoxide in the reaction mixture, and the coordination of this anionic chiral ligand to zinc both accelerates the transfer of zinc's alkyl groups to the aldehyde and makes that transfer enantioselective.



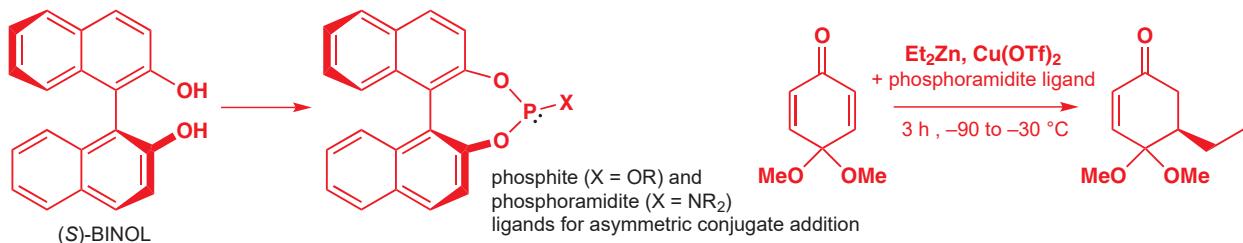
With alkyne nucleophiles, this reaction works with just catalytic amounts of zinc because the alkynylzinc forms in the reaction mixture when a weak base is added. It's a good way of making alkyne-containing alcohols.



Interactive mechanism for catalytic enantioselective organozinc addition to aldehydes

### Asymmetric conjugate addition

In Chapter 22 we discussed the fact that copper promotes conjugate addition to electron-deficient double bonds. We can again exploit the low reactivity of organozinc compounds with carbonyl compounds, and with alkenes, if we add a catalytic amount of copper and a chiral phosphorus-containing ligand based on the atropisomeric binaphthyl structure you saw in BINAP. The organozinc has to transmetallate to the organocupper in order to react, and the copper always remains bound to the chiral ligand. Conjugate addition can only take place in a chiral environment, and good ees result.

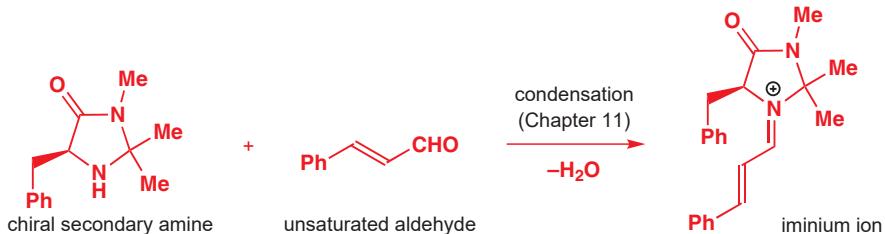


### Organocatalysis

It will not have escaped your notice that most of the reactions we have presented in this chapter have made use of metals. Metals have labile coordination sites that can carry chiral ligands at the same time as they allow substrates and reagents to meet together in a chiral environment and then let the products dissociate so that the catalytic cycle can proceed. But in the early years of the 21st century, several chemists around the world realized that it is not always necessary to use a metal to initiate high levels of enantioselectivity in catalytic reactions. Simple chiral and enantiomerically pure organic molecules, many of them amines, can also react reversibly with substrates, providing a chiral environment and simultaneously activating them towards enantioselective attack.

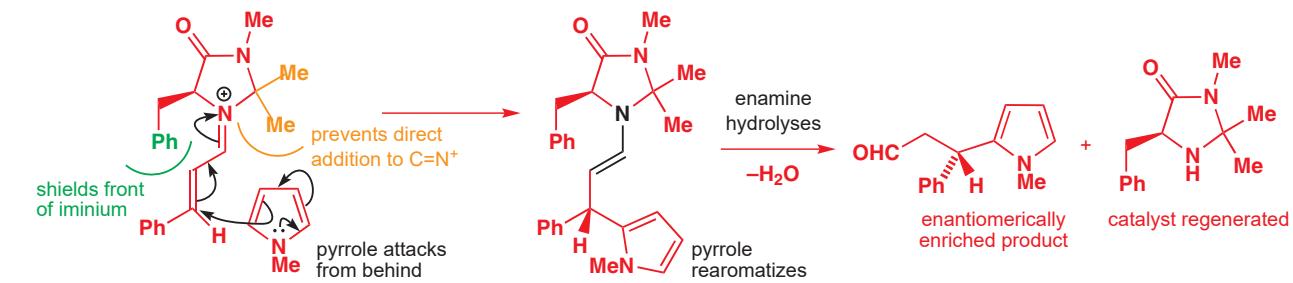
Here is an example, which picks up where we left off: a catalytic enantioselective conjugate addition. As you know from Chapter 11, aldehydes and ketones react with secondary amines to form enamines, via iminium ions. But this unsaturated aldehyde can't form an enamine because the iminium ion that is generated by condensation with the cyclic secondary amine

cannot lose a proton. The iminium ion is the end of the line for this condensation: it is very reactive towards attack by water (which would reversibly regenerate starting materials), but also towards attack by other nucleophiles. We have just what we want for good asymmetric catalysis—an intermediate species that is reactive, chiral, and enantiomerically pure.

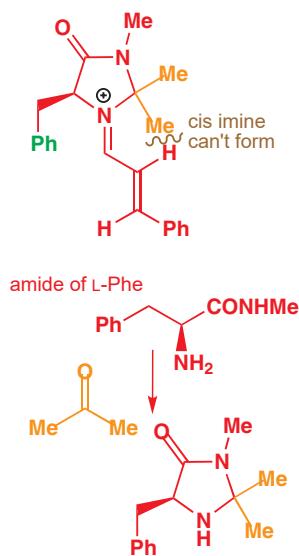


▶ See p. 733 of Chapter 29 for some reactions of pyrrole. You should certainly look back to Chapter 29 if you need reminding why pyrrole reacts in its 2-position.

If this condensation is done in the presence of a weak nucleophile—strong enough to attack the positively charged iminium ion but not strong enough to attack the aldehyde itself—an addition reaction takes place. A pyrrole will do: pyrroles react well with cations. The phenyl ring highlighted in green hangs over the front of the molecule so the pyrrole has no choice but to attack diastereoselectively, from behind. The product is an enamine, which in the acid conditions of the reaction is hydrolysed by the water generated in the initial condensation, revealing the aldehyde in enantiomerically enriched form (93% ee) and regenerating the secondary amine catalyst.



Interactive mechanism for enantioselective organocatalytic Friedel–Crafts alkylation



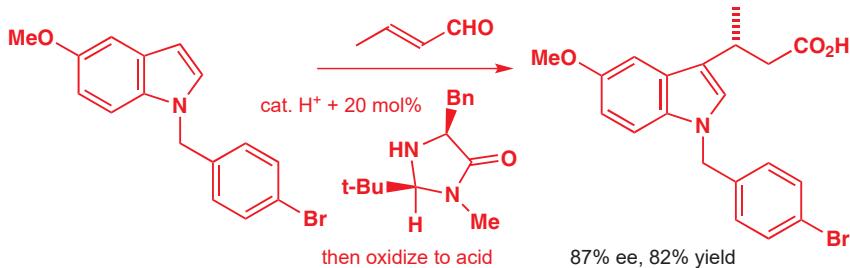
This catalyst and strategy were invented by the Glaswegian chemist David MacMillan at the California Institute of Technology (now at Princeton in New Jersey) and given the name ‘organocatalysis’. Organocatalysis makes use of small organic molecules to achieve catalytic asymmetric transformations, and can be distinguished from the more widespread methods of catalysis which typically use metals. We’ll introduce another type of organocatalysis towards the end of the chapter, but before we move on it’s worth looking at this amine catalyst and the way it works in a little more detail.

The geminal dimethyl group highlighted in orange above is also important to the functioning of the catalyst. Without it, there is clearly a danger that the pyrrole will add directly to the C=N bond of the iminium ion, a reaction that would kill the catalyst because the product is an amine and not an enamine. The methyl groups on both faces of the iminium C=N bond stop this happening. The other thing it ensures is the geometry of the iminium C=N bond. This bond is *trans* so that the alkene can keep away from the quaternary carbon bearing the two orange groups; the benzyl group with the green phenyl may be bigger in terms of total number of atoms, but there is more space for the alkene on that side because the nearest carbon also carries just an H atom. Why is the geometry of the imine important? Well, if any of it were *cis*, it would present the other face to the pyrrole and would be likely to give the opposite enantiomer of product.

Catalysts aren’t used in such great quantities as chiral auxiliaries, and so in general their synthesis does not need to be quite so direct. Nonetheless as you can see from the examples here, organocatalysts are still generally used in much greater quantities (10–20 mol%) than some of the best metal catalysts. In this case you should be able to spot that the left-hand

portion of the cyclic amine is a derivative of L-phenylalanine. Condensation of its N-methyl amide with an equivalent of acetone gives the catalyst itself.

Here's a related catalyst—as with the Rh- and Ru-catalysed reactions, fine tuning of the catalyst is important—being used in the synthesis of an important pharmaceutical compound, a COX-2 inhibitor. This time the nucleophile is an indole reacting characteristically at its 3-position.



Interactive mechanism for enantioselective organocatalytic indole alkylation

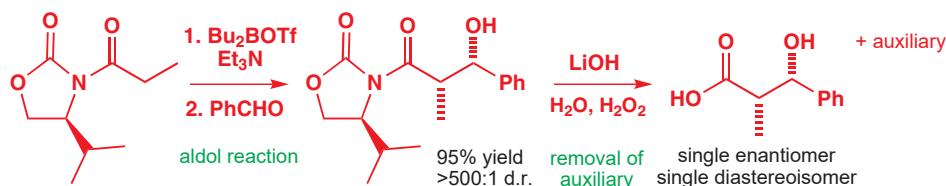
## Asymmetric aldol reactions

You saw in Chapter 33 that it is possible to use aldol reactions to create two new chiral centres in a single step, and that the relative stereochemistry of the two chiral centres depends in many cases on the geometry of the enolate used to do the aldol reaction. The power of an *asymmetric* aldol reaction is easy to see: it creates two new chiral centres with control over their absolute stereochemistry, and also constructs a new C–C bond. What is more, the products of aldol reactions are very common features in a huge number of natural products known as polyketides—as you will see in the next chapter, polyketides are made by living things using a series of successive enzyme-controlled aldol reactions.

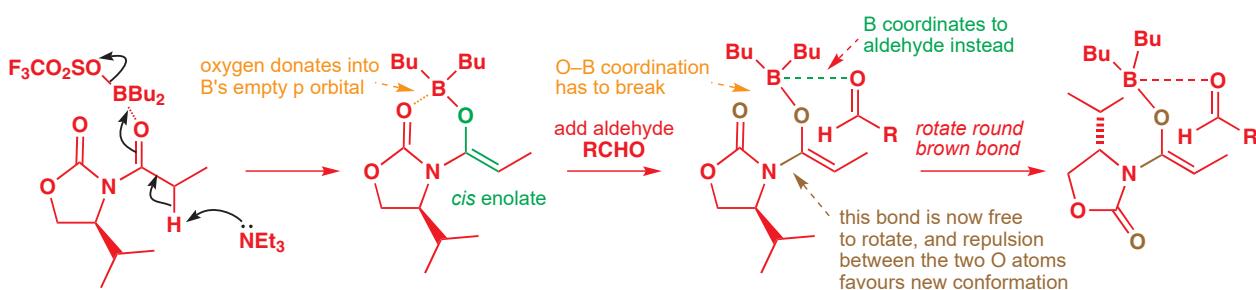
### Chiral auxiliary-controlled aldol reactions: the Evans aldol

An aldol reaction is the addition of an enolate to an electrophile, where the electrophile is an aldehyde or a ketone. You have already seen earlier in this chapter how enolates can be used to make new C–C bonds enantioselectively when we explained how to control enolate alkylation with Evans' chiral auxiliaries. Evans' auxiliaries also provide one of the most straightforward ways of carrying out asymmetric aldol reactions, and we will start with an example before explaining how asymmetric aldol reactions can be done using catalytic methods.

This aldol reaction is carried out using a base (triethylamine) and dibutylboron triflate plus benzaldehyde. The aldol product is formed with outstandingly good selectivity and in high yield, and all that remains is to remove the auxiliary with base and isolate the hydroxy-acid as a single diastereoisomer and a single enantiomer.



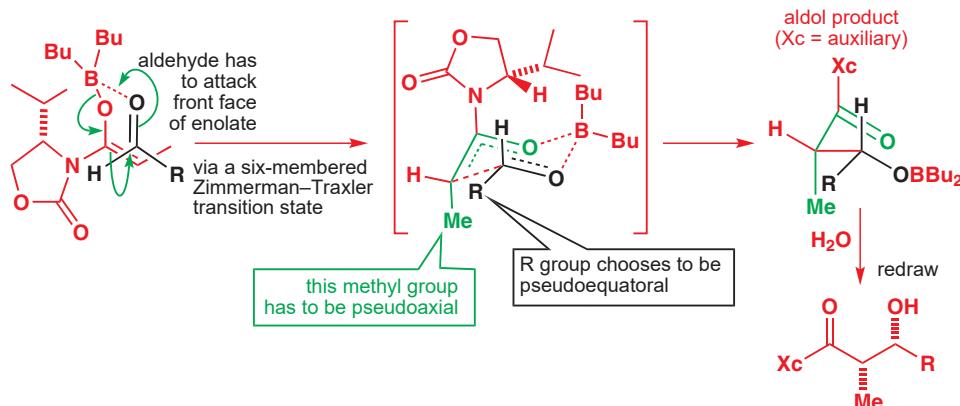
Aldol reactions using the lithium enolate of the acylated auxiliary shown here fail to give good selectivities, so instead we use the boron enolate. The combination of triethylamine and the boron triflate form the stable boron enolate, which has to be *cis* because the size of the auxiliary prevents the *trans* enolate forming. Boron has an empty p orbital, and donation into this orbital from the oxygen of the carbonyl group stabilizes the enolate.



Now the aldehyde is added. If the reaction is to take place, the aldehyde must coordinate to the boron because boron enolates aren't reactive enough to attack aldehydes unless they are activated by coordination to a Lewis acid. However, the aldehyde can't simply coordinate to the boron atom of the enolate because then the boron will end up with five bonds, which is impossible for a first-row element. So, if the reaction is to continue, the boron has to let go of the auxiliary's carbonyl group and coordinate to the aldehyde instead.

At this stage something rather remarkable happens: now that the boron is no longer holding the two oxygen atoms of the enolate close together, repulsion between them (they are both electron-rich atoms) forces the auxiliary part of the enolate to swing round through 180° and end up pointing in the opposite direction. This is highly significant for what happens next because you can see from the last structure in the scheme above that this rotation ends up swinging the isopropyl group of the auxiliary round to the underside of the enolate and therefore forcing the auxiliary to react from the front instead of the back.

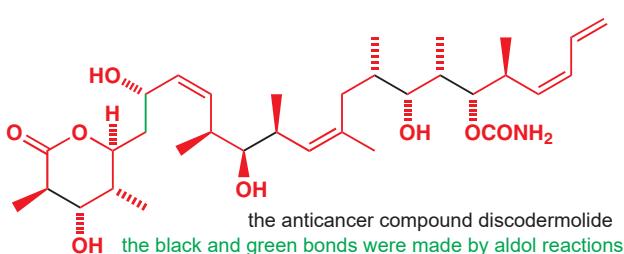
The diagrams below continue the story. The aldehyde has to attack the front face of the auxiliary, but it also has to do so through what we termed in Chapter 33 a 'Zimmerman–Traxler transition state'—a six-membered, chair-like cyclic structure which allows the enolate to attack the aldehyde while simultaneously transferring the metal (here the boron) from the enolate oxygen to the new hydroxyl group.



► You may wish to refresh your memory of the cyclic transition state for aldol reactions from p. 868.

Interactive mechanism for the chiral auxiliary-controlled aldol reaction

All the usual advantages and disadvantages of chiral auxiliaries apply here: the products are formed in very high selectivity and can be purified to high ee, but the extra steps required to introduce and remove the auxiliary may compromise the overall yield and efficiency of the reaction. Nonetheless, using this method and many others like it, it has now become possible routinely to make polyketide natural products by successive aldol reactions, mimicking nature's approach to these compounds. In a spectacular demonstration of the power of synthetic chemistry to outperform natural sources, chemists at the Swiss pharmaceutical company Novartis made 60 g of the anticancer compound discodermolide by a synthetic route, including five aldol reactions. Four of these, shown by black C–C bonds in the structure below, used the aldol or alkylation reactions controlled by Evans' oxazolidinone chiral auxiliaries. To obtain the same quantity from the natural source, the sponge *Discodermia*, is impossible: the sponge produces minuscule amounts of discodermolide and can be harvested only by using manned submersible vehicles, at some cost to the marine environment.

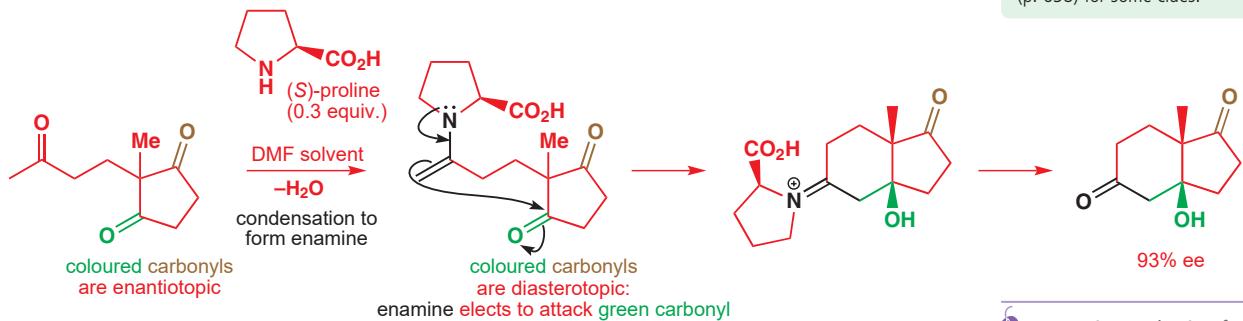


### Aldol reactions catalysed by proline

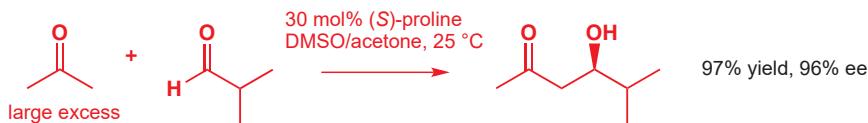
A variety of catalytic ways of doing asymmetric aldol reactions have also been invented, but space prevents us discussing all but one. This one we highlight firstly because it illustrates the use of a supremely simple biologically derived compound to catalyse a complex reaction, and secondly because this discovery was part of the revolution in catalytic thinking which launched the field of organocatalysis in the early years of the 21st century.

The catalyst we will use is the amino acid L-proline—no derivatization or protection required. It was actually back in 1971 that it was first noted that L-proline will catalyse asymmetric aldols, but until the year 2000 examples were limited to this one cyclization. Treatment of a triketone with proline leads to selective cyclization onto one of the two enantiotopic carbonyl groups. A molecule of proline must condense with the least hindered ketone, and in this case an enamine (rather than an iminium ion) can form. The chiral enamine can select to react with only one of the two other carbonyl groups, and it turns out that it chooses with rather high selectivity the one coloured green in the scheme below. Cyclization, in the manner of a Robinson annelation, and hydrolysis of the resulting iminium ion follow on, releasing the molecule of L-proline to start another catalytic cycle. The isolated product is the bicyclic ketone, in 93% ee.

► You saw the racemic example of this Robinson annelation on p. 638.



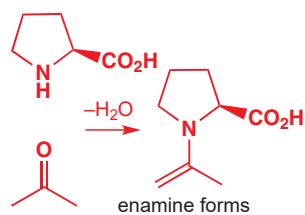
This remained an oddity of a reaction until 2000, when chemists at the Scripps Institute in California, and then others around the world, took the simple expedient of adding L-proline to many other aldol reactions, with considerable success. With care, excellent results can be obtained. Here is an example.



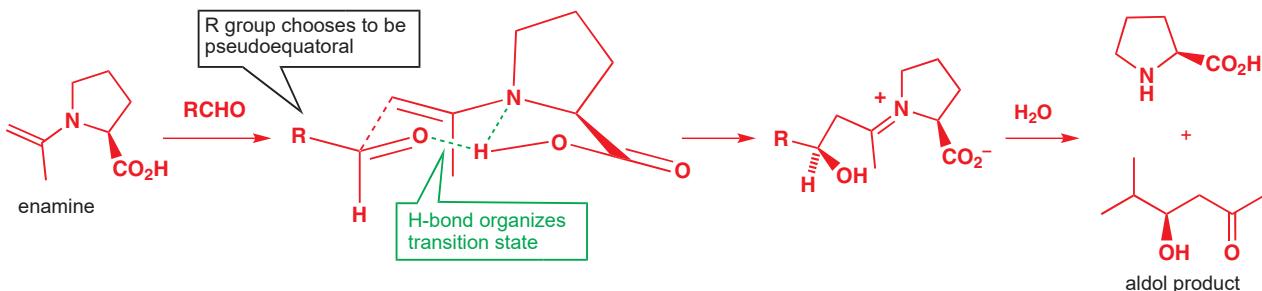
You will remember from Chapter 26 that crossed aldol reactions between enolizable partners, like these, usually need one of the reagents to be converted to an enolate equivalent to ensure selective reaction. Here, the acetone is in excess, but the components are just stirred together at room temperature in DMSO! The key to success is that one of the two components must be more able to form a reactive enamine with proline than the other. In the case above, the acetone-derived enamine is favoured because (1) enamine formation is reversible, (2) the acetone is in excess, and (3) the enamine from acetone is less hindered and more reactive than the enamine that would arise from the aldehyde.

► Interactive mechanism for the proline-catalysed Robinson annelation

■ It has an odd name too: the cyclization is sometimes called the Hajos–Parrish–Eder–Sauer–Wiechert reaction, after its discoverers, but only by those who want to impress their friends.



In the aldol reaction itself, proline's carboxyl group has a key role to play because it can participate in a hydrogen bond that organizes the six-membered transition state in such a way that only one of the possible enantiomeric products can form. The diagram below shows how. Water generated in the initial condensation hydrolyses the iminium product of the aldol and regenerates the proline catalyst.

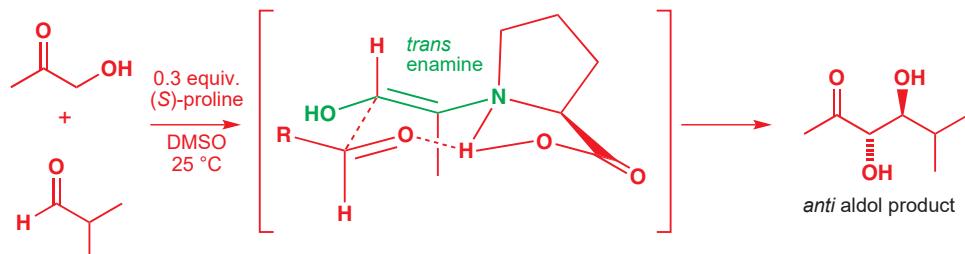


Interactive mechanism for the proline-catalysed enantioselective aldol reaction

▶ See p. 868 for a discussion of enolate geometry and *syn* and *anti* aldols.

Interactive mechanism for the proline-catalysed *anti* selective aldol reaction

Organocatalytic aldol reactions also work well with hydroxylated ketones—the reaction below, for example. In this case, the enamine forms with an *E* double bond, which means that the hydroxyl group has to be equatorial on the six-membered transition state. You should be able to work out from this that the *anti* aldol has to form.

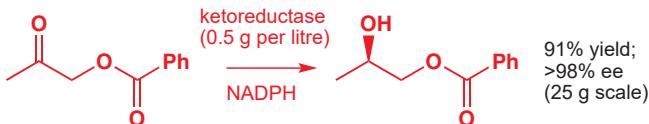


## Enzymes as catalysts

We pointed out at the beginning of the chapter that all enantiomeric purity must ultimately derive from nature. We have almost come full circle: the reactions we have just been looking at use one of nature's protein building blocks, L-proline, directly as a catalyst. Even more intriguingly, the reaction just above, which forms a ketodiol, is extremely reminiscent of the aldol reactions which nature uses to build carbohydrates, as you will see in the next chapter.

Yet nature does not use single amino acids to catalyse asymmetric reactions, it uses enzymes. Enzymes are vastly more efficient than L-proline and catalyse a much wider range of reactions, but while they are also much more complicated, their reactivity derives ultimately from the amino acids they are made up of.

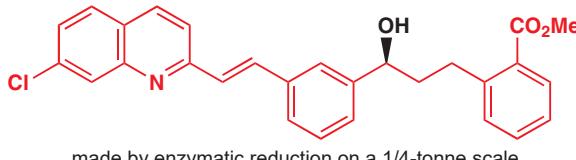
Life uses enzymes to catalyse asymmetric reactions, so the question is—can chemists? The answer is yes, and there are many enzymes that can be produced in quantities large enough to be used in the catalytic synthesis of enantiomerically pure molecules. This field—known as biocatalysis—melds ideas in chemistry and biology, and we do not have the space here to discuss it in detail. We leave you with just one example: the reduction of a ketone to an alcohol with an enzyme known as a ketoreductase.



▶ The structure of NADPH is on p. 1150.

The ketoreductase takes hydride from the reducing agent NADPH (which you will meet in the next chapter) and transfers it enantioselectively to the carbonyl group in the active site of

the enzyme. This ketoreductase, isolated from yeast, may never have met this non-biological substrate—benzoyloxyacetone—before, but the reaction works. In fact this sort of reaction works so well that ketoreductases are used to carry out the reduction needed to produce the pharmaceutical intermediate discussed on p. 1116 on a 230 kg scale.



Many other groups of enzymes behave similarly: they have evolved to take part in particular biochemical pathways, but they are sufficiently promiscuous that they will happily accept alternative substrates and provide chemically useful products from them. Enzymes are catalysts, like any other. In the next chapter, we take a more detailed look at those biochemical pathways and discuss the organic chemistry of life.

### ● Summary of the main methods for asymmetric synthesis

Method	Advantages	Disadvantages	Examples
resolution	both enantiomers available	maximum 50% yield	synthesis of BINAP
chiral pool	100% ee usually guaranteed	often only one enantiomer available	amino acid and sugar derived syntheses
chiral auxiliary	often excellent ees; can recrystallize to purify to high ee	extra steps to introduce and remove auxiliary	oxazolidinones
chiral reagent	achieve some otherwise difficult transformations	only a few reagents are successful and often for few substrates	alkyllithium-( $-$ )-sparteine complex
chiral catalyst	economical: only small amounts of recyclable material used	only a few reactions are really successful; recrystallization can improve only already high ees	asymmetric hydrogenation, epoxidation, dihydroxylation

## Further reading

For an overview of the relationship between smell and stereochemistry, see R. Bentley, *The Nose as a Stereochemist: Enantiomers and Odour*, *Chem. Rev.*, 2006, **106**, 4099. Interesting examples of the use of asymmetric methods in the large scale synthesis of drug molecules are given in M. Ikunaka, *Chem. Eur. J.* 2003, **9**, 379. The prevalence of chiral drugs and the relative importance of asymmetric synthesis and resolution are discussed in B. Kasprzyk-Hordern, *Chem. Soc. Rev.*, 2010, **39**, 4466 and in J. S. Carey, D. Laffan, C. Thomson and M. T. Williams *Org. Biomol. Chem.* 2006, 2337.

For a more advanced treatment of asymmetric synthesis see P. Wyatt and S. Warren, *Organic Synthesis: Strategy and Control*, Wiley, Chichester, 2007, chapters 22–31 and the accompanying *Workbook*, also Wiley, 2008. Very detailed advanced mechanistic discussion of asymmetric hydrogenation and asymmetric epoxidation methods may be found in *Asymmetric Synthesis*, vol. 5, ed. J. D. Morrison, Academic Press, New York (1985). This five-volume set is now rather dated but provides some very valuable discussion of the

classic methods of asymmetric synthesis. There are reviews of asymmetric dihydroxylation in *Chem. Rev.* 1994, **94**, 2483 and *Org. Synth.* 1996, **73**, 1 and of asymmetric hydrogenation in *Acc. Chem. Res.* 2007, pp. 1237–1419 and the *Handbook of homogeneous hydrogenation* published by Wiley, 2007. A very recent comprehensive overview of asymmetric methods can be found in the multi-volume set *Comprehensive Chirality*, pub. Elsevier, 2011.

The Cilag resolution of the pyridyl amino acid is described in *Org. Process Res. Dev.* 2001, **5**, 23. For an informative comparison of different auxiliary and catalytic methods for the synthesis of a simple chiral carboxylic acid, see *Org. Process Res. Dev.* 2003, **7**, 370. For a leading reference to the use of enzymes to reduce ketones, see the account of the Codexis work on montelukast in *Org. Process Res. Dev.* 2010, **14**, 193. The spectacular synthesis of discodermolide by Novartis using a series of aldol reactions is described in *Org. Process Res. Dev.* 2004, **8**, 92, 101 and 107.

## Check your understanding



To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 42

## 有机化学与生命

### 联系

#### → 基础

- Acidity and basicity ch8
- Carbonyl chemistry ch10 & ch11
- Stereochemistry ch14
- Conformational analysis ch16
- Enolate chemistry and synthesis ch25 & ch26
- Sulfur chemistry ch27
- Heterocycles ch29 & ch30
- Asymmetric synthesis ch41

#### 目标

- Nucleic acids store information for the synthesis of proteins
- Modified nucleosides can be used as antiviral drugs
- Proteins catalyse reactions and provide structure
- Other amino acid derivatives act as methylating and reducing agents
- Sugars store energy, enable recognition, and protect sensitive functional groups
- How to make and manipulate sugars and their derivatives
- Lipids form the basis of membrane structures
- The main sorts of natural products are alkaloids, polyketides, terpenes, and steroids
- Alkaloids are amines made from amino acids
- Fatty acids are built up from acetyl CoA and malonyl CoA subunits

#### → 展望

- Three more comprehensive web chapters:
  - The chemistry of life
  - Mechanisms in biological chemistry
  - Natural products
- Organic chemistry today ch43

Secondary metabolism is, by contrast, chemistry less fundamental to the workings of life and restricted to smaller groups of organisms. Later in this chapter you will meet alkaloids produced by some plants and terpenes produced by others.

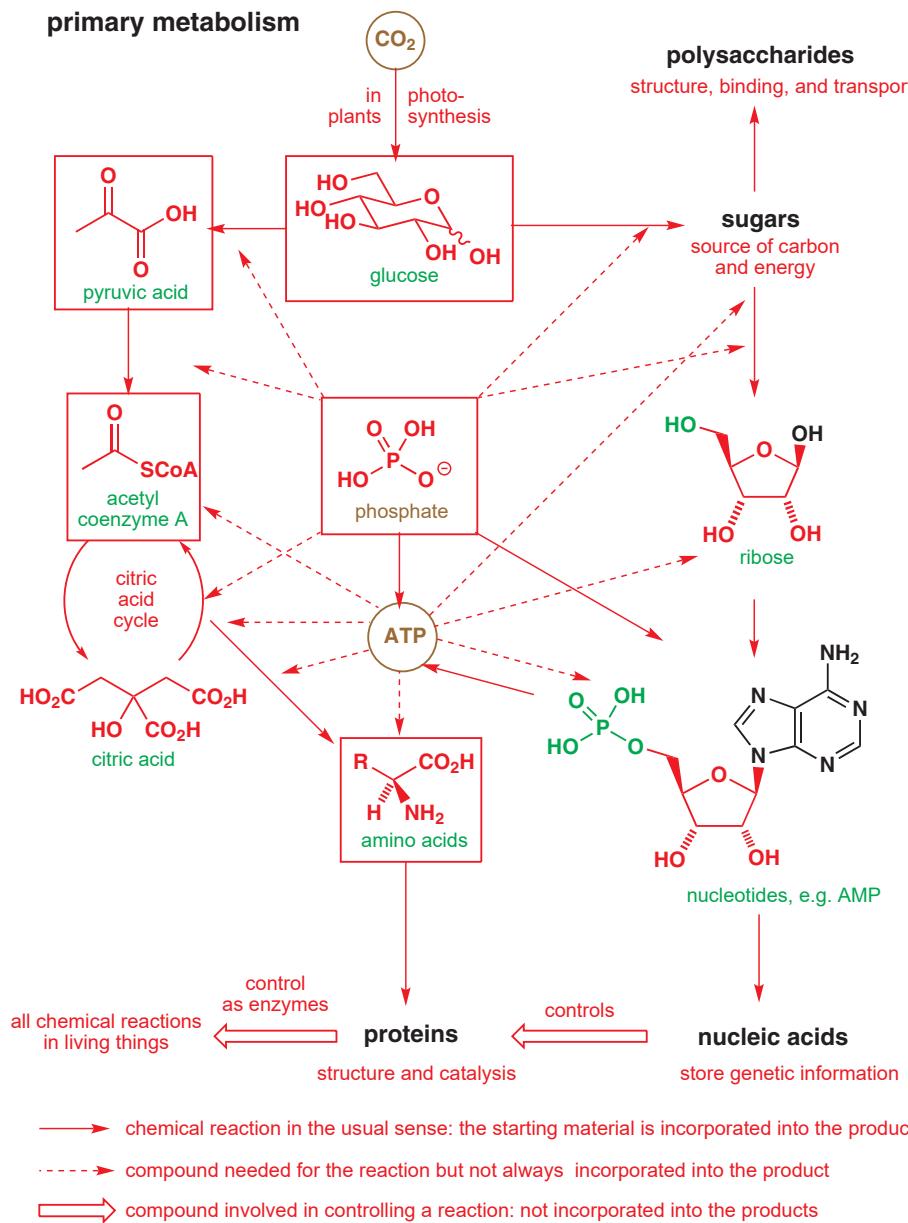
Humans produce neither of these, but we do make steroids, as do other animals (and a few plants). All of these molecules are the products of secondary metabolism.

## Primary metabolism

Life runs on chemistry, and the chemical side of biology is fascinating for that reason alone. It is humbling to realize that the same molecules are present in all living things, from the simplest single-cell creatures to ourselves. Nucleic acids contain the genetic information of every organism, and they control the synthesis of proteins. Proteins are partly structural—as in connective tissue—and partly functional—as in enzymes, the catalysts for biological reactions. Sugars and lipids used to be thought of as the poor relations of the other two, storing energy and building membranes, but it is now clear that they also have a vital part to play in recognition and transport.

The chemistry common to all living things is known as *primary metabolism* and the chart overleaf shows the molecules of primary metabolism and the connections between them, and needs some explanation. It shows a simplified relationship between the key structures (emphasized in large black type). It shows their origins—from CO<sub>2</sub> in the first instance—and picks out some important intermediates. Glucose, pyruvic acid, citric acid, acetyl coenzyme A (acetyl CoA), and ribose are players on the centre stage of metabolism and are built into many

important biological molecules. Use this chart to keep track of the relationships between the molecules of metabolism as you develop a more detailed understanding of them. We start with nucleic acids.

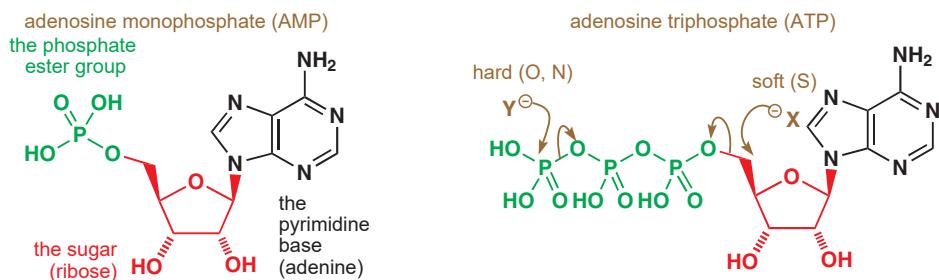


## Life begins with nucleic acids

Nucleic acids store genetic information. They are polymers whose building blocks (monomers) are the nucleotides, themselves made of three parts—a heterocyclic base, a sugar, and a phosphate ester. In the example below, adenine is the base (shown in black), adenosine is the nucleoside (base and sugar), and the nucleotide is the whole molecule (base + sugar + phosphate). This nucleotide is called AMP—adenosine monophosphate. Phosphates are key compounds in nature because they form useful stable linkages between molecules and can also be built up into reactive molecules by simply multiplying the number of phosphate residues. The most important of these nucleotides is also one of the most important molecules in nature—adenosine triphosphate or ATP.

### Nucleosides and nucleotides

A nucleoside differs from a nucleotide in lacking the phosphate—a nucleoside is just a base and a sugar.



ATP is a highly reactive molecule because phosphates are stable anions and good leaving groups. It can be attacked by hard nucleophiles at a phosphate group (usually the end one) or by soft nucleophiles at the CH<sub>2</sub> group on the sugar. When a new reaction is initiated in nature, very often the first step is a reaction with ATP to make the compound more reactive. This is rather like our use of TsCl to make alcohols more reactive or converting acids to acid chlorides to make them more reactive.

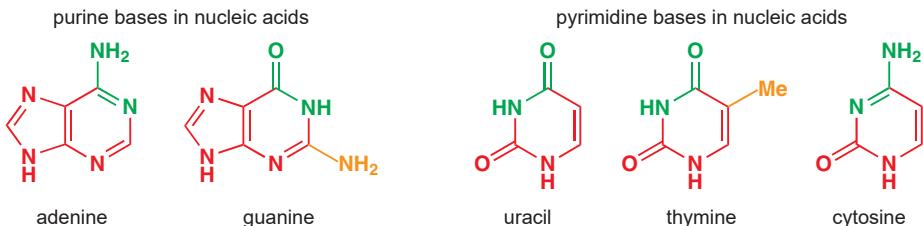
**There are five heterocyclic bases in DNA and RNA**

Nucleic acids are made up of a selection of five bases, two sugars, and the phosphate group. The bases are monocyclic pyrimidines or bicyclic purines and are all aromatic.

- There are only two purine bases found in nucleic acids: adenine (A), which we have already met, and guanine (G)
  - The three pyrimidine bases are simpler: uracil (U), thymine (T), and cytosine (C). Cytosine is found in DNA and RNA, uracil in RNA only, and thymine in DNA only.

The coloured parts of the molecules below emphasize the characteristic features of the bases.

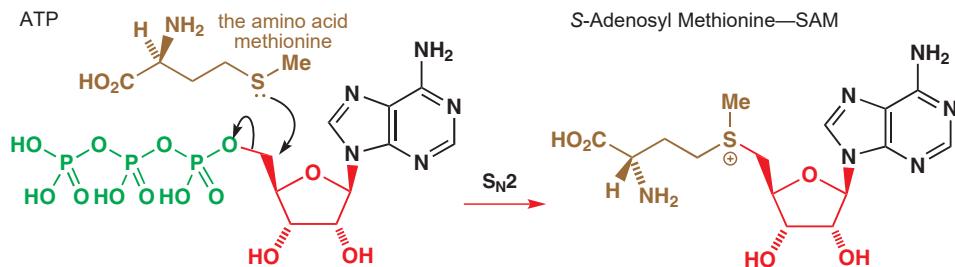
- You met pyrimidines in Chapter 29 and learned how to make them in Chapter 30, but the purine ring system may be new to you. Make sure you can find the six (or ten) electrons making these compounds aromatic. You may need to draw delocalized structures, especially for U, T, and G.



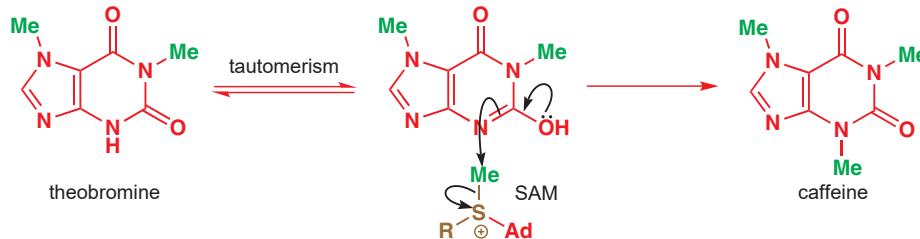
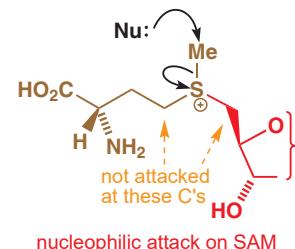
**The stimulants in tea and coffee are methylated purines**

An important stimulant for many is a fully methylated purine present in tea and coffee— caffeine. Caffeine is a crystalline substance easily extracted from coffee or tea with organic solvents. It is extracted industrially with supercritical CO<sub>2</sub> (or, if you prefer, ‘nature’s effervescence’) to make decaffeinated tea and coffee.

If we, as chemists, were to add those methyl groups we would choose to use a reagent such as methyl iodide, but nature uses a much more complicated molecule. There is a great deal of methylating going on in living things—and the methyl groups are usually added by (*S*)-adenosyl methionine (or SAM), formed by reaction of methionine with ATP. This is a good reaction because sulfur is a good soft nucleophile, triphosphate is a good leaving group, and substitution at primary carbon is easy.



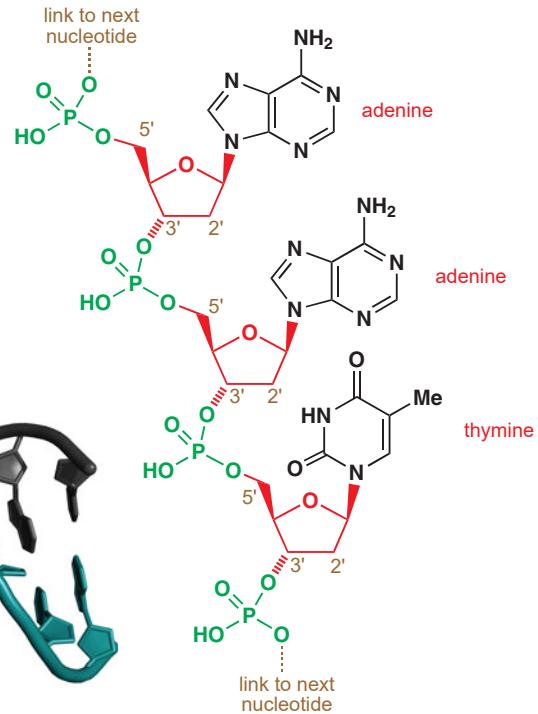
SAM is a sulfonium salt and could be attacked by nucleophiles at three different carbon atoms. Two are primary centres—good for  $S_N2$  reactions—but the third is the methyl group, which is even better. Many nucleophiles attack SAM in this way. In the coffee plant, theobromine (a purine also found in cocoa) is converted into caffeine with a molecule of SAM. The methylation occurs on nitrogen partly because this preserves both the aromatic ring and the amide functionality and also because the enzyme involved brings the two molecules together in the right orientation for *N*-methylation.



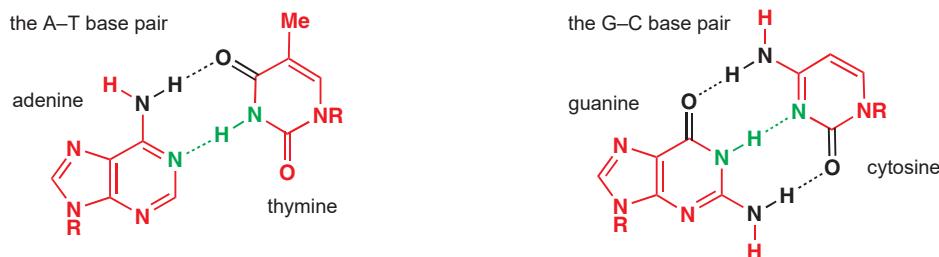
At this point we should just point out something that it's easy to forget: there is *only one chemistry*. There is no magic in biological chemistry, and nature uses the same chemical principles as we do in the chemical laboratory. All the mechanisms that you have studied so far will help you to draw mechanisms for biological reactions and most reactions that you have met have their counterparts in nature. The difference is that nature is very, very good at chemistry, and we humans are only just learning. We still do much more sophisticated reactions *inside* our bodies without thinking about them than we can do *outside* our bodies with all the most powerful ideas available to us in the 21st century.

### Nucleic acids exist in a double helix

One of the most important discoveries of modern science was the elucidation of the structures of DNA and RNA as the famous double helix by Watson and Crick in 1953. They realized that the basic structure of base–sugar–phosphate was ideal for a three-dimensional coil. The structure of a small part of DNA is shown on the right. Notice that the 2' (pronounced ‘two prime’) position on the ribose ring is vacant. There is no hydroxyl group there: that is why it is called *deoxyribonucleic acid*. The nucleotides link the two remaining OH groups on the ribose ring and these are called the 3'- and 5'-positions. This piece of DNA has three nucleotides (adenine, adenine, and thymine) and so would be called –AAT– for short.



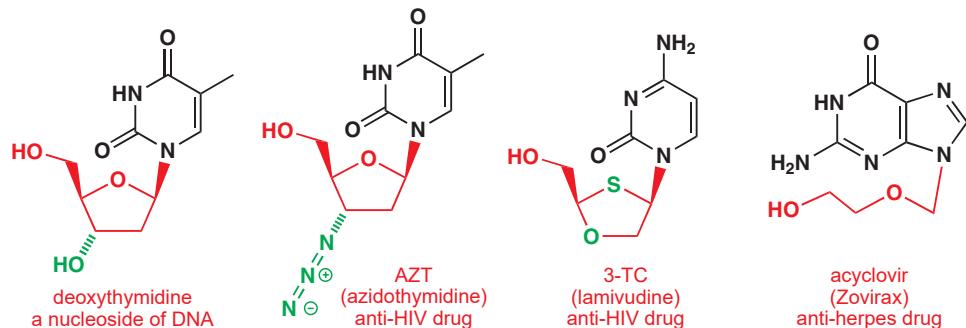
Each polymeric strand of DNA coils up into a helix and is bonded to another strand by hydrogen bonds between the bases. Each base pairs up specifically with another base—adenine with thymine (A–T) and guanine with cytosine (G–C)—like this.



There is quite a lot to notice about these structures. Each purine (A or G) is bonded specifically to one pyrimidine (T or C) by two or by three hydrogen bonds. The hydrogen bonds are of two kinds: one links an amine to a carbonyl group (black in the diagram) and one links an amine to an imine (green in the diagram). A purine has to pair with a pyrimidine because only the combination of larger purine and smaller pyrimidine bridges the gap between the nucleic acid coils. Look back at the green and orange parts of the structures on p. 1136 and you will see that only one hydrogen bond pairing pattern can work. In this way, each nucleotide reliably recognizes another and reliably pairs with its partner. The short strand of DNA above ( $-AAT-$ ) would pair reliably with  $-TTA-$ .

### HIV and AIDS are treated with modified nucleosides

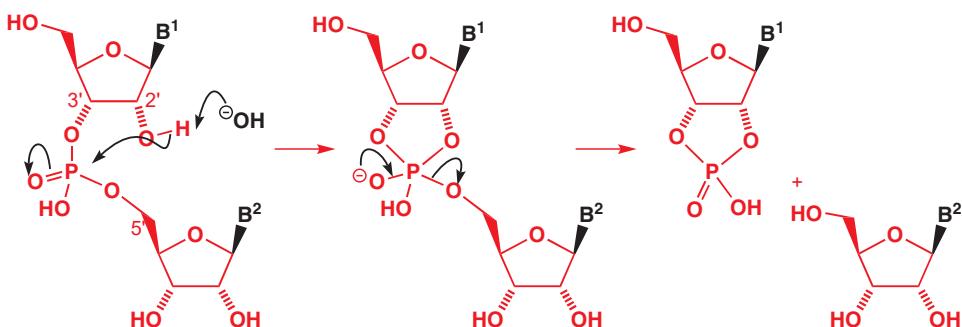
Modified nucleosides are among the best antiviral compounds. The anti-HIV drug AZT (zidovudine) is a slightly modified DNA nucleoside (3'-azidothymidine). It has an azide at C3' instead of the hydroxyl group in the natural nucleoside. A more radically modified nucleoside 3-TC (lamivudine) is active against AZT-resistant viruses. This drug is based on cytosine with the sugar replaced by a different heterocycle, although it is recognizably similar, especially in the stereochemistry. Acyclovir (Zovirax), the cold sore (herpes) treatment, is a modified guanosine in which only a ghost of the sugar remains. There is no ring at all and no stereochemistry.



### Cyclic nucleosides and stereochemistry

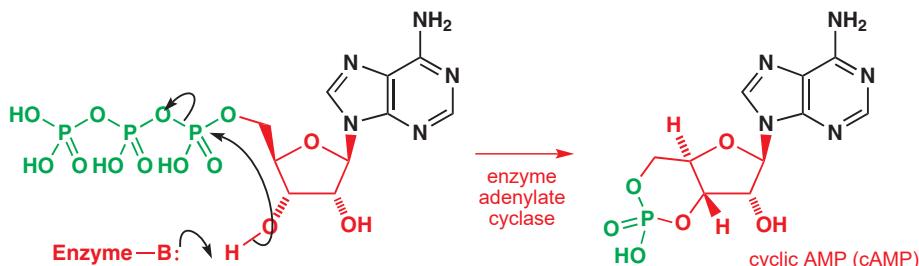
DNA is more stable than RNA because its sugars lack the 2' hydroxyl groups. In ribonucleic acids, the fact that the 2'- and 3'-OH groups are on the same side of the ring makes alkaline hydrolysis exceptionally rapid by intramolecular nucleophilic catalysis.

The substituents  $B^1$  and  $B^2$  represent any purine or pyrimidine base.



The base removes a proton from the 2'-OH group, which cyclizes on to the phosphate link—possible only if the ring fusion is *cis*. The next reaction involves breakdown of the pentacovalent phosphorus intermediate to give a cyclic phosphate. One nucleoside is released by this reaction and the second follows when the cyclic phosphate is itself cleaved by base.

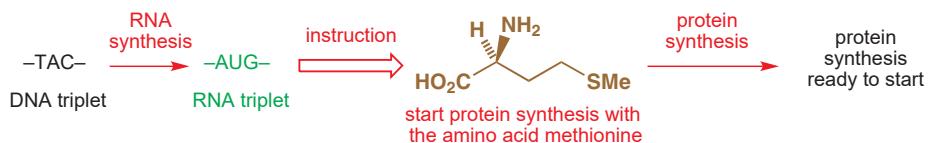
Another cyclic phosphate that can be formed from a nucleotide is important as a biological messenger that helps to control such processes as blood clotting and acid secretion in the stomach. It is cyclic AMP (cAMP), formed enzymatically from ATP by nucleophilic displacement of pyrophosphate by the 3'-OH group.



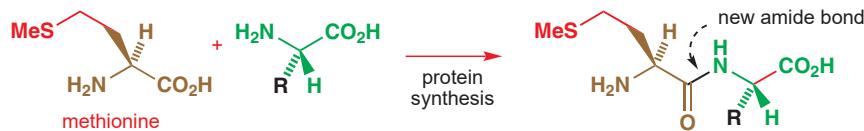
■ Note that cAMP has a *trans* 6,5-fused ring junction.

## Proteins are made of amino acids

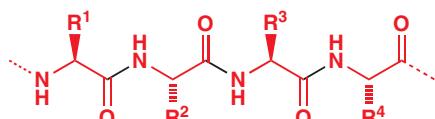
DNA encodes the information needed to make proteins in the form of triplets of bases (codons), for example thymine–adenine–cytosine (TAC) in the diagram below. As RNA is synthesized from DNA, these are turned into complementary codons (in the example below, AUG) by pairing up the bases as shown on p. 1138. This RNA forms the instructions for protein synthesis by the ribosome—perhaps the most elaborate molecular structure in the known universe. Each codon of the RNA chain tells the ribosome to add a specific amino acid to the growing protein. For example, the codon AUG indicates methionine, which we met as a component of SAM. Methionine is a typical amino acid of the kind present in proteins, but is also the starter unit of all proteins.



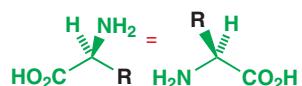
The next codon of RNA directs the ribosome to add the next amino acid, linked to the previous one in the chain by an amide bond. Amino acids used to make proteins have the same basic structure and stereochemistry, shown in the margin, and differ only in the group R.



The process continues as more amino acids are added in turn to the right-hand end of the growing molecule. A section of the final protein might look like the structure below. The skeleton of the protein zig-zags up and down in the usual way; the amide bonds (shown in black) are rigid because of the amide conjugation and are held in the shape shown.



two views of the general amino acid structure



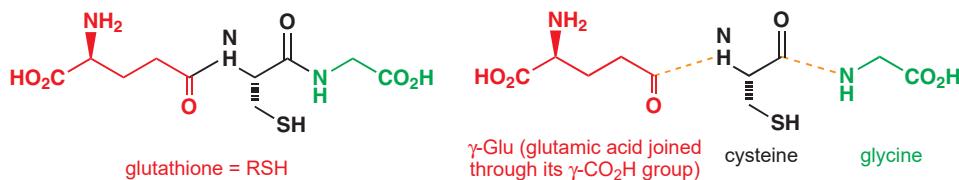
► There is a list of the naturally occurring amino acids in Chapter 23 (p. 554), where we discussed the laboratory synthesis of peptides.

■ Much of the function of enzymes and other proteins derives from their detailed folded conformation, discussion of which is beyond the scope of this book.

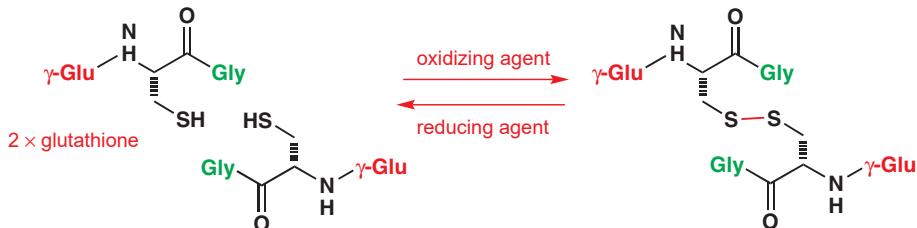
### Amino acids combine to form peptides and proteins

In nature, the amino acids are combined to give proteins with hundreds or even thousands of amino acids in each one. Small assemblies of amino acids are known as **peptides** and the amide bond that links them is called a **peptide bond**.

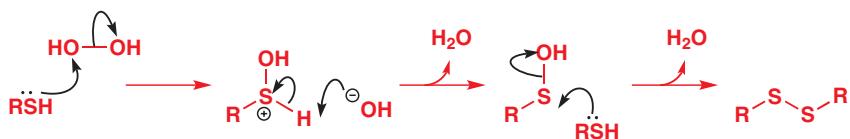
An important tripeptide is **glutathione**, present in the tissues of both animals and plants. Glutathione is the ‘universal thiol’ that removes dangerous oxidizing agents by allowing itself to be oxidized to a disulfide. Glutathione is, however, not quite a typical tripeptide. The left-hand amino acid is normal glutamic acid but it is joined to the next amino acid through its  $\gamma$ -CO<sub>2</sub>H group instead of the more normal  $\alpha$ -CO<sub>2</sub>H group. The middle amino acid is the vital one for the function—cysteine with a free SH group. The C-terminal acid is glycine.



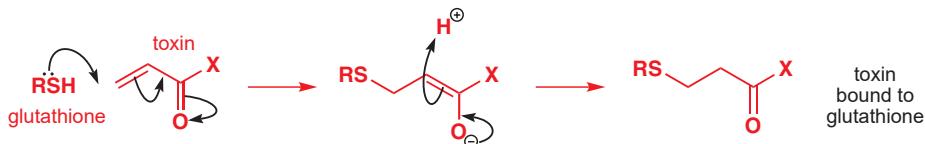
Thiols are easily oxidized to disulfides and glutathione sacrifices itself if it meets an oxidizing agent. The oxidized form of glutathione can later be converted back to the thiol by reduction with NADH, which you will meet later in this chapter.



With a stray oxidizing agent such as a peroxide, say H<sub>2</sub>O<sub>2</sub>, the mechanism below shows how this can be reduced to water as glutathione (represented as RSH) is oxidized to a disulfide.



Glutathione also detoxifies some of the compounds we described earlier in this book as dangerous carcinogens such as Michael acceptors and 2,4-dinitrohalobenzenes. The thiol acts as a nucleophile, inactivating the electrophiles. Covalently bound to glutathione they are harmless and can be excreted. More glutathione will be synthesized from glutamic acid, cysteine, and glycine to replace that which is lost.



Some short peptides, of around ten amino acids, are hormones. Angiotensin II, for example, is a peptide that causes blood pressure to rise—a very necessary thing in some situations but too much and too often leads to heart attacks and strokes.

Angiotensin-converting enzyme (ACE) is the zinc-dependent enzyme that cleaves two amino acids from the end of angiotensin I to give angiotensin II, and ACE inhibitors are used as treatment for high blood pressure because they inhibit this enzyme. Lisinopril is an example: it is a dipeptide mimic, having two natural amino acids and something else. The ‘something else’ is the left-hand part of the molecule, linked to the dipeptide (Lys-Pro) through an amine and not

▶ See, for example, the discussion in Chapter 22, p. 516.

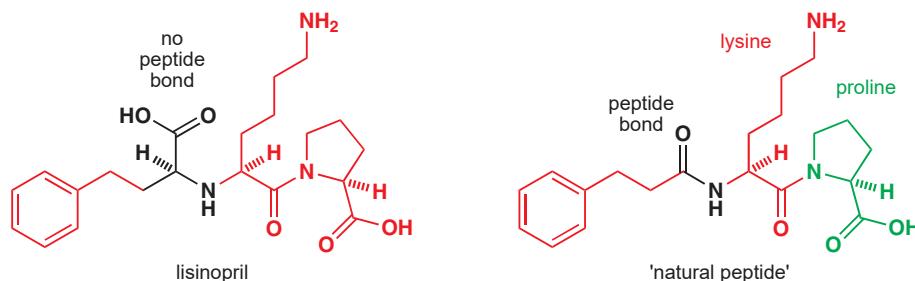
▶ You saw some examples in Chapter 23.

angiotensin I  
ten amino acids  
no effect on blood pressure

Zn<sup>2+</sup> | angiotensin-converting enzyme (ACE)

angiotensin II  
eight amino acids  
increases blood pressure

by an amide bond. This stops enzymes from hydrolysing the molecule. Lisinopril binds to ACE because it is *like* a natural dipeptide but it inhibits it because it is *not* a natural dipeptide. Many people are alive today because of this simple deception practised on an enzyme.



### Structural proteins must be tough and flexible

In contrast with the functional enzymes, proteins such as collagen are purely structural. Collagen is the tough protein of tendons and connective tissue, and is present in skin, bone, and teeth. It contains large amounts of glycine (every third amino acid is glycine), proline, and hydroxyproline (again about a third of the amino acids are either Pro or Hyp).

Hydroxyproline is a specialized amino acid that appears almost nowhere else and, along with proline, it establishes a very strong triply coiled structure for collagen. The glycine is necessary as there is no room in the triple coil for any larger amino acid. Functionalized amino acids are rare in collagen.

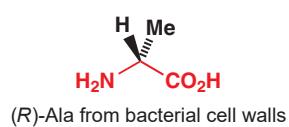
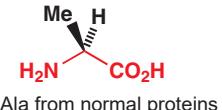
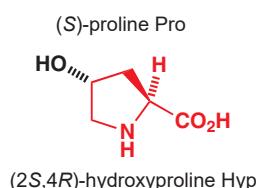
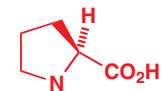
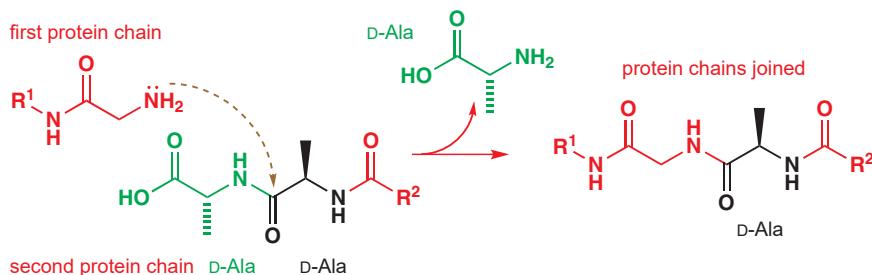
#### Hydroxyproline and scurvy

Hydroxyproline is a very unusual amino acid. It is not incorporated into the growing protein chain when collagen is synthesized—instead the collagen molecule is assembled with Pro where Hyp is need. Once the protein is complete, some of the proline residues are oxidized to hydroxyproline. This oxidation requires vitamin C, and without it collagen cannot be formed. This is why vitamin C deficiency causes scurvy—the symptoms of scurvy suffered by 18th-century sailors (loose teeth, sores, and blisters) were caused by the inability to make collagen.

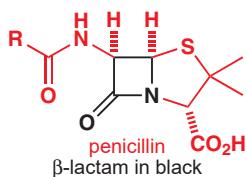
### Antibiotics exploit the special chemistry of bacteria

We have repeatedly emphasized that all life has very similar chemistry. From the biochemical point of view the most important division is that separating *prokaryotes* from *eukaryotes*. Prokaryotes, which include bacteria, evolved first and have simple cells with no nucleus. Eukaryotes, which include plants, mammals, and all other multicellular creatures, evolved later and have more complex cells, including nuclei. Even then, much of the biochemistry on both sides of the divide is the same.

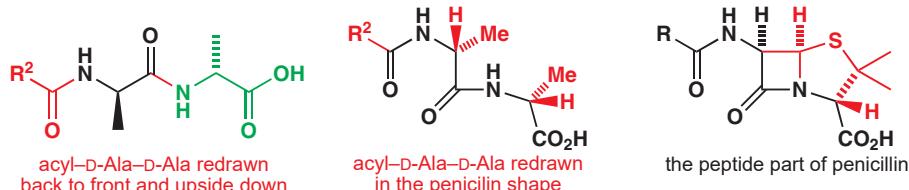
When medicinal chemists are looking for ways to attack bacteria, one approach is to interfere with chemistry carried out by prokaryotes but not by us. The most famous of these attacks is aimed at the construction of the cell walls of some bacteria that contain ‘unnatural’ (*R*)- (or *D*-) amino acids. Bacterial cell walls are made from glycopeptides of an unusual kind. Polysaccharide chains are cross-linked with short peptides containing (*R*)-alanine (*D*-Ala). Before they are linked up, one chain ends with a glycine molecule and the other with *D*-Ala–*D*-Ala. In the final step in the cell wall synthesis, the glycine attacks the *D*-Ala–*D*-Ala sequence to form a new peptide bond by displacing one *D*-Ala residue.



■ The reason bacteria have evolved to use these ‘unnatural’ *D*-amino acids in their cell walls is to protect them against the enzymes in animals and plants, which cannot digest proteins containing *D*-amino acids.

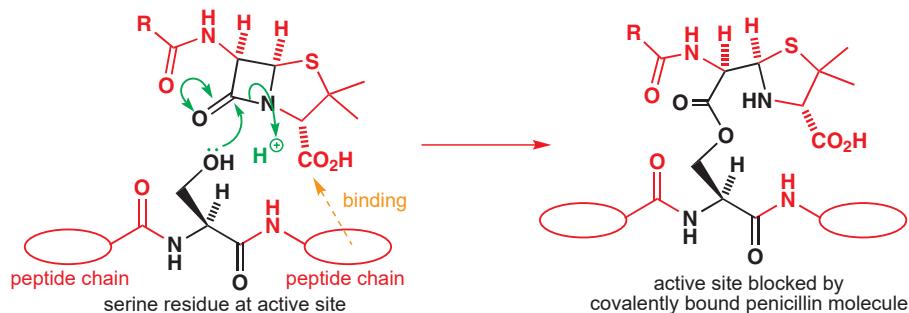


The antibiotic penicillin works by interfering with this step—although this was not even suspected when penicillin was discovered. Penicillin inhibits the enzyme that catalyses the D-Ala transfer in a very specific way. It first binds specifically to the enzyme (so it must be a mimic of the natural substrate) and it then reacts with the enzyme and inactivates it by blocking a vital OH group at the active site. If we emphasize the peptide nature of penicillin and compare it with D-Ala–D-Ala, the mimicry may become clearer.



Penicillin imitates D-Ala and binds to the active site of the enzyme, encouraging the OH group of a serine residue to attack the reactive strained β-lactam. This same OH group of the same serine residue would normally be the catalyst for the D-Ala–D-Ala cleavage used in the building of the bacterial cell wall. The reaction with penicillin ‘protects’ the serine and irreversibly inhibits the enzyme. The bacterial cell walls cannot be completed, and the bacterial cells literally burst under the pressure of their contents. Penicillin does not kill bacteria whose cell walls are already complete but it does prevent new bacteria being formed.

Our current last line of defence against bacteria resistant to penicillin, and other antibiotics, is vancomycin. Vancomycin works by binding to the D-Ala–D-Ala sequences of the bacterial cell wall.



## Sugars—just energy sources?

Sugars are the building blocks of carbohydrates. They used to be thought of as essential but rather dull molecules whose function was principally the (admittedly useful) storage of energy. In fact they have much more interesting and varied roles than that. We have already noted that ribose plays an intimate role in DNA and RNA structure and function. Sugars are also often found in intimate association with proteins and are involved in recognition and adhesion processes.

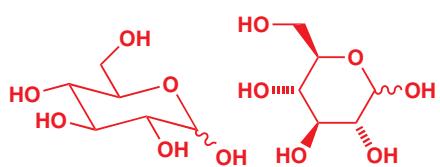
Here are two examples. How does a sperm recognize the egg and penetrate its wall? Recognition of a carbohydrate attached to the membrane of the egg was the first event in all of our lives. And how does a virus get inside a cell? Here again, the recognition process involves specific carbohydrates. One of the ways in which AIDS is being tackled with some success is by a combination of the antiviral drugs we met earlier in this chapter with HIV protease inhibitor drugs, which aim to prevent recognition and penetration of cells by HIV.

### Sugars normally exist in cyclic forms with much stereochemistry

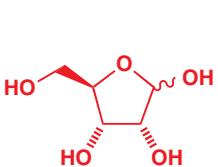
The most important sugar is glucose. It has a saturated six-membered ring containing oxygen and it is best drawn in a chair conformation with nearly all the substituents equatorial. It can also be drawn as a flat configurational diagram. We have already met one sugar in this chapter, ribose, because it was part of the structure of nucleic acids. This sugar is a five-membered saturated oxygen heterocycle with many OH groups. Indeed, you can define a sugar as an oxygen heterocycle with every carbon atom bearing an oxygen-based functional group—usually OH, but alternatively C=O.

- There is more about the development of drugs for treating HIV in Chapter 43.

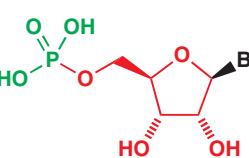
two representations of glucose



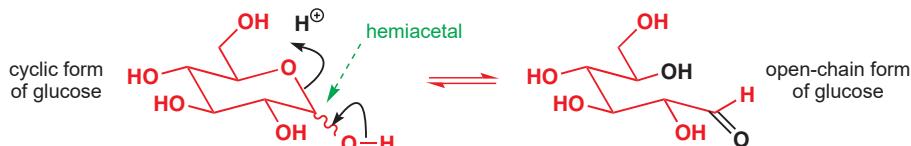
ribose



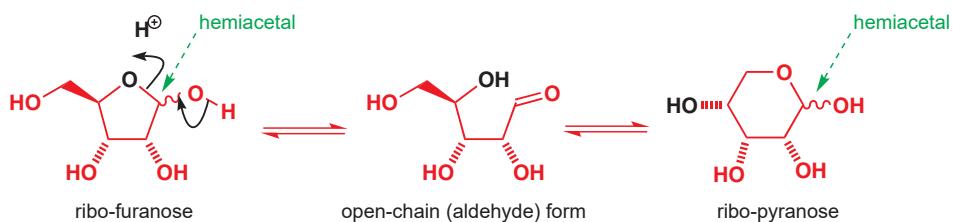
a ribonucleotide



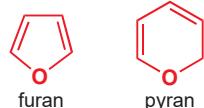
The drawings of glucose and ribose show a number of stereogenic centres, with one centre undefined—an OH group shown with a wavy bond. This is because one centre in both sugars is a hemiacetal and therefore the molecule is in equilibrium with an open-chain hydroxy-aldehyde. For glucose, the open-chain form is this.



When the ring closes again, any of the OH groups could cyclize on to the aldehyde but there is no real competition—the six-membered ring is more stable than any of the alternatives (which could have three-, four-, five-, or seven-membered rings—check for yourself). However, with ribose there is a reasonable alternative.



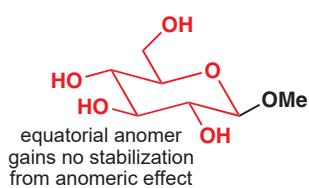
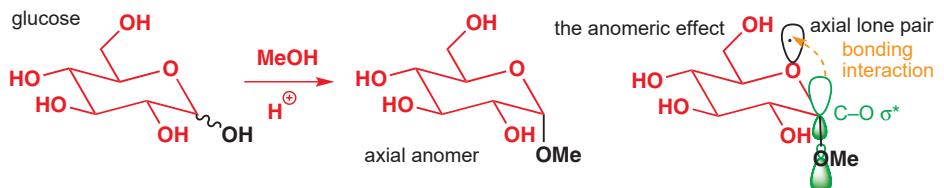
The most important sugars may exist in an open-chain form, as a five-membered oxygen heterocycle (called a *furanose*, after the five-membered aromatic compound furan) or a six-membered oxygen heterocycle (called a *pyranose*, after the six-membered pyran). Glucose prefers the pyranose structure; ribose prefers the furanose structure.



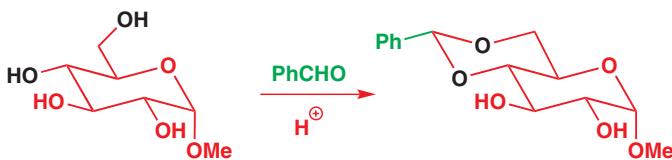
### Sugars can be fixed in one shape by acetal formation

The simplest way to fix glucose in the pyranose form is to trap it as an acetal. Acid-catalysed condensation with an alcohol, methanol, for example, gives an acetal and, remarkably, the acetal has an *axial* OR group. Acetal formation is under thermodynamic control (Chapter 11) so the axial compound must be the more stable. This is because of the anomeric effect—so-called because this C atom is called the anomeric position and the acetal diastereoisomers are called anomers. The effect is a bonding interaction between the axial lone pair on the oxygen atom in the ring and the  $\sigma^*$  orbital of the OMe group.

► The anomeric effect was discussed in Chapter 31, and you should check that you can still write down the mechanism of acetal formation you learned in Chapter 11.

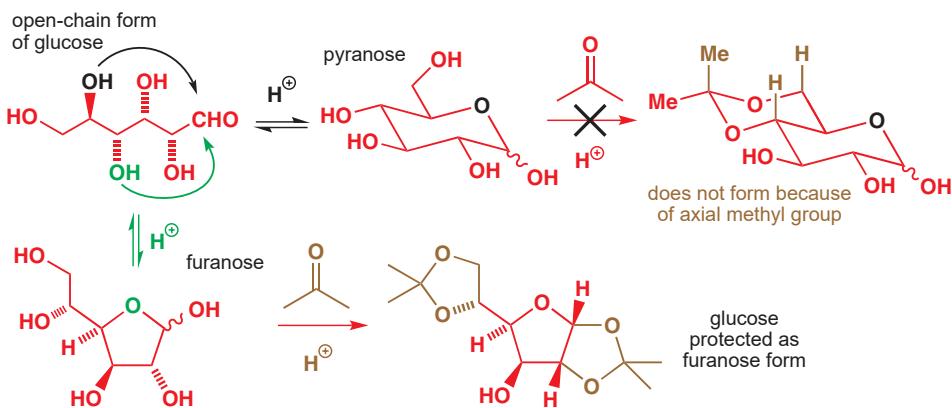


The formation of acetals allows a remarkable degree of control over the chemistry of sugars. Apart from the simple glucoside acetal we have just seen, there are three important acetals worth understanding because of the way in which they illustrate stereoelectronic effects—the interplay of stereochemistry and mechanism. If we make an acetal from methyl glucoside and benzaldehyde, we get a single compound as a single stereoisomer.



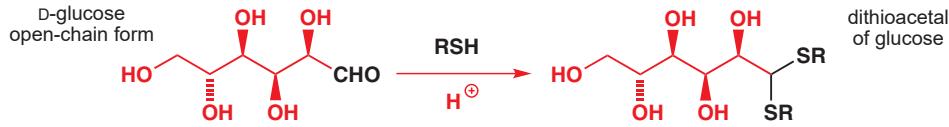
The new acetal could have been formed between any of the adjacent OH groups in the starting material but it chose the only pair (the black OH groups) which give a six-membered ring. The stereochemistry of glucose is such that the new six-membered ring is *trans*-fused to the old so that a beautifully stable all-chair bicyclic structure results, with the phenyl group in an equatorial position in the new chair acetal ring. Acetal formation is under thermodynamic control and this product is the most stable possible acetal.

Acetal formation from sugars and acetone shows quite different selectivity. For a start, cyclic acetals of acetone prefer to be five- rather than six-membered rings. In a six-membered ring, one of the acetone's methyl groups would have to be axial, so the five-membered ring is preferred. A 5,5 or 5,6 ring fusion is more stable if it is *cis*, and so acetone acetals (acetonides) form preferentially from *cis* 1,2-diols. Glucose has no neighbouring *cis* hydroxyls in the pyranose form, but in the furanose form it can have two pairs. Formation of an acetal with acetone fixes glucose in the furanose form. This is all summarized in the scheme below.



The open-chain form of glucose is in equilibrium with both the pyranose and the furanose forms through reversible hemiacetal formation using the black and green OH groups, respectively. Normally, the pyranose form is preferred, but the furanose form can form a double acetal with acetone, one acetal having two *cis*-fused five-membered rings and the other being on the side chain. This double acetal is the product isolated from the reaction.

If we want to fix glucose in the open-chain form, we must make an 'acetal' of quite a different kind using a thiol ( $\text{RSH}$ ) instead of an alcohol, an aldehyde, or a ketone. The thiol combines with the aldehyde group of the open-chain form to give a stable dithioacetal. The dithioacetal is evidently more stable than the alternative hemiacetals or monothioacetals that could be formed from the pyranose or furanose forms.

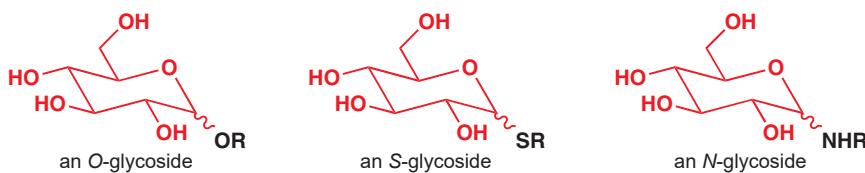


**■ The most important *N*-glycosides are, of course, the nucleotides, which we have already described in some detail.**

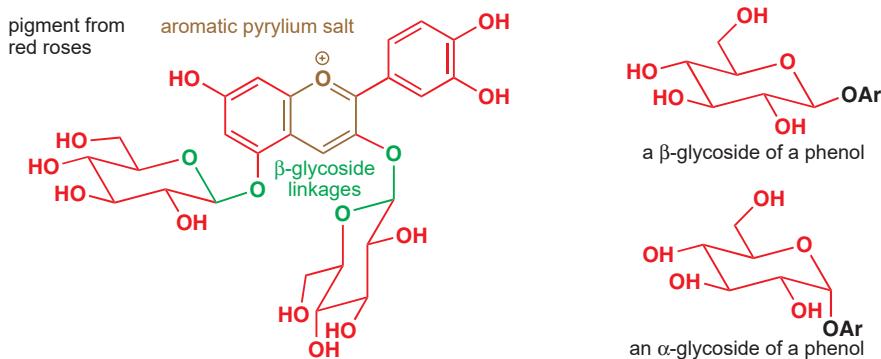
► You saw an example in Chapter 6 (p. 129) where acetone cyanohydrin is found in the cassava plant as a glucoside.

### Glycosides in nature

Many alcohols, thiols, and amines occur in nature as glycosides, that is as *O*-, *S*-, or *N*-acetals at the anomeric position of glucose. The purpose of attaching these compounds to glucose is often to improve solubility or transport across membranes—to expel a toxin from the cell, for example. Sometimes glucose is attached in order to stabilize the compound so that glucose appears as nature's protecting group, rather as a chemist might use a THP group (Chapter 23).



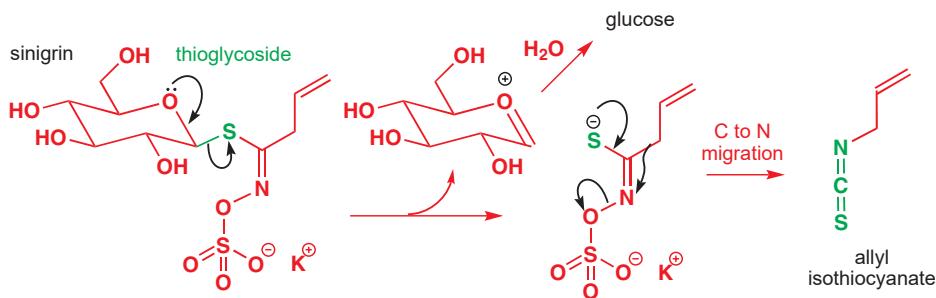
O-Glycosides occur in immense variety with glucose and other sugars being joined to the OH groups of alcohols and phenols to form acetals. The stereochemistry of these compounds is usually described by the Greek letters  $\alpha$  and  $\beta$ . If the OR bond is down, it's an  $\alpha$ -glycoside; if up, a  $\beta$ -glycoside. An attractive example is the pigment of red roses, which is an interesting aromatic oxygen heterocycle (an anthocyanidin). Two of the phenolic OH groups are present as  $\beta$ -glycosides.



### $\alpha$ - and $\beta$ -glycosides

It is easy to remember which is which, as long as you accept that people who devise nomenclature must be maliciously foolish. Just as *E* means *trans* and *Z* means *cis* (each letter has the shape of the *wrong* isomer), so  $\alpha$  means *below* and  $\beta$  means *above*—each word begins with the *wrong* letter.

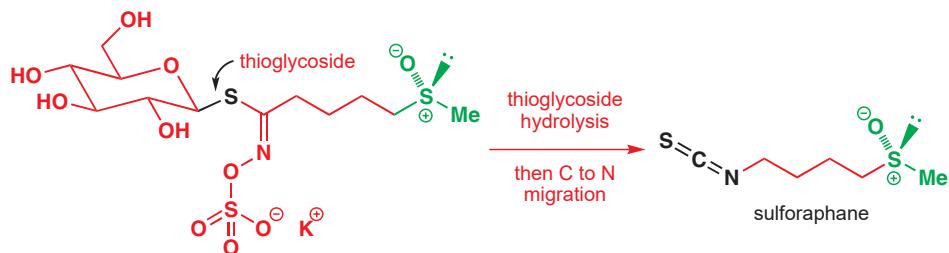
It's often proposed that there are special benefits to health in eating broccoli and brussels sprouts because of the sulfur-containing antioxidants they contain. These compounds are unstable isothiocyanates. They are not usually present in the plant; damage—by cutting or cooking, for example—induces a glycosidase (an enzyme which hydrolyses glycosides) to releases the sulfur compound from its glucose protection. A simple example is sinigrin. The S-glycosides of the sinigrin group start to hydrolyse in the same way. The sulfur atom is the better leaving group when it leaves as an anion (though worse than oxygen when the hydrolysis occurs in acidic conditions) and the anion is additionally stabilized by conjugation.



The next step is surprising. A rearrangement occurs, rather similar to the Beckmann rearrangement, in which the alkyl group migrates from carbon to nitrogen and an isothiocyanate ( $\text{R}-\text{N}=\text{C}=\text{S}$ ) is formed. Sinigrin occurs in mustard and horseradish, and it is the release of the allyl isothiocyanate that gives these their 'hot' taste. When mustard powder is mixed with water, the hot taste develops over some minutes as sinigrin is hydrolysed to the isothiocyanate.

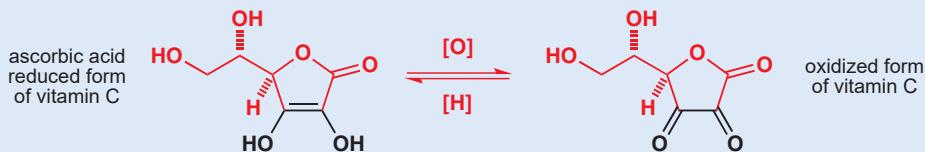
→ The Beckmann rearrangement is described in Chapter 36, p. 958.

The S-glycoside in broccoli and brussels sprouts that is proposed to offer protection from cancer is somewhat similar but has one more carbon atom in the chain and contains a sulfoxide group as well. Hydrolysis of the S-glycoside is followed by the same rearrangement, producing a molecule called sulforaphane. Sulforaphane protects against cancer-causing oxidants by inducing the formation of a reductive enzyme.



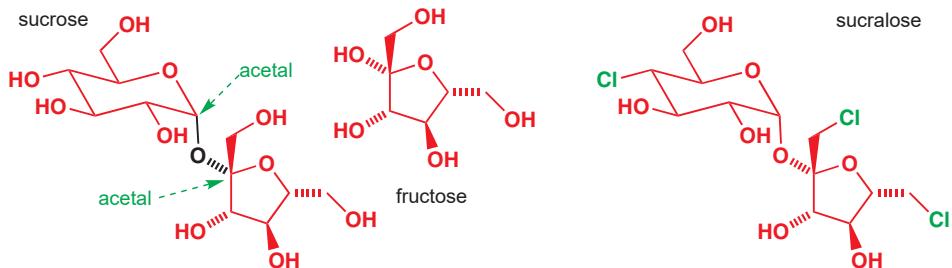
### Vitamin C is a derivative of glucose

Nature makes some important compounds from simple sugars. Vitamin C—ascorbic acid—is one of these. It certainly looks very like a sugar as it has six carbon atoms, each having an oxygen atom as substituent as well as an oxygen heterocycle. Like glutathione, it protects cells from stray oxidants as well as being involved in primary redox pathways (we mentioned earlier its role in collagen synthesis). Its reduced and oxidized forms are shown below.



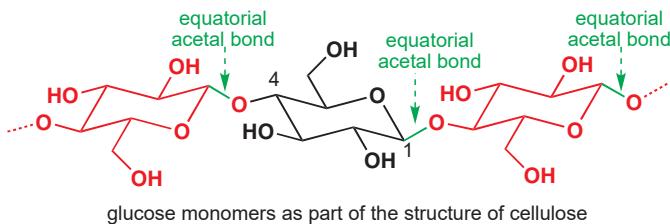
### Most sugars are embedded in complex carbohydrates

The most familiar of all sugars is sucrose—the mixed acetal formed from glucose and fructose. Sucrose is of course sweet, and is easily metabolized into fats. But if three of the OH groups in sucrose are replaced by chlorine atoms, a compound 600 times as sweet is produced: less of it is needed to get the same sweet taste and the chlorines reduce the rate of metabolism so that much less fat is made. This is the compound sucralose, discovered by chemists at Tate & Lyle and now used to sweeten soft drinks.



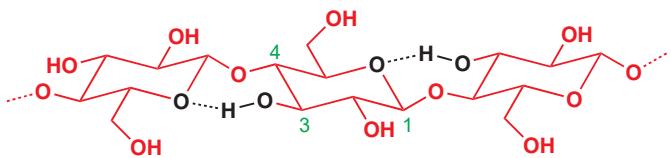
$10^{15}$  kg per year of cellulose is literally an astronomical amount: it's about the mass of one of the moons of Mars, Deimos. Our moon weighs  $10^{22}$  kg.

Sucrose is a disaccharide—two simple sugars linked by an acetal. In general, saccharides have the same relationship to sugars as peptides and proteins have to amino acids. One of the most abundant compounds in nature is a saccharide: cellulose, the structural material of plants. It is a glucose polymer and is produced in simply enormous quantities (about  $10^{15}$  kg per year). Each glucose molecule is joined to the next through an acetal formed by attack of the C4 hydroxyl group of one glucose molecule on the anomeric carbon atom of the next. Here is that basic arrangement.



glucose monomers as part of the structure of cellulose

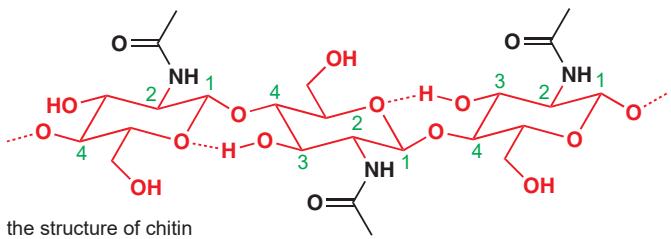
Notice that the anomeric bonds are all equatorial. This means that the cellulose molecule is linear in general outline. It is made rigid by extra hydrogen bonds between the 3-OH groups and the ring atoms—like this.



The polymer is also coiled to increase stability still further. All this makes cellulose very difficult to hydrolyse, and humans cannot digest cellulose as we do not have the necessary enzymes. Other mammals have evolved devices such as multiple stomachs (in ruminants, such as cattle) to enable them to degrade cellulose.

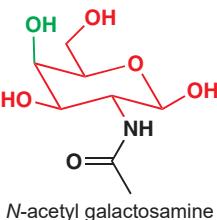
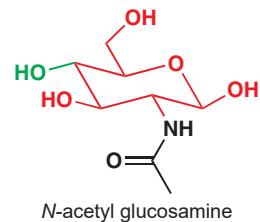
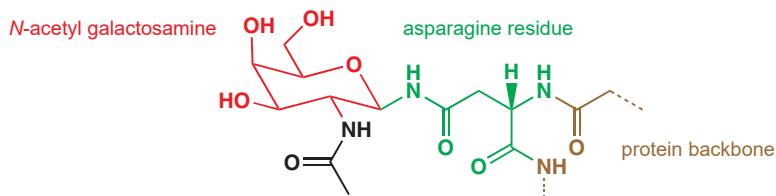
### Amino sugars add versatility to saccharides

Amino sugars are carbohydrates into which nitrogen is incorporated. These molecules allow proteins and sugars to combine and produce structures of remarkable variety and beauty. The most common amino sugars are *N*-acetyl glucosamine and *N*-acetyl galactosamine, which differ only in stereochemistry. The hard outer skeletons of insects and crustaceans contain chitin, a polymer very like cellulose but made of acetyl glucosamine instead of glucose itself. It coils up in a similar way and provides the toughness of crab shells and beetle cases.



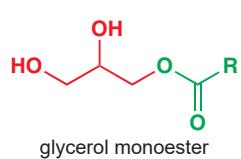
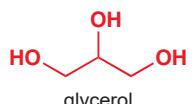
the structure of chitin

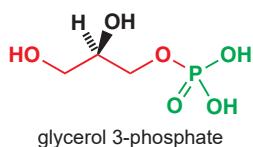
Cell membranes must not be so impermeable as they need to allow the passage of water and complex molecules. These membranes contain *glycoproteins*—proteins with amino sugar residues attached to asparagine, serine, or threonine in the protein. The attachment is at the anomeric position so that these compounds are *O*- or *N*-glycosides of the amino sugars. The structure below shows *N*-acetyl galactosamine attached to an asparagine residue as an *N*-glycoside.



## Lipids

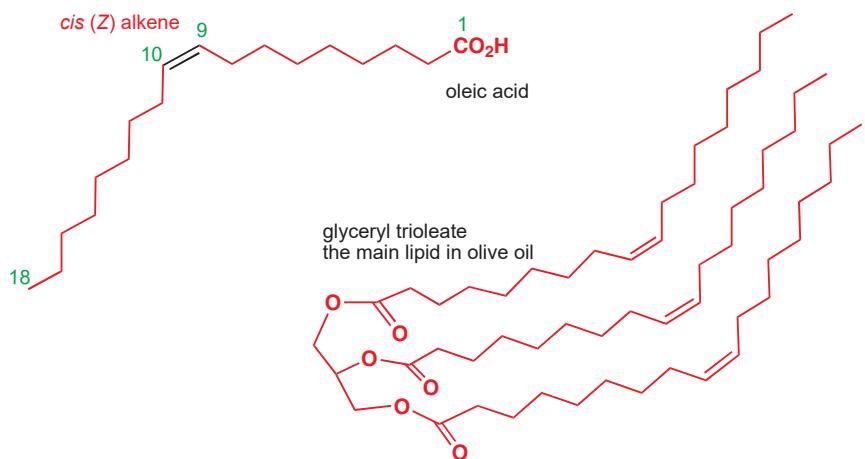
Lipids (fats) are the principal components of cell membranes. Along with cholesterol, also a component of the cell membrane, they have acquired a bad name, but they are nonetheless essential to the function of membranes as selective barriers to the movement of molecules. The most common types of lipids are esters of glycerol. Glycerol is just propane-1,2,3-triol but it has interesting stereochemistry. It is not chiral as it has a plane of symmetry, but the two primary OH groups are enantiotopic. If one of them is modified—by esterification, for





example—the molecule becomes chiral. Natural glycerol 3-phosphate is such an ester and it is optically active.

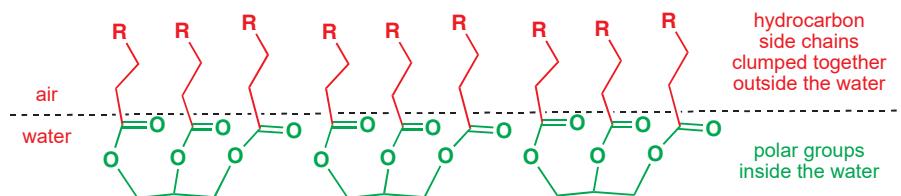
A typical lipid in foodstuffs is the triester formed from glycerol and oleic acid, which is the most abundant lipid in olive oil. Oleic acid is a mono-unsaturated fatty acid—it has one *Z* double bond in the middle of the C<sub>18</sub> chain. This bond gives the molecule a marked kink in the middle. The compound actually present in olive oil is the triester, also kinked.



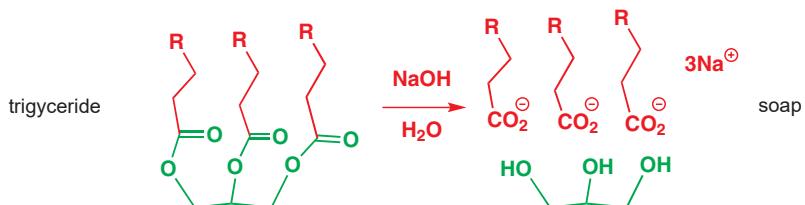
### Oil and water do not mix

You may have done the Langmuir trough experiment in a physical chemistry practical class. This involves measuring the size of a molecule by allowing an oil to spread on the surface of water in a unimolecular layer.

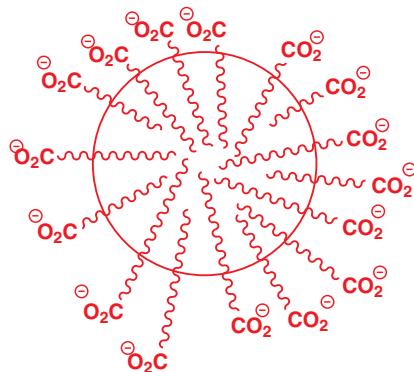
The lipid has, more or less, the conformation shown in the diagram with all the polar ester groups at one end and the hydrocarbon chains bunched together in a non-polar region. Oil and water do not mix, it is said, but triglyceride lipids associate with water in a special way. A drop of oil spreads out on water in a very thin layer. It does so because the ester groups sit inside the water and the hydrocarbon side chains stick out of the water and associate with each other.



When triglycerides are boiled with alkali, the esters are hydrolysed and a mixture of carboxylate salts and glycerol is formed. This is how soap is made—hard soap is the sodium salt and soft soap the potassium salt.



When a soap is suspended in water, the carboxylate groups have a strong affinity for the water and so oily globules or **micelles** are formed with the hydrocarbon side chain inside. It is these globules that remove greasy dirt from you or your clothes.



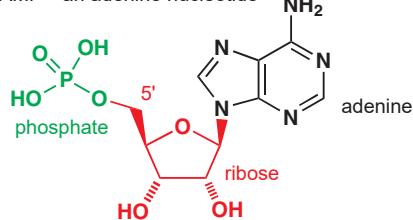
## Mechanisms in biological chemistry

Nature uses the same chemistry as we do in the laboratory, and to do that chemistry she needs reagents. Chemists are free to use temperatures typically ranging 100 °C either side of 20 °C, any solvents they choose, inert or reactive atmospheres, and so on. Not so nature: all nature's reagents must work at ambient temperature in the presence of water and in the presence of a reactive gas, oxygen. In this section we will survey some of nature's solutions to these challenges.

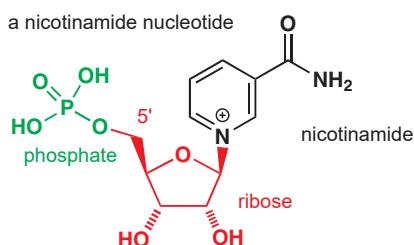
### Nature's NaBH<sub>4</sub> is a nucleotide: NADH or NADPH

You met nucleotides, and their role in the structure of nucleic acids, earlier in this chapter. Nature also uses nucleotides as reagents. Here is the structure of AMP, just to remind you of a structure you met before, side by side with a pyridine-containing nucleotide.

AMP—an adenine nucleotide



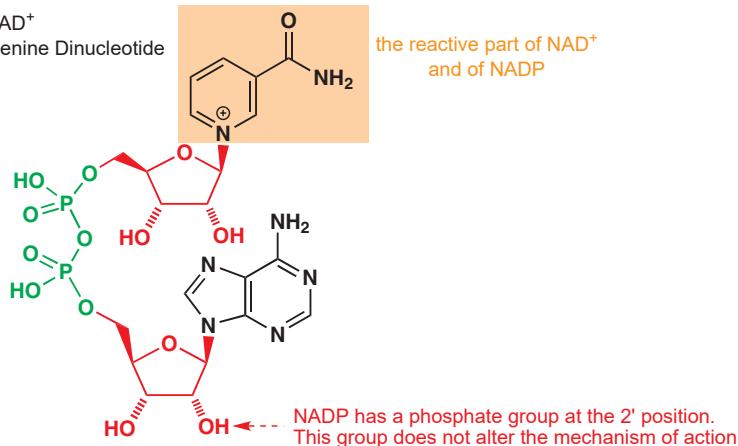
a nicotinamide nucleotide



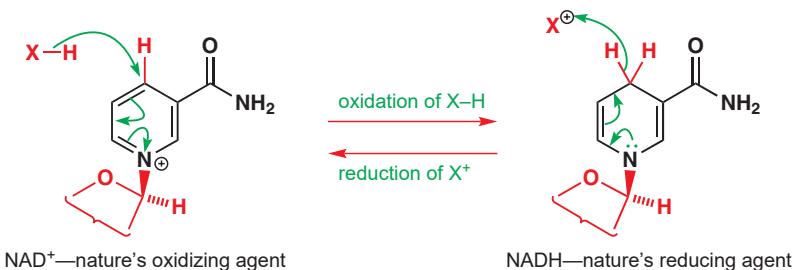
These two nucleotides can combine together as a pyrophosphate to give a dinucleotide called nicotinamide adenine dinucleotide, or NAD (or NAD<sup>+</sup>—note the positively charged pyridinium). Notice that the link is not at all the same as in the nucleic acids. The latter are joined by one phosphate that links the 3' and 5' positions. Here we have a pyrophosphate link between the two 5' positions.

NAD<sup>+</sup>  
Nicotinamide Adenine Dinucleotide

the reactive part of NAD<sup>+</sup> and of NADP

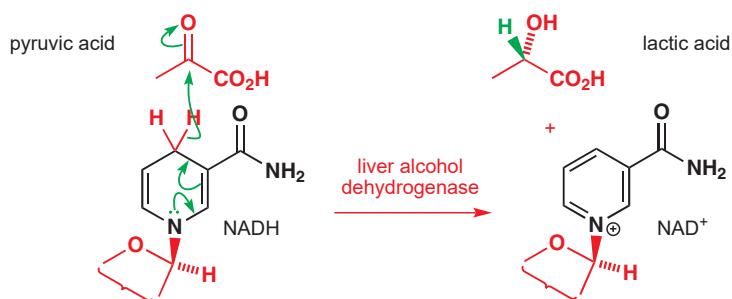


The positively charged pyridinium ring is the part of the molecule which does all the work and from now on we will draw only the reactive part for clarity. NAD<sup>+</sup> is one of nature's most important oxidizing agents. Some biochemical pathway reactions use NADP instead, but this differs only in having an extra phosphate group on the adenosine portion so the same part structure will do for both. NAD<sup>+</sup> and NADP both work by accepting a hydrogen atom and a pair of electrons from another compound. The reduced compounds are called NADH and NADPH.

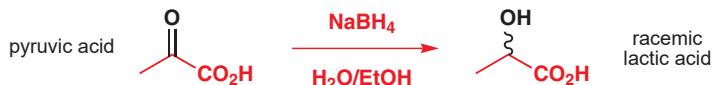


The names of enzymes are usually chosen to tell us where they come from and what job they do and the name ends '-ase'. A **dehydrogenase** is a redox enzyme which catalyses the removal (or, as in this case, the addition) of hydrogen.

The reduction of NAD<sup>+</sup> (and NADP) is reversible, and NADH is itself a reducing agent. We will first look at one of its reactions: a typical reduction of a ketone. The ketone is pyruvic acid and the reduction product is lactic acid—both important metabolites. The reaction is catalysed by an alcohol dehydrogenase.



This is a reaction that would also work in the laboratory with NaBH<sub>4</sub> as the reducing agent, but there is a big difference. The product from the NaBH<sub>4</sub> reaction *must* be racemic—the starting material, reagent, and solvent are all achiral.



► If you are not clear about enantioselective reactions and why NaBH<sub>4</sub> must give a racemic mixture, re-read Chapter 41. If you are not clear about the terms 'enantiotopic' and 'prochiral' re-read Chapters 31 and 33. If you are not clear about what enantiomers are, you must re-read Chapter 14 now.

► For more on reductive amination, see Chapter 11.

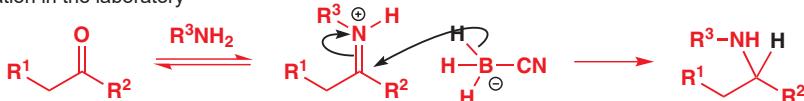
But the product from the enzymatic reaction is optically active. The two faces of pyruvic acid's carbonyl group are enantiotopic and, by controlling the addition so that it occurs from one face only, the enzyme-catalysed reaction gives a single enantiomer of lactic acid.



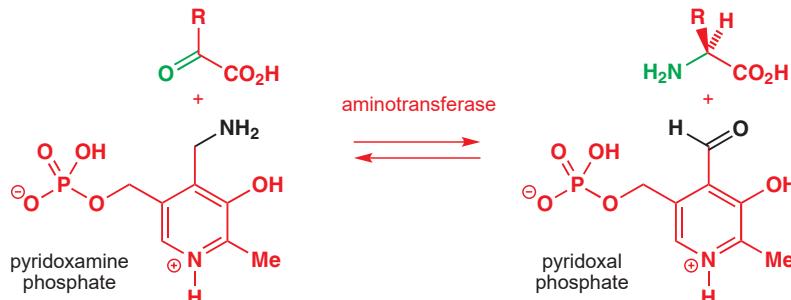
### Reductive amination in nature

One of the best methods for making amines in the laboratory is **reductive amination**, in which an imine (formed from a carbonyl compound and an amine) is reduced to a saturated amine. Common reducing agents include NaCNBH<sub>3</sub> and hydrogen with a catalyst.

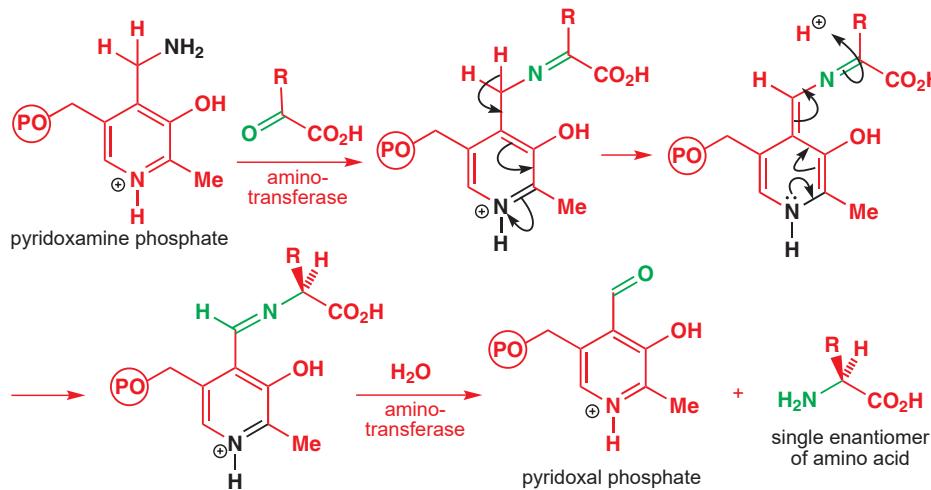
reductive amination in the laboratory



This reaction, of course, produces racemic amines. But nature transforms this simple reaction into an enantioselective and reversible one that is beautiful in its simplicity. The reagents are a pair of substituted pyridines called pyridoxamine and pyridoxal, and the enzyme is an aminotransferase.



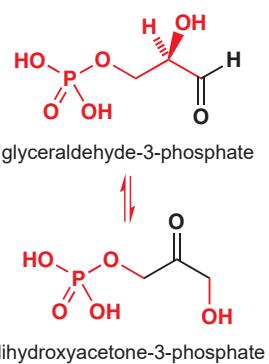
The mechanism of the amination starts with the formation of an imine from the black amino group and the green carbonyl. Removal of the now very acidic proton between the protonated pyridine and the conjugated imino-carboxylic acid gives a dihydropyridine, which rearomatizes by protonation next to the carboxylic acid. This step is enantioselective, with the proton being delivered from the enzyme. Finally, hydrolysis of the new imine gives pyridoxal and a single enantiomer of the amino acid.

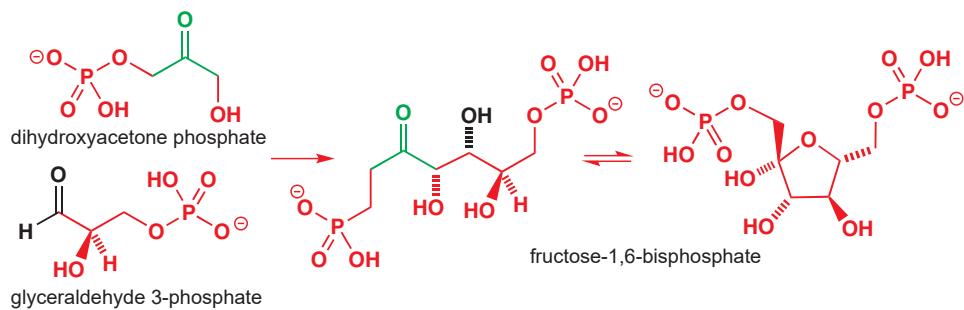


■ 'OP' or 'P' in a circle is commonly used to represent a phosphate group.

### Nature's enolate equivalents: lysine enamines and coenzyme A

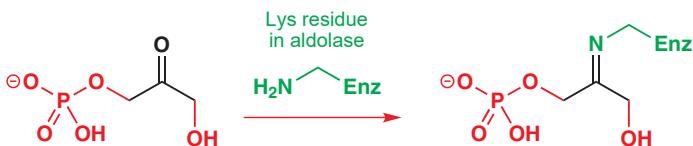
Nature breaks down glucose to produce energy, and in doing so produces smaller molecules which enter the citric acid cycle and are converted ultimately to carbon dioxide. In the other direction, the six-carbon sugar fructose can be made from two three-carbon fragments. The key reaction in both cases is the step in which the C–C bond linking the two C<sub>3</sub> sugars is formed or broken. The C<sub>3</sub> sugars are glyceraldehyde and dihydroxyacetone, both as their phosphate esters, and the reaction between them is an aldol condensation. The enol of dihydroxyacetone phosphate attacks the electrophilic aldehyde carbonyl group of glyceraldehyde 3-phosphate, catalysed by an enzyme named aldolase. The product is a ketohexose (i.e. a six-carbon sugar with a ketone carbonyl group), fructose-1,6-bisphosphate.



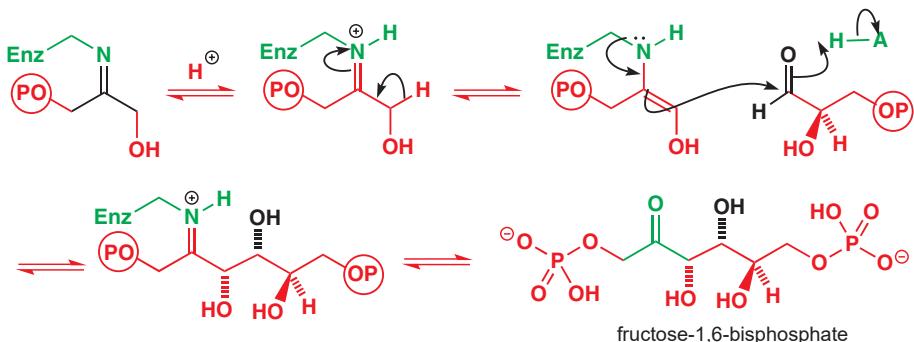


No enolate ion is formed in this aldol reaction. Instead a lysine residue in the aldolase enzyme forms an imine with the keto-triose.

The rest of the aldolase molecule is represented by 'Enz'.

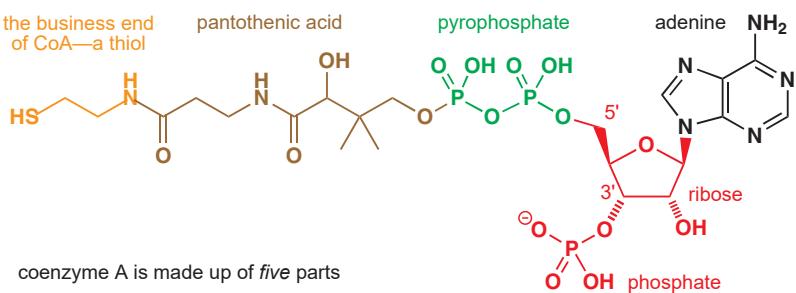


Proton transfers allow this imine to be converted into an enamine, which acts as the nucleophile in the aldol reaction. Stereochemical control (it's a *syn* aldol) comes from the way in which the two molecules are held by the enzyme as they combine. The product is the imine, which is hydrolysed to the open-chain form of fructose-1,6-bisphosphate.



Many other reactions in nature use enamines, mostly those formed from lysine. However, a more common enol equivalent is based on thiol esters derived from coenzyme A. Coenzyme A is an adenine nucleotide at one end, linked by a 5'-pyrophosphate to pantothenic acid, a compound that looks rather like a tripeptide, and then to an amino thiol. Here is the structure broken down into its parts.

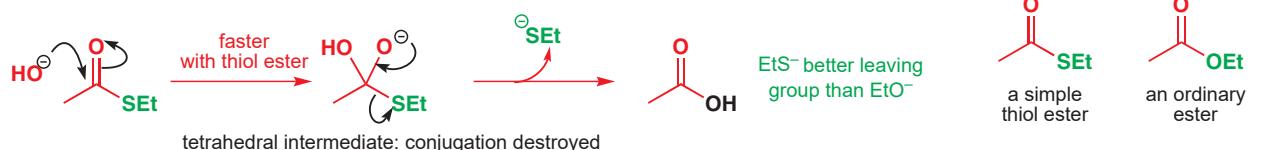
Compare this structure with that of NAD—the adenine nucleotide is the same, as is the 5'- pyrophosphate link. The difference is at the other end of that link where we find this new tripeptide-like molecule and not another nucleotide. There is also a 3'-phosphate on the ribose ring not present in NAD (and note that while NADP contains a phosphorylated ribose, its phosphate is on the 2' hydroxyl group!).



By now you will realize that most of this molecule is there to allow interaction with the various enzymes that catalyse the reactions of coenzyme A. Coenzyme A is conveniently abbreviated in structures to CoASH, where the SH is the vital thiol functional group, and all the

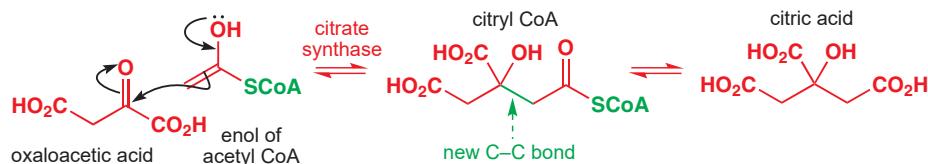
reactions we will be interested in are those of esters of CoASH. These are thiol esters, as opposed to normal alcohol esters, and the difference is worth a few comments.

Thiol esters are less conjugated than ordinary esters, and ester hydrolysis occurs more rapidly with thiol esters than with ordinary esters because in the rate-determining step (nucleophilic attack on the carbonyl group) there is less conjugation to destroy. The thiolate is also a better leaving group.

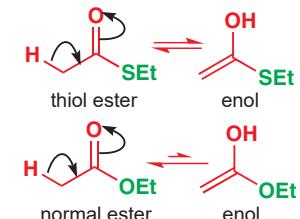


Another reaction that goes better with thiol esters than with ordinary esters is enolization. This is an equilibrium reaction and the enol has lost the conjugation present in the ester. Again, a thiol ester has less to lose so is more enolized, and it is the enolization of thioesters of coenzyme A that we are now going to discuss.

We mentioned the citric acid cycle earlier but we have not so far discussed the chemistry involved. The citric acid cycle allows metabolism to shunt carbon atoms between small molecules, and the key step is the synthesis of citric acid from oxaloacetate and acetyl CoA. The reaction is essentially an aldol reaction between the enol of an acetate ester and an electrophilic ketone, and the enzyme which catalyses the reaction is known as citrate synthase.

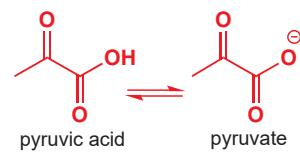


The mechanism shows the enol of acetyl CoA attacking the reactive ketone. In nature all these reactions are catalysed by the enzyme. In the C–C bond-forming step, one histidine residue removes the enol proton and another histidine, in its protonated form, is placed to donate a proton to the oxygen atom of the ketone. You should see now why histidine is so useful to enzymes: its imidazole ring means it can act either as an acid or as a base at neutral pH.



► The pK<sub>a</sub> of protonated imidazole is about 7: see Chapter 8.

► This is general acid catalysis, as described in Chapter 39.

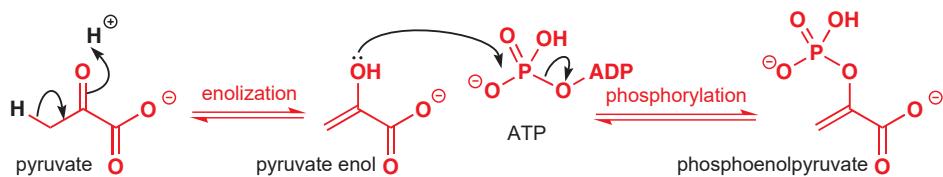


► For an explanation of the effect of two adjacent carbonyl groups, see Chapter 26, p. 643.

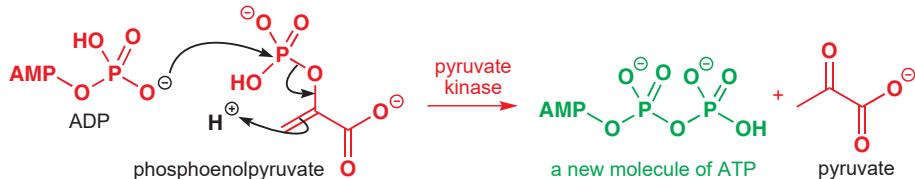
## Phosphoenolpyruvate

Pyruvic acid is an important metabolite in its own right, as we shall see shortly. It is the simplest  $\alpha$ -keto-acid (2-oxopropanoic acid). Having the two carbonyl groups adjacent makes them more reactive: the ketone is more electrophilic and enolizes more readily, and the acid is stronger.

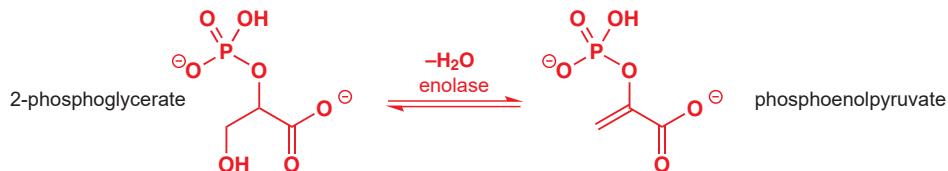
Nature uses the enol phosphate of pyruvic acid (phosphoenolpyruvate or PEP) as an important reagent. We might imagine making this compound by first forming the enol and then esterifying on oxygen by some phosphorylating agent such as ATP.



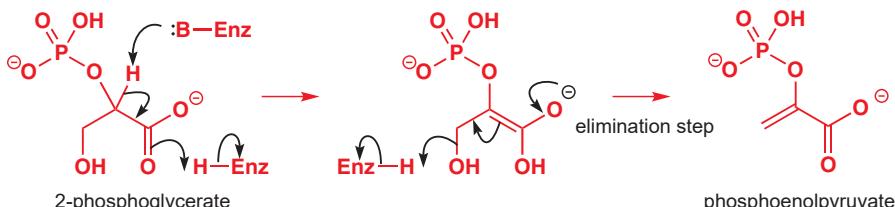
Now, in fact, this reaction does occur in nature as part of the glycolysis pathway, but it occurs almost entirely in reverse. PEP is used as a way to make ATP from ADP during the oxidation of energy-storing sugars. An enol is a better leaving group than an ordinary alcohol, especially if it can be protonated at carbon. The reverse reaction might look like this.



PEP is also used as an enol in the making of carbon–carbon bonds when the electrophile is a sugar molecule. But if PEP is not made by enolization of pyruvate, how is it made? The answer is by dehydration. The phosphate is already in place when the dehydration occurs, catalysed by the enzyme enolase.



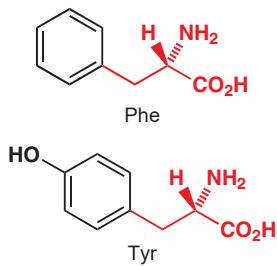
You saw in Chapter 17 how simple OH groups can be lost in dehydration reactions. Either the OH group was protonated by strong acid (this is not an option in living things) or an enol or enolate pushed the OH group out in an E1cB-like mechanism. This must be the case here as the better leaving group (phosphate) is ignored and the worse leaving group (OH) expelled.

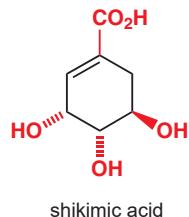
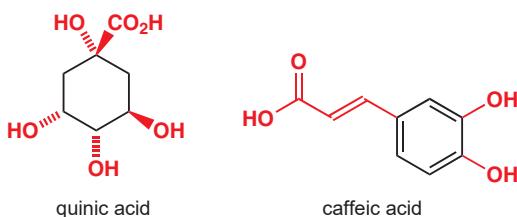
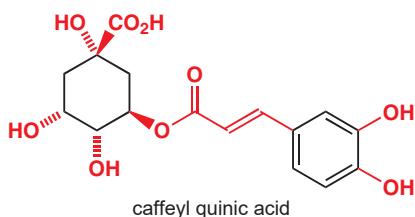


### The shikimic acid pathway

The shikimic acid pathway is responsible for the biosynthesis of a large number of aromatic compounds, particularly in plants. Most important for many mammals is the fact that plants manufacture the aromatic amino acids Phe (phenylalanine), Tyr (tyrosine), and Trp (tryptophan). These are ‘essential’ amino acids for humans—we have to have them in our diet as we cannot make them ourselves.

So how do plants make aromatic rings? A clue to the chemistry involved comes from the structure of caffeic quinic acid, a compound that forms about 13% of the soluble solids from coffee beans. A substantial proportion of instant coffee is caffeic quinic acid.

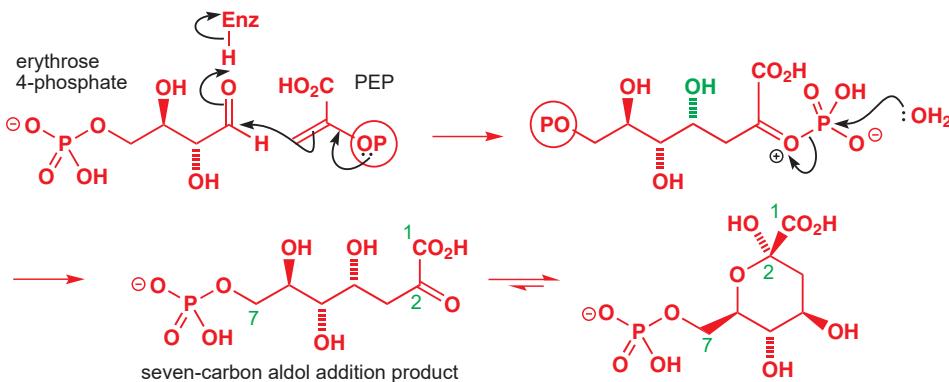




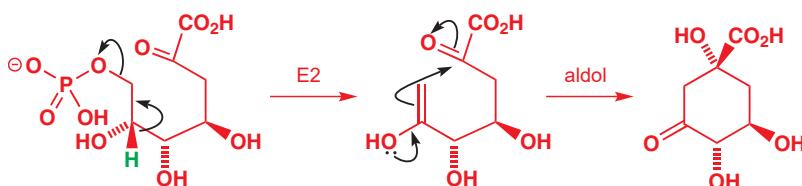
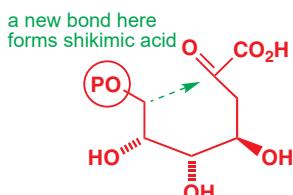
This ester has two six-membered rings—one aromatic and one saturated. You might imagine making an aromatic ring by the dehydration (losing three molecules of water) of a cyclohexane triol and the saturated ring in caffeyl quinic acid looks a good candidate. It is now known that both rings (shown in black) come from the same intermediate, shikimic acid.

→ Quinic acid will reappear in Chapter 43 as a synthetic precursor to the important anti-flu compound oseltamivir.

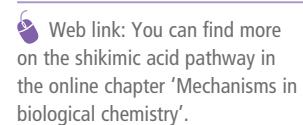
This key intermediate has given its name to nature's general route to aromatic compounds and many other related six-membered ring compounds: the shikimic acid pathway. This pathway contains some of the most interesting reactions (from a chemist's point of view) in biology. It starts with an aldol reaction between phosphoenol pyruvate as the nucleophilic enol component and the C<sub>4</sub> sugar erythrose 4-phosphate as the electrophilic aldehyde.

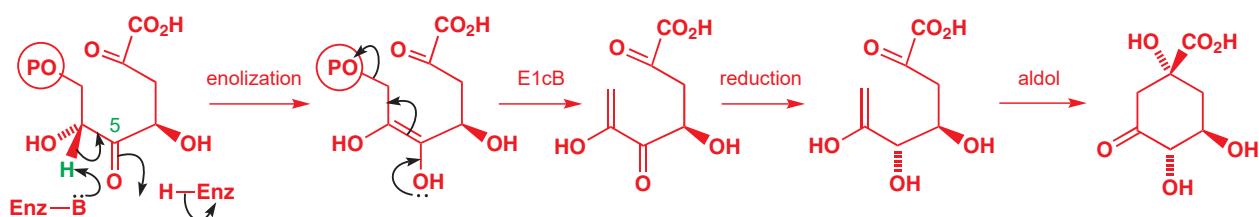


Hydrolysis of the phosphate releases the aldol product, a C<sub>7</sub>  $\alpha$ -keto-acid with one new stereogenic centre, which is in equilibrium with a hemiacetal, just like a sugar. This intermediate has the right number of carbon atoms for shikimic acid and the next stage is a cyclization. If we redraw the uncyclized C<sub>7</sub>  $\alpha$ -keto-acid in the right shape for cyclization we can see what is needed. The green arrow shows which bond needs to be formed. This bond could be formed by another aldol reaction, and there is an obvious route to the required enol by elimination of phosphate. However, this would require the removal of a proton (green in the diagram) that is not at all acidic.



The problem can be avoided if the hydroxyl group at C<sub>5</sub> is first oxidized to a ketone (using NAD<sup>+</sup> as the oxidant). Then the green proton is much more acidic, and the elimination becomes an E1cB reaction, similar to the one in the synthesis of PEP. True, the ketone must be reduced back to the alcohol afterwards but nature can deal with that easily. There are obviously several more steps to get to shikimic acid but all the C–C bonds are in place, the most significant of them being formed by aldol reactions.





You can find more on the shikimic acid pathway in the online chapter 'Mechanisms in biological chemistry'.

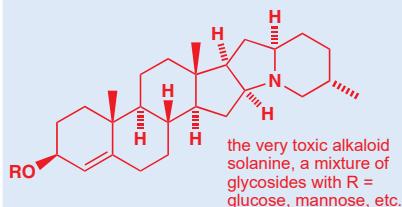
## Natural products

Organic chemists mean something particular by the phrase 'natural products'. Of course, all the compounds we have so far discussed are natural and their chemistry is common to most living things. But living things also make chemicals by the processes of secondary metabolism that are found in few, if any, other organisms. The flavouring principles of herbs and fruit, the antibiotics from moulds and the toxic alkaloids in plants are all examples. These compounds are what we mean by 'natural products', especially if they are useful to humans.

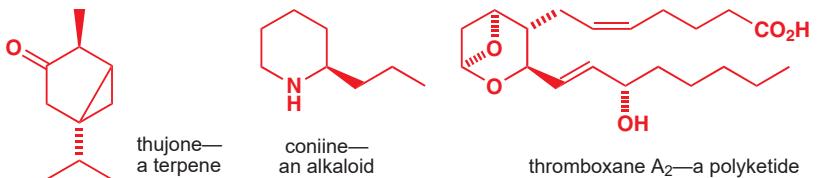
Natural products often seem to have little value to the organism itself, and are made by the processes of secondary metabolism. They are classified by the way they are made into terpenes and steroids, alkaloids, and polyketides.

### Solanaceae alkaloids

The Solanaceae family includes not only deadly nightshade (*Atropa belladonna*—hence atropine) plants but also potatoes and tomatoes. Parts of these plants also contain toxic alkaloids, for example you should not eat green potatoes because they contain the toxic alkaloid solanine.



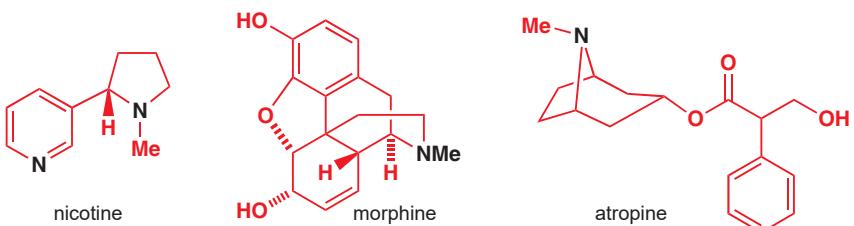
Atropine is a racemic compound but the  $(S)$ -enantiomer occurs in henbane (*Hyoscyamus niger*) and was given a different name, hyoscyamine, before the structures were known. In fact, hyoscyamine racemizes very easily just on heating in water or on treatment with weak base. This is probably what happens in the deadly nightshade plant.



Thujone is a terpene that is thought to be the poisonous principle in absinthe—the drink that reduced many artists and writers to idiocy in Paris around 1900. Coniine is an alkaloid and the poison in hemlock with which Socrates was executed. Thromboxane is a polyketide involved in blood-clot formation and is a human natural product.

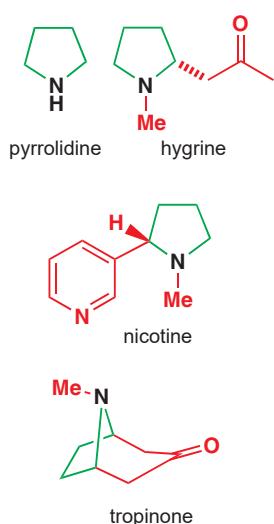
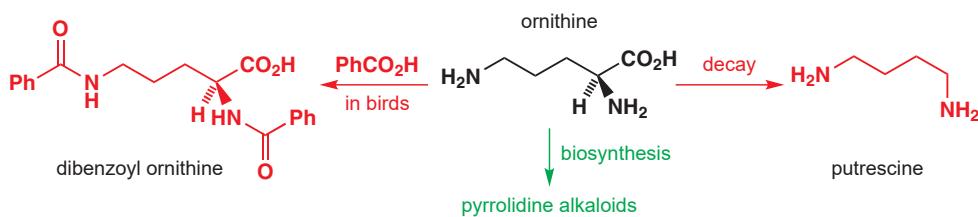
### Alkaloids are made by amino acid metabolism

Alkaloids were known in ancient times because they are easy to extract from plants and some of them have powerful and deadly effects. Any plant contains thousands of chemical compounds, but some plants, like the deadly nightshade, can be mashed up and extracted with aqueous acid to give a few compounds soluble in that medium, which precipitate on neutralization. These compounds were seen to be 'like alkali' and in 1819 Meissner, the apothecary from Halle, named them 'alkaloids'. Lucrezia Borgia already knew all about this and put the deadly nightshade extract atropine in her eyes (to make her look beautiful: atropine dilates the pupils) and in the drinks of her political adversaries to avoid any trouble in the future. Now, we would simply say that they are basic because they are amines. Below is a selection with the basic amino groups marked in black. Natural products are often named by a combination of the name of the organism from which they are isolated and a chemical part name. These compounds are all *amines* so all their names end in '-ine'. They appear very diverse in structure but all are made in nature from amino acids.

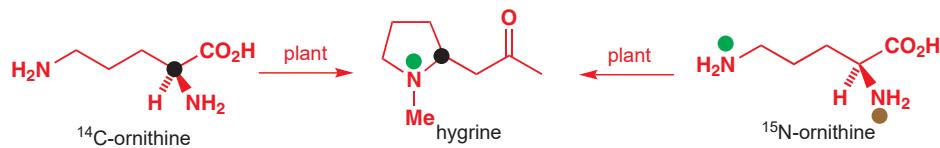


## Pyrrolidine alkaloids are made from the amino acid ornithine

Pyrrolidine is the simple five-membered cyclic amine and pyrrolidine alkaloids such as nicotine contain this ring. All are made in nature from ornithine. Ornithine is an amino acid not usually found in proteins (it's one carbon atom shorter than lysine) but most organisms use it, often in the excretion of toxic substances. If birds are fed benzoic acid ( $\text{PhCO}_2\text{H}$ ) they excrete dibenzoyl ornithine. When dead animals decay, the decarboxylation of ornithine leads to putrescine, the smell of rotten meat.

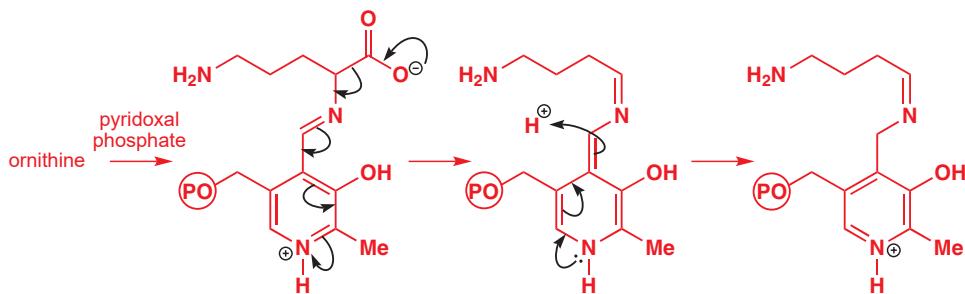


Biosynthetic pathways are usually worked out by isotopic labelling of potential precursors and in the schemes below the isotopically labelled atom is shown with a coloured blob. Some plants—notably the coca plant—produce the simple pyrrolidine alkaloid hygrine, which we will take as an illustration. If ornithine is made with a  $^{14}\text{C}$  label at its  $\alpha$  position and fed to the plant, labelled hygrine is isolated. If each amino group in ornithine is labelled in turn with  $^{15}\text{N}$ , the  $\alpha$  amino group is lost but the  $\gamma$  amino group is retained.



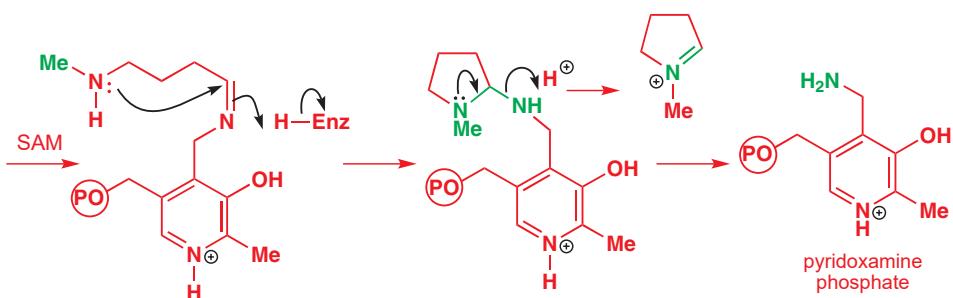
Further labelling experiments along these lines showed that the  $\text{CO}_2\text{H}$  group as well as the  $\alpha$  amino group was lost from ornithine and that the rest of the molecule makes the pyrrolidine ring. The three-carbon side chain in hygrine comes from acetate, or rather from acetyl CoA, and the  $N$ -methyl group comes from (S)-adenosyl methionine (SAM, see p. 1136).

Labelling studies such as these tell us the origin of the atoms in the natural product, and we can now work through the biosynthesis—how the molecule is put together from those precursors. The first step is a pyridoxal-catalysed decarboxylation of ornithine.

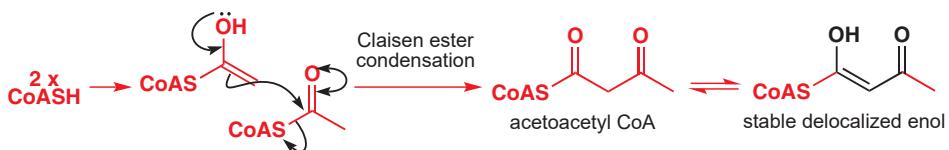


→ You saw pyridoxal phosphate becoming involved in a reductive amination on p. 1151: here—and in other biochemical pathways too—a similar mechanism leads to decarboxylation.

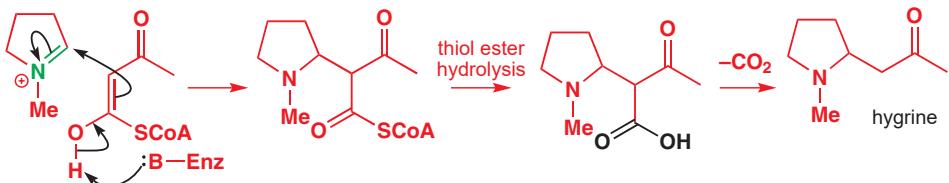
Now the terminal amino group is methylated by SAM and the secondary amine cyclizes onto the pyridoxal imine to give an aminal. Decomposition of the aminal the other way round expels pyridoxamine and releases the salt of an electrophilic imine.



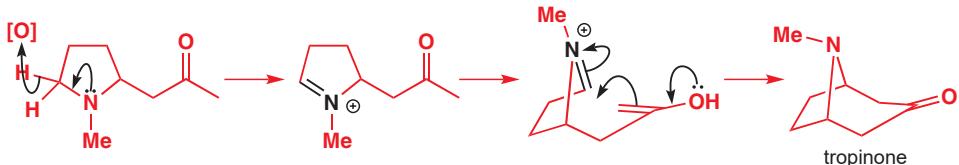
The rest of the hygrine structure comes from two molecules of acetyl CoA. We saw earlier in this chapter that the thiol ester is a good electrophile and also enolizes easily. We need both reactivities now in a Claisen ester condensation of acetyl CoA. The new keto-ester is very like the acetoacetates we used in Chapter 25 to make stable enolates and the CoA thiol ester will exist mainly as its enol, stabilized by conjugation.



The cell has a good stock of acetyl CoA and its condensation product, and as soon as the iminium ion above is generated, it is attacked by the acetoacetyl CoA. All that remains to form hygrine is the hydrolysis of the CoA thiol ester and decarboxylation of the keto-acid. This is standard chemistry, but you should ensure that you can draw the mechanisms for these steps.

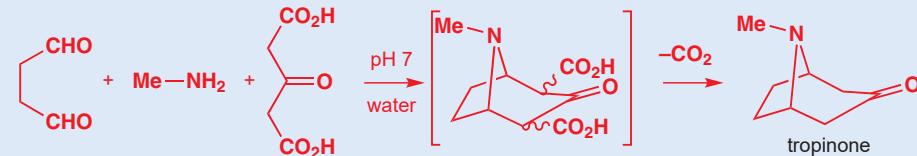


Tropinone is made from hygrine and it is clear what is needed. The methyl ketone must enolize and it must attack another iminium ion resembling the first but on the other side of the ring. A biological oxidant such as NADP is needed.



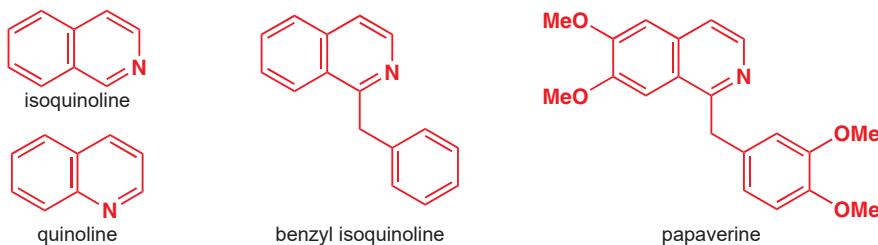
### Robinson's tropinone synthesis

This complex route to tropinone was imitated as long ago as 1917 in one of the most celebrated reactions of all time, Robinson's tropinone synthesis. Robinson argued on purely chemical grounds that the sequence of imine salts and enols, which later (as shown in 1970) turned out to be nature's route, could be produced under 'natural' conditions (aqueous solution at pH 7) from a C<sub>4</sub> dialdehyde, MeNH<sub>2</sub>, and acetone dicarboxylic acid. It worked and the intermediates must be very similar to those in the biosynthesis.

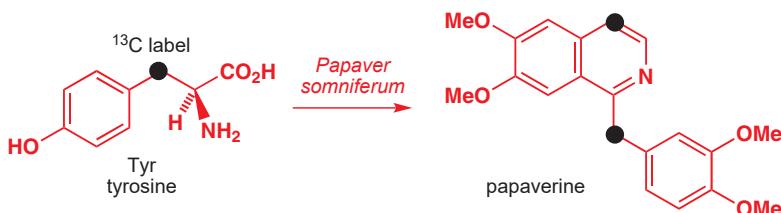


### Benzyl isoquinoline alkaloids are made from tyrosine

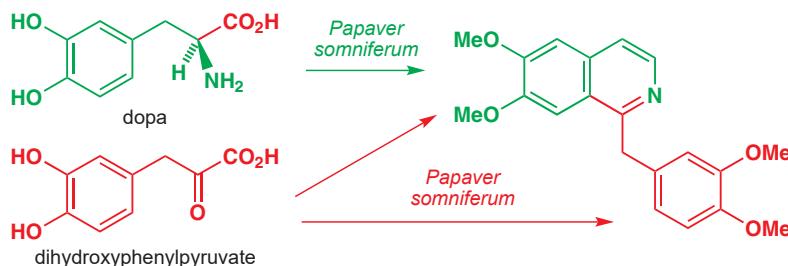
The benzyl isoquinolines are another family of alkaloids of rather different structure. They all have a benzyl group attached to position 2 of an isoquinoline ring. Usually the alkaloids are oxygenated on the benzene ring and many are found in opium poppies (*Papaver somniferum*). For all these reasons papaverine is an ideal example.



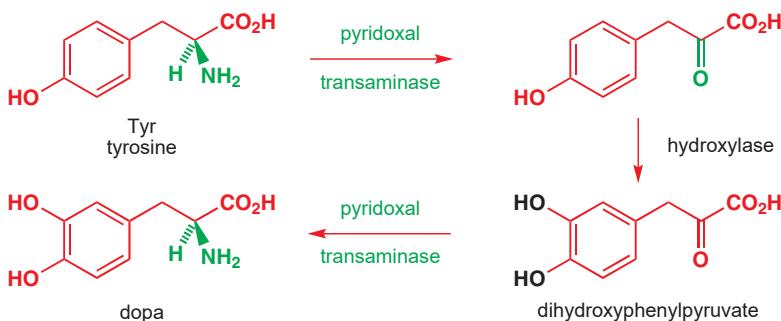
Labelling shows that these alkaloids come from two molecules of tyrosine. One must lose  $\text{CO}_2$  and the other  $\text{NH}_3$ . We can easily see how to divide the molecule in half, but the details will have to wait a moment.



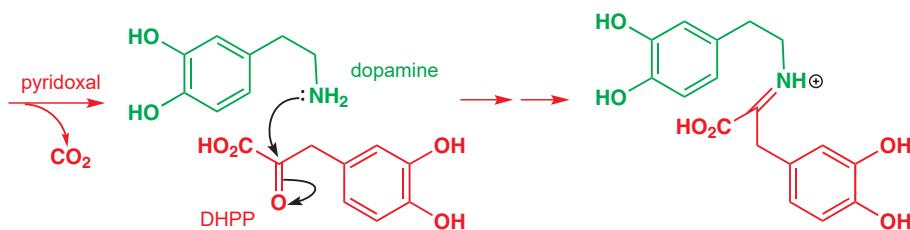
The question of when the extra OH groups are added was also solved by labelling and it was found that dihydroxyphenyl pyruvate (DHPP) was incorporated into both halves but the dihydroxyphenylalanine (an important metabolite, and also a useful medicine, usually called dopa) was incorporated only into the isoquinoline half.



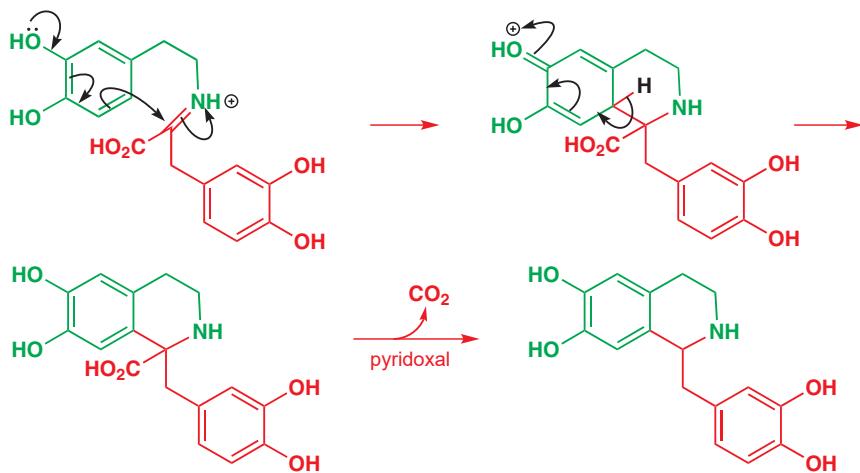
The amino acid and the keto-acid are related by a pyridoxal-mediated transaminase and the hydroxylation must occur right at the start.



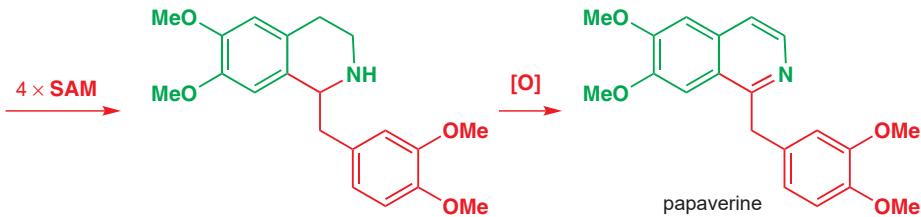
Pyridoxal-mediated decarboxylation of dopa gives dopamine and this reacts with the keto-acid to form an iminium ion perfectly placed for an intramolecular electrophilic aromatic substitution by the electron-rich dihydroxyphenyl ring.



This closes the isoquinoline ring in a Mannich-like process with the phenol replacing the enol in the pyrrolidine alkaloid biosynthesis.

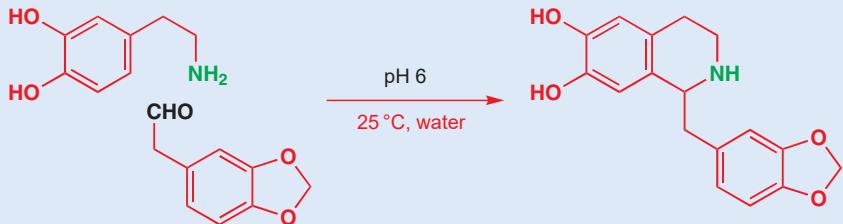


The cyclization product is still an amino acid and it can be decarboxylated by pyridoxal. Now we have something quite like papaverine but it lacks the methyl groups and the aromatic heterocyclic ring, which are introduced by methylation with SAM and oxidation.

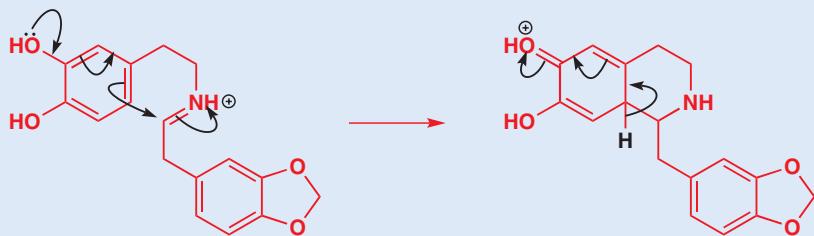


### Synthesis of isoquinolines

As with tropinone, it is possible to make benzyl isoquinoline alkaloids very simply under mild conditions in the laboratory, providing that we use an aldehyde as the carbonyl component. The reaction (sometimes known as the Pictet–Spengler reaction) gives a reduced heterocyclic ring, as does the biosynthesis, but chemical oxidation can be used to give the isoquinoline.



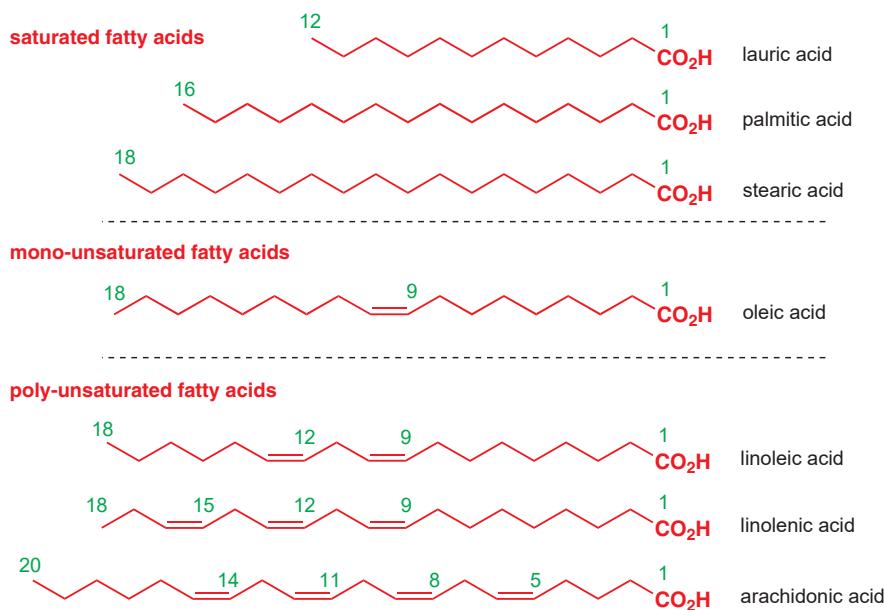
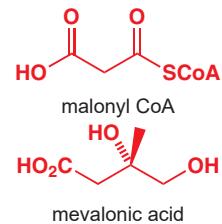
The mechanism is straightforward—the imine is formed and will be protonated at pH 6, ready for the C–C bond formation, which is both a Mannich reaction and an electrophilic aromatic substitution.



Notice that it was not necessary to protect the OH groups—the acetal on the lower ring is not for protection, and this group (methylenedioxy or dioxolane) is present in many benzyl isoquinoline alkaloids. It is formed in nature by oxidation of an MeO group *ortho* to an OH group on a benzene ring.

## Fatty acids and other polyketides are made from acetyl CoA

In the last part of this chapter we will show how nature can take a very simple molecule—acetyl CoA—and build it up into an amazing variety of structures. There are two main pathways from acetyl CoA through malonyl CoA and mevalonic acid and each gives rise to two important series of natural products. Malonyl CoA leads to fatty acids and polyketides while mevalonic acid gives terpenes and steroids. We start with the simplest, the fatty acids. The list below shows just a few of the fatty acids that exist: all are present in a typical diet and you'll find many referred to on the labels of processed foods.



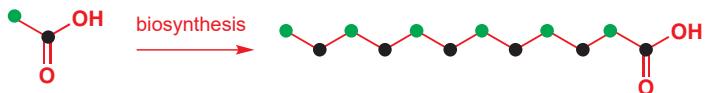
Fatty acids have some important features which you should note:

- They have straight chains with no branching.
- They have even numbers of carbon atoms.
- They may be saturated with no double bonds in the chain or they may have one or more C=C double bonds in the chain, in which case they are usually *cis* (*Z*) alkenes. If there is more than one C=C double bond, they are not conjugated (either with the CO<sub>2</sub>H group or with each other)—there is normally one saturated carbon atom between them.

Palmitic acid (C<sub>16</sub> saturated) is the most common fatty acid in living things. Oleic acid (C<sub>18</sub> mono-unsaturated) is the major fatty acid in olive oil. Arachidonic acid (C<sub>20</sub> tetra-unsaturated)

is a rare fatty acid, which is the precursor of the very important biological messengers the prostaglandins, thromboxanes, and leukotrienes.

The prevalence of fatty acids with even numbers of carbon atoms suggests a two-carbon building block, the most obvious being acetate. If labelled acetate is fed to plants, the fatty acids emerge with labels on alternate carbons like this.



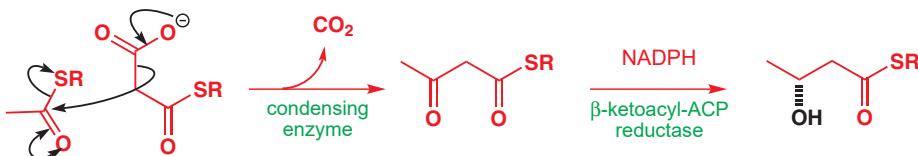
The green blob might represent deuterium (as a  $\text{CD}_3$  group) and the black blob  $^{13}\text{C}$ . In fact, the reactions are more complex than this suggests as  $\text{CO}_2$  is also needed as well as CoA and it turns out that only the first two-carbon unit is put in as acetyl CoA. The remainder are added as malonyl CoA. If labelled malonyl CoA is fed, the starter unit, as it is called, is not labelled.

### Malonyl CoA

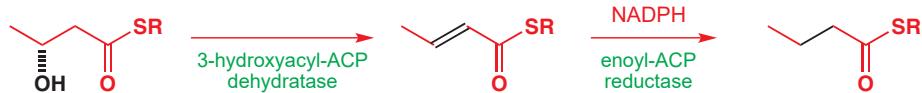
Malonyl CoA is the thiol ester of CoASH and malonic acid. It is biosynthesized by acylation of acetyl CoA with carbon dioxide.



The first stage in fatty acid biosynthesis is a condensation between acetyl CoA (the starter unit) and malonyl CoA with the loss of  $\text{CO}_2$ . This reaction could be drawn like this, with  $\text{CO}_2$  being lost as the new C–C bond is formed. When chemists use malonates, we like to make the stable enol using both carbonyl groups, condense, and only afterwards release  $\text{CO}_2$  (Chapter 25). As you saw on p. 1158, nature does this in making acetoacetyl CoA during alkaloid biosynthesis, but here things work differently.



The next step is reduction of the ketone group. This NADPH reaction is typically stereo- and chemoselective, although the stereochemistry is rather wasted here as the next step is a dehydration, typical of what is now an aldol product, and occurring by an enzyme-catalysed E1cB mechanism. The elimination is known to be a *cis* removal of H and OH, and the double bond is exclusively *trans* (*E*). Finally in this cycle, the double bond is reduced using another molecule of NADPH to give the saturated side chain.



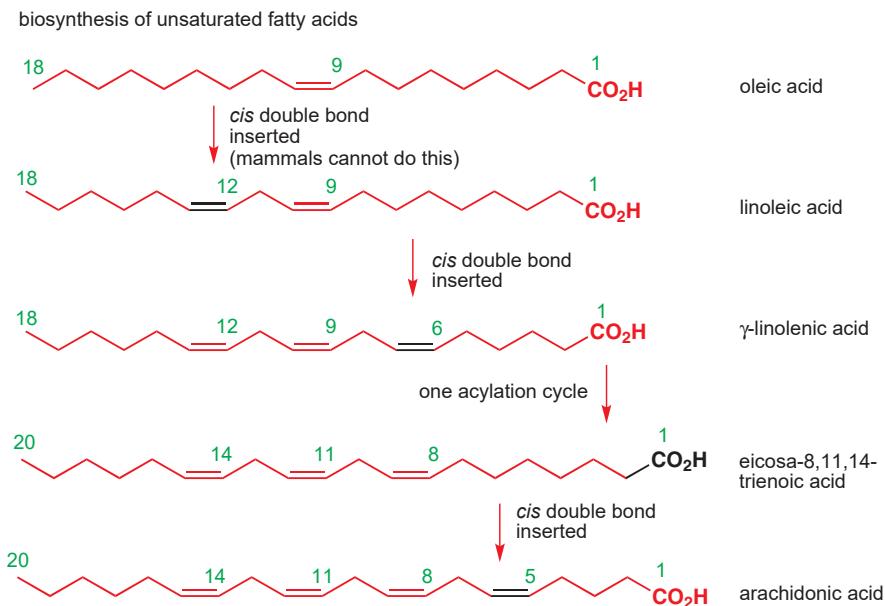
Now the whole cycle can start again using this newly made  $\text{C}_4$  fatty acid as the starter unit and building a  $\text{C}_6$  fatty acid and so on. Each time the cycle turns, two carbon atoms are added to the acyl end of the growing chain.



### What is so important about unsaturated fatty acids?

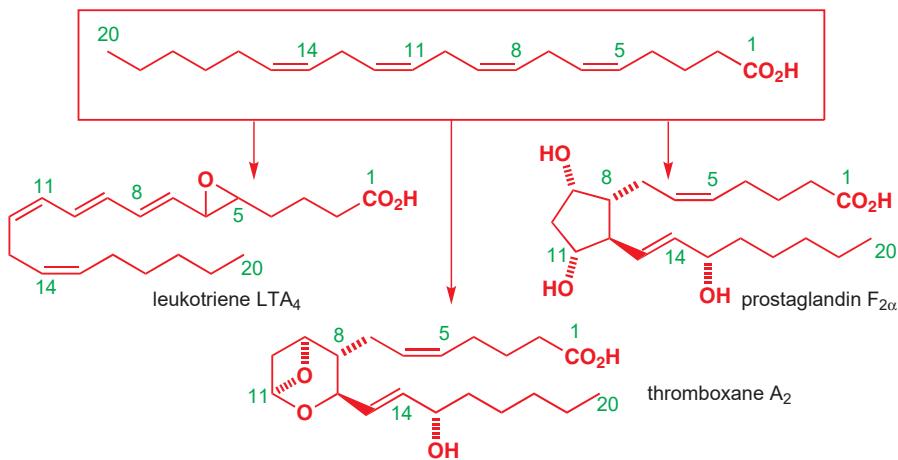
Mammals can insert a *cis* alkene into the chain, providing that it is no further away from the carbonyl group than C9. We cannot synthesize linoleic or linolenic acids (see chart on p. 1161) directly as they have alkenes at C12 and C15, so these acids must be present in our diet.

But why are we so keen to have them? They are needed for the synthesis of arachidonic acid, a C<sub>20</sub> tetraenoic acid that is the precursor for some very interesting and important compounds. This is the biosynthesis of arachidonic acid.



The final product of this chain of events—arachidonic acid—is one of the eicosanoids, so-called because *eicosa* is Greek for twenty. The leukotrienes resemble arachidonic acid most closely, the prostaglandins have a closed chain forming a five-membered ring, and the thromboxanes resemble the prostaglandins but have a broken chain. All are C<sub>20</sub> compounds with the sites of the alkenes (C5, C8, C11, and C14) marked by functionality or some other structural feature.

compounds synthesized from arachidonic acid



These compounds, made by oxidation of arachidonic acid, are all unstable and all are involved in transient events such as inflammation, blood clotting, fertilization, and immune responses. They are produced locally and decay quickly, and are implicated in autoimmune diseases like asthma and arthritis.

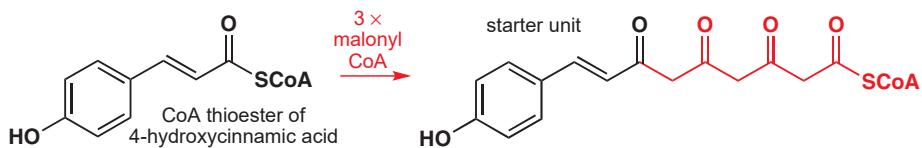


Full details of the biosynthesis of the fatty acids and their metabolites are in the online chapter 'Natural products'.

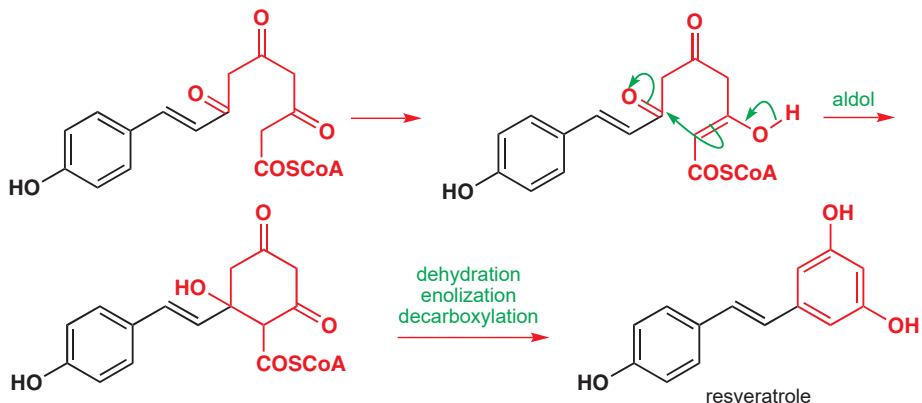
### Aromatic polyketides

Other starter units such as 4-hydroxycinamic acid, made from shikimic acid, can be used to build up aromatic compounds. The addition of three malonyl CoA units gives a linear

tetraketone (hence the same of this class of natural product) that can cyclize to resveratrol, a compound in red grape skins that has been suggested as one of the compounds in red wine that protects against heart disease.

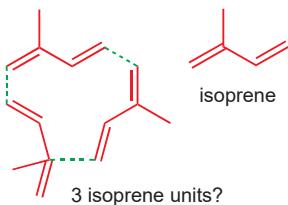
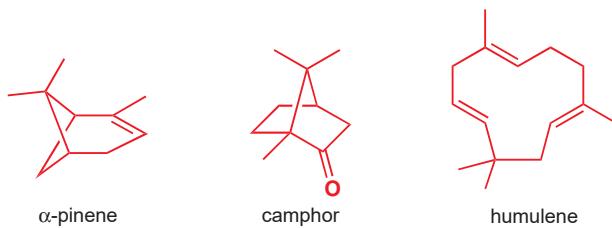


Redrawing this intermediate shows how easily it can cyclize to a six-membered ring. Enol formation allows a very favourable aldol cyclization to give a six-membered ring then dehydration and enolization to make the aromatic ring with hydrolysis of the CoA ester and decarboxylation gives resveratrol.



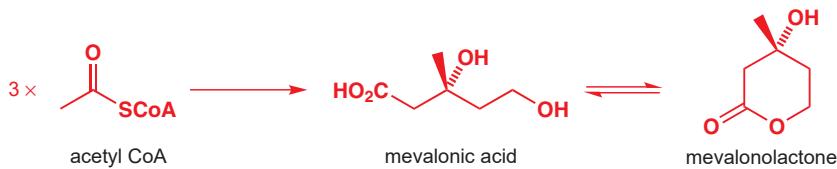
## **Terpenes are volatile constituents of plants**

Terpenes were originally named after turpentine, the volatile oil from pine trees used in oil painting, whose major constituent is  $\alpha$ -pinene. The term was rather vaguely used for all the volatile oily compounds, insoluble in water and usually with resinous smells from plants. Oils distilled from plants, which often contain perfumery or flavouring materials, are called essential oils and these too contain terpenes. Examples include camphor from the camphor tree, which is used to preserve clothes from moths, and humulene from hops, which helps to give beer its flavour.

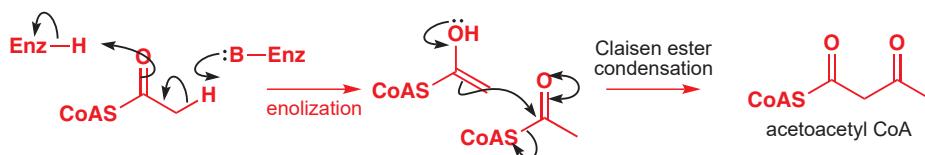


You will notice that they are all aliphatic compounds with a scattering of double bonds and rings, few functional groups, and an abundance of methyl groups. A better definition (that is, a biosynthetically based definition) arose when it was noticed that all these compounds have  $5n$  carbon atoms. Pinene and camphor are  $C_{10}$  compounds while humulene is  $C_{15}$ . It seemed obvious that terpenes were made from a  $C_5$  precursor and the favourite candidate was isoprene (2-methylbuta-1,3-diene) as all these structures can be drawn by joining together 2-, 3-, or 4-isoprene skeletons end to end.

In fact, this is not correct. Isoprene is not an intermediate, and the discovery of the true pathway started when acetate was, rather surprisingly, found to be the original precursor for all terpenes. The key intermediate is mevalonic acid, formed from three acetate units and usually isolated as its lactone.



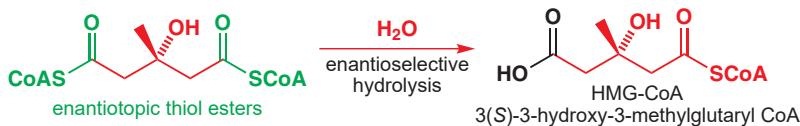
The first step is the Claisen ester condensation of two molecules of acetyl CoA, one acting as an enol and the other as an electrophilic acylating agent to give acetoacetyl CoA. We saw the same reaction in the biosynthesis of the pyrrolidine alkaloids earlier in this chapter.



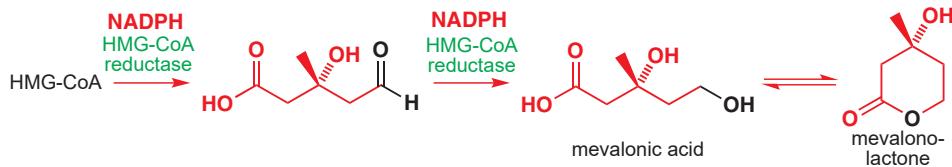
The third molecule of acetyl CoA also functions as a nucleophilic enol and attacks the keto group of acetoacetyl CoA. This is not a Claisen ester condensation—it is an aldol reaction between the enol of a thiol ester and an electrophilic ketone.



We have drawn the product with stereochemistry even though it is not chiral. This is because one of the two enantiotopic thiol esters is hydrolysed while this intermediate is still bound to the enzyme, so a single enantiomer of the half-acid/half-thiol ester results.

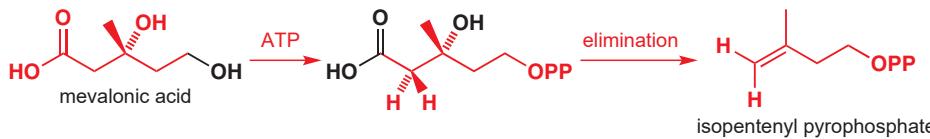
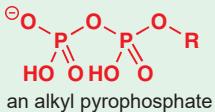


The remaining thiol ester is more electrophilic than the acid and can be reduced by the nucleophilic hydride from NADPH. Just as in  $\text{LiBH}_4$  reductions of esters (Chapter 23), the reaction does not stop at the aldehyde level, and two molecules of NADPH are used to make the alcohol. This is mevalonic acid.

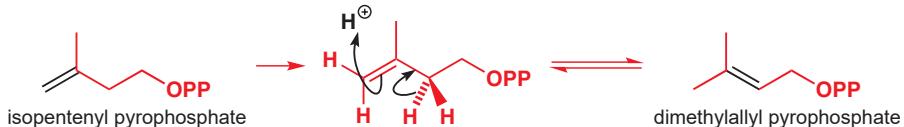


Mevalonic acid is indeed the true precursor of the terpenes but it is a  $C_6$  compound and so it must lose a carbon atom to give the  $C_5$  precursor. The spare carbon atom becomes  $\text{CO}_2$  by an elimination reaction. First, the primary alcohol is pyrophosphorylated with ATP; then the  $\text{CO}_2\text{H}$  group and the tertiary alcohol are lost in a concerted elimination.

■ 'PP' indicates the pyrophosphate group transferred from ATP.



So is isopentenyl pyrophosphate the C<sub>5</sub> intermediate at last? Well, yes and no. There are actually two closely related C<sub>5</sub> intermediates, each of which has a specific and appropriate role in terpene biosynthesis. Isopentenyl pyrophosphate is in equilibrium with dimethylallyl pyrophosphate by a simple allylic proton transfer.



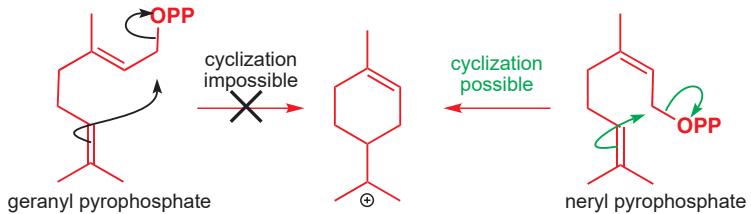
The two C<sub>5</sub> intermediates now react with each other. The dimethylallyl pyrophosphate is the better electrophile because it is allylic, and allylic compounds are good at both S<sub>N</sub>1 and S<sub>N</sub>2 reactions (Chapter 15). Isopentenyl pyrophosphate is the better nucleophile because it can react through an unhindered primary carbon atom to produce a tertiary cation—we can draw the reaction like this:



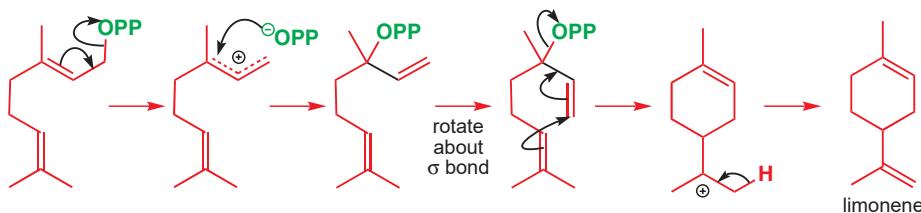
Although this idea reveals the thinking behind the reaction, in fact it does not quite like this. The product is one particular positional and geometrical isomer of an alkene and the cation is not an intermediate. Indeed, the reaction is also stereospecific (discovered again by proton labelling, but we will not give the rather complex details) and this too suggests a concerted process.



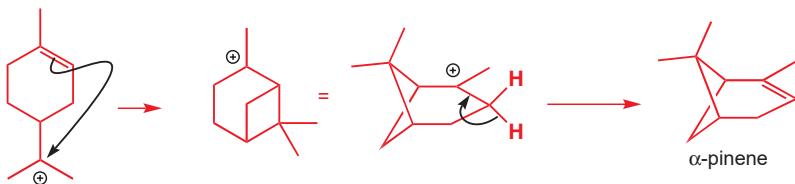
As soon as we start to make typical cyclic monoterpenes from geranyl pyrophosphate we run into a snag. We cannot cyclize geranyl pyrophosphate because it has a *trans* double bond! We *could* cyclize the *cis* compound (neryl pyrophosphate), and it used to be thought that this was formed from the *trans* compound as an intermediate.



It is now known that nature gets round this problem without making neryl pyrophosphate. An allylic rearrangement occurs to move the pyrophosphate group to the tertiary centre. This is an unfavourable rearrangement thermodynamically and probably occurs via the allyl cation and is catalysed by Mg(II). There is no longer any geometry about the alkene. The molecule can now rotate freely about a single bond and cyclization can occur. Even if only a small amount of the rearranged allylic pyrophosphate is present, that can rearrange and more can isomerize.

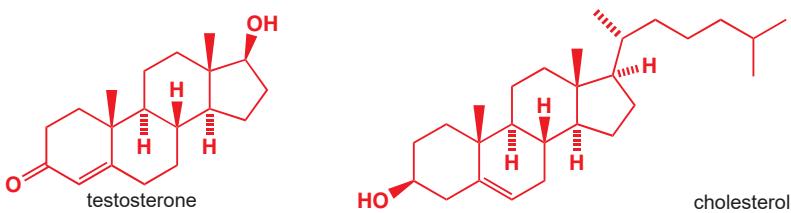


More interesting compounds come from the cyclization of the first formed cation. The remaining alkene can attack the cation to form what looks at first to be a very unstable compound but which is actually a tertiary carbocation with the pinene skeleton. There are many thousands of terpenes with multiple C<sub>5</sub> units all made from mevalonic acid.



The steroids are another group of compounds derived from mevalonic acid. They include sex hormones such as testosterone and progesterone, and the cholesterol needed to build cell membranes but also implicated in the damage to arteries caused by atherosclerosis.

The synthesis of the steroids is discussed in the online chapter 'Natural products'.



The elucidation of the ways in which organic chemistry underpins life, along with the use of organic chemistry to construct in the laboratory the molecules used by nature, has been one of the greatest scientific success stories of recent decades. In this chapter we have revealed but a glimpse of the immense complexity of the world of biological organic chemistry; you will find an extended version of this discussion in the three chapters on the web, and a book on biochemistry will fill in more detail. The beautiful molecular structures of nature and the reactions used to make them have provided an example for organic chemists to follow—sometimes at a distance, but always in hot pursuit. The next and final chapter of this book tells a few stories of how such scientific inspiration is the key to the future of chemistry, not only for its own sake, but also for the sake of the millions of people whose lives have been improved or even saved by the ingenuity of chemists.

## Further reading

P. A. Frey and A. D. Hegeman, *Enzymatic Reaction Mechanisms*, Oxford University Press, Oxford, 2007. A more basic treatment is in two Oxford Primers by J. Mann, *Chemical Aspects of Biosynthesis*, OUP, 1994 and by T. Bugg, *Introduction to Enzyme and Coenzyme Chemistry*, OUP, Oxford, 2004. A more comprehensive treatment is in J. E. McMurry and T. P. Begley, *The Organic Chemistry of Biological Pathways*, Roberts, 2005. For an introduction to biosynthesis, see F. J. Leeper and J. C. Vedera, *Biosynthesis: Polyketides and Vitamins*, Springer, 2000.

Three full chapters from the first edition expand this chapter and are available for download from the website: The chemistry of life, Mechanisms in biological chemistry, and Natural products.

## Check your understanding

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To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 如今的有机化学

## 联系

### → 基础

- The rest of the book ch1–ch42

### 目标

- How organic chemistry produced an AIDS treatment in collaboration with biologists
- How organic chemists are in the front line of the fight against epidemics
- Where organic chemistry might be going next

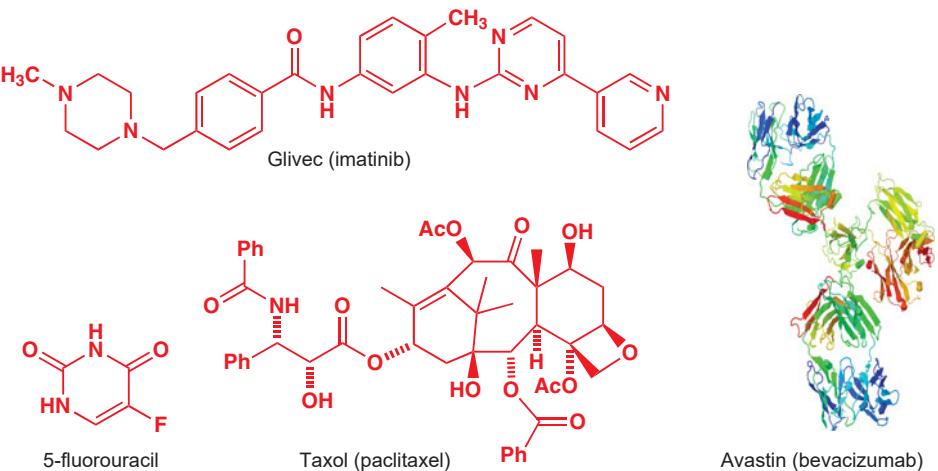
### → 展望

- Life as a chemist

## Science advances through interaction between disciplines

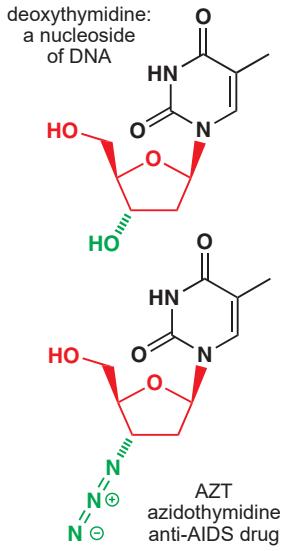
Just as the stonemasons who worked out how to build the great gothic cathedrals of the middle ages transformed architecture, the organic chemists who build molecules on a scale  $10^{10}$  times smaller have transformed our expectations of everyday life. When we are ill, we expect there to be a drug to treat us; when we need to mend something, we expect there to be a sealant, glue, or coating to solve our problem. We expect paints, plastics, and clothes of any colour. If an engineer needs a material with certain properties of strength and flexibility, she expects organic chemists to be able to make it. If a biologist needs a molecule to inhibit an enzyme selectively, he expects organic chemists to be able to make it. In the future the same will be true of plastics that conduct electricity or emit light, or drugs tailored to your own individual genetic makeup. The creative art of organic chemistry has transformed our ability to understand and manipulate the world on a molecular scale and above, and it has been able to do this because of the collaboration between those who can make molecules and those who can use them—between chemists, physicists, engineers, and materials scientists.

The most dramatic scientific developments involving organic chemistry at the beginning of the 21st century are new methods in medicine from collaborations between organic chemists and biologists. Progress is slow but secure across a whole range of diseases long thought impregnable to treatment. That media favourite, ‘the cure for cancer’, is already not just ‘a cure’ but hundreds of successful cures for the hundreds of diseases collectively called ‘cancer’. At the turn of the twenty-first century, it was the case that there was *some* chance of survival for all known types of childhood cancer. The drug Glivec, launched in 2001, now essentially cures 75% of patients with chronic myeloid leukemia. 5-Fluorouracil is a well-established chemotherapy drug that slows down the progression of cancer. But in conjunction with Avastin, which prevents tumours developing their own blood supply, it is much more effective against certain colon cancers. Avastin in conjunction with Taxol (launched in 1992) increases Taxol’s effectiveness against breast cancer. Avastin was launched in 2004, and is expected to be the world’s biggest selling drug by 2014.



5-Fluorouracil could hardly be simpler: it interferes with cell proliferation by modifying natural uracil to incorporate a stubbornly unreactive fluorine. Taxol is a rare metabolite of the Pacific yew tree that can be made at great expense in the laboratory, and for a while was produced by chemical modification of a common precursor that can be harvested. It is now made by fermentation using cultured yew tree cells. Avastin is at the other end of the scale of complexity: it is an antibody against a protein involved in blood vessel growth, and we have represented only its gross structure: a detailed structural diagram would be huge. The antibody was induced in mice, its protein sequence was determined and then modified using the techniques of molecular biology which grew out of organic chemistry in the 1960s and 1970s, and it is produced by expression of the modified gene in bacteria. Which of this is chemistry, which is biology, and which is medicine? There is no point deciding.

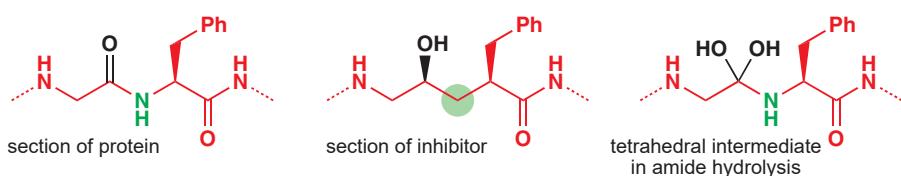
## Chemistry vs viruses



We are going to spend most of this chapter discussing two medical developments, both battles pitting chemists against viruses: one is partly won, and one has fortunately not yet been fought. Like cancer, viruses are an insidious menace because they subvert the body's own biochemical machinery to cause harm, but since the middle of the last century, with antibiotics being used to treat bacterial infections, the threat from infectious disease seemed to be in retreat. So when AIDS (acquired immune deficiency syndrome) first came into the news in the 1980s, medics struggled to explain the mysterious deaths from normally harmless diseases after the patient's immune system had been weakened and eventually destroyed. But the cause was soon identified by biologists as a new virus, HIV (human immunodeficiency virus), and antiviral drugs, notably AZT, were used with some success. These drugs imitate natural nucleosides (AZT imitates deoxythymidine) and inhibit the virus from copying its RNA into DNA inside human cells by inhibiting the reverse transcriptase enzyme.

As is often the problem with antiviral (and anticancer) chemotherapy, the drugs also inhibit the normal function of essential human enzymes and are very toxic. But biologists discovered an alternative point of attack. An enzyme unique to the virus cuts up long proteins into small pieces essential for the formation of new HIV particles. If this enzyme could be inhibited, no new viruses would be formed and neither should the inhibitor interfere with human biochemistry.

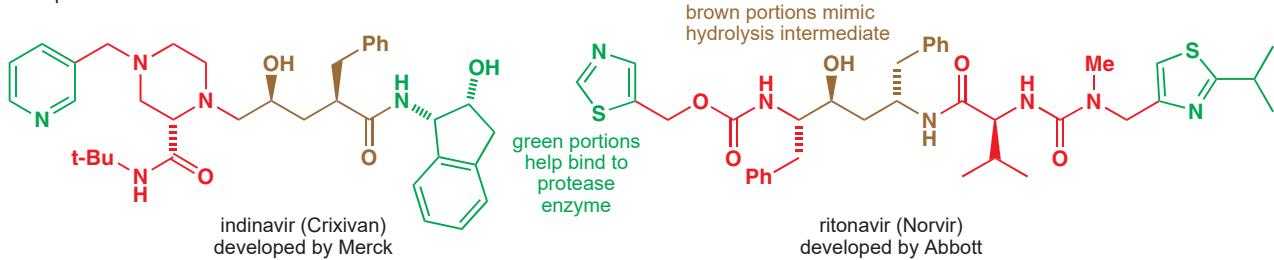
Blocking HIV protease inhibitors means mimicking the proteins they slice up, but real peptides are usually poor drugs because humans have their own peptidases which quickly cut up ingested proteins by hydrolysis of the amide link. The solution is to make a drug which looks like the peptide but can't be hydrolysed because the C–N bond of the peptide has been replaced by a C–C bond (green parts of the structures below).



This stops the drug being hydrolysed, but the drug also has to stop the viral protein being hydrolysed. To get it to do this, medicinal chemists used another trick. Enzymes work by binding the transition state for a reaction, and while of course the chemists couldn't make a transition state (it is by its nature unstable) they made a molecule with a sufficient resemblance to the tetrahedral intermediate for amide hydrolysis (black parts of molecules above) that the protease is tricked into taking it into its active site, where it blocks the protease's function.

The knowledge that only one of the two hydroxyl groups of the tetrahedral intermediate was needed was acquired from an X-ray crystal structure showing how the enzyme binds the substrate. Other structural information was also used to design the drugs: for example, HIV protease is a dimeric enzyme and experience with this class of protease suggested correctly that more or less symmetrically placed aromatic or heterocyclic rings would greatly improve binding. Two successful protease inhibitors are shown below, with the active site binding portion in brown and the heterocyclic binding portions in green.

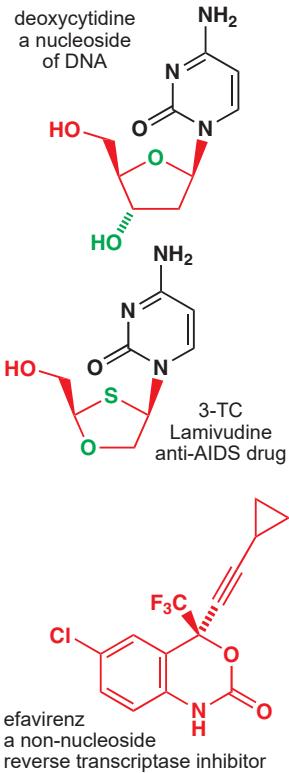
HIV protease inhibitors



These developments looked so promising that Merck set up a new research station at West Point, Pennsylvania, dedicated to this work. The biochemist in charge, Dr Irving Sigal, was one of the victims of the Lockerbie bombing in 1988 but his work lived on in Crixivan (indinavir). In combination with the antiviral agents AZT and 3TC (Lamivudine), shown with the nucleoside it imitates, indinavir revolutionized the treatment of HIV in the 1990s. Before the use of 'combination therapy', as it is known, most of those with HIV were dead within 2 years. Now no-one knows how long they will survive as the combination of the three drugs reduces the amount of virus to undetectably low levels.

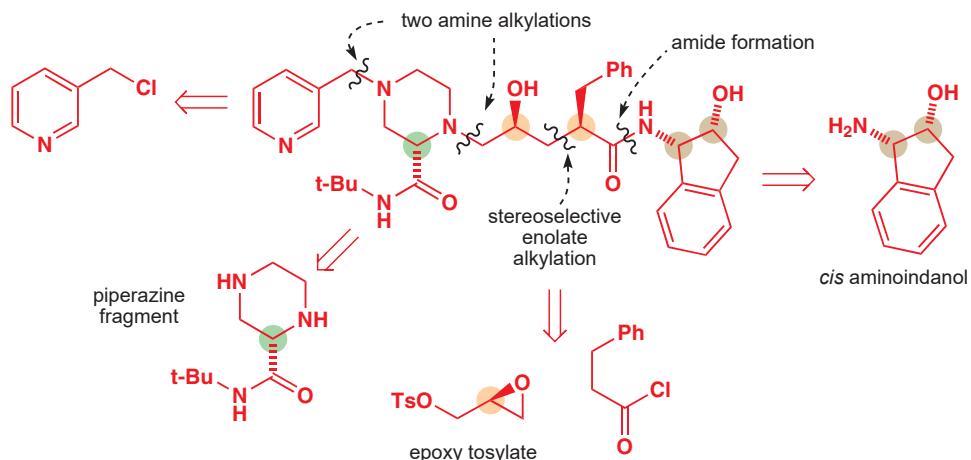
The AIDS crisis led to cooperation between the pharmaceutical companies unparalleled since the development of penicillin during the Second World War. Fifteen companies set up an AIDS drug development collaboration programme, with government agencies and universities contributing as well. The battle is not yet won, of course, and the HIV protease inhibitors have now been joined by a new generation of non-nucleoside reverse transcriptase inhibitors, such as the DuPont–Merck compound efavirenz. These commonly join the other drugs of the types mentioned above as part of the drug regimes known as 'highly active antiretroviral therapy' or HAART. The mixture of drugs used to combat HIV changes as discoveries are made, but life-saving combination therapy of this sort would not be possible without the sort of collaboration between organic chemists, biochemists, virologists, X-ray crystallographers, and molecular modellers that went into discovering and making indinavir.

After indinavir was found to be effective, the job of the chemists was an exceptionally urgent task. They knew that a kilo of compound was needed to keep each patient alive and well for a year (newer HIV protease inhibitors require much smaller doses). Merck built a dedicated plant for the manufacture of Crixivan at Elkton, Virginia, in 1995. Within a year, production was running at full blast and there are millions of people alive today as a result.



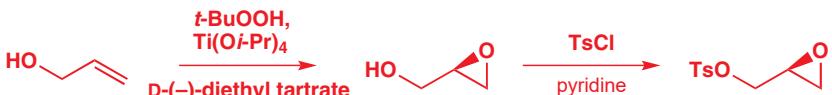
### The synthesis of indinavir

Indinavir was a formidable synthetic target. It was probably the most complex compound ever made in quantity by organic synthesis and the 3 g per day dose meant that huge quantities were required. The complexity largely arises from the stereochemistry. As with all chiral new drugs, it is a single enantiomer: there are five stereogenic centres, marked with coloured circles on the diagram below, and their disposition means that three separate pieces of asymmetric synthesis must be devised.



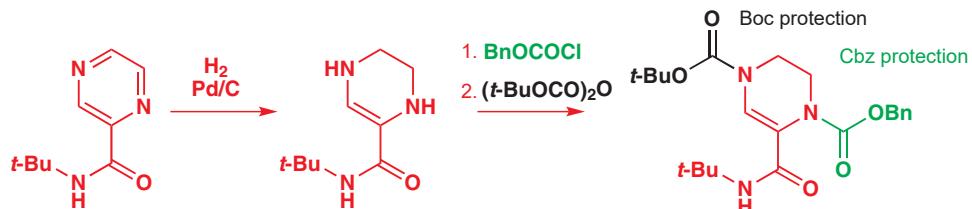
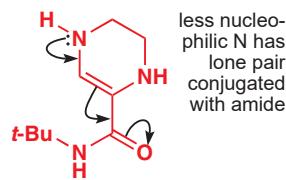
The challenge with indinavir, as with any drug, is to make it efficiently: high yields, few steps. We can start by looking at some likely disconnections, summarized in the scheme above. They are all disconnections of the sorts you met in Chapter 28, and they all correspond to reliable reactions. These disconnections split the molecule into five manageable fragments, three of which contain stereogenic centres and will have to be made as single enantiomers. One of the orange stereogenic centres would have to be made in the enolate alkylation step, so this step will need to be diastereoselective.

Let's take the three chiral fragments in turn. First, the simplest one: the central epoxide. The reagent we need here will carry a leaving group, such as a tosylate, to allow it to alkylate the piperazine to the left, and it can easily be made from an epoxyalcohol. This gives a very good way of making this compound as a single enantiomer—a Sharpless asymmetric epoxidation of allyl alcohol.

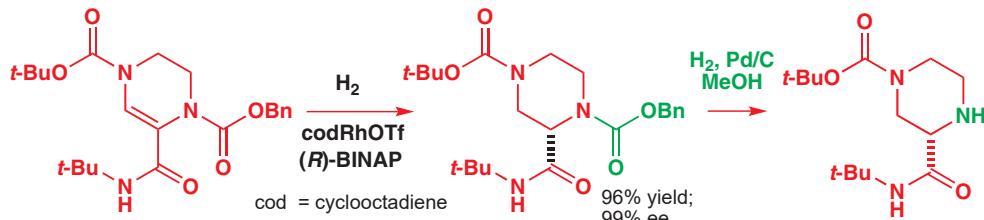


Sharpless asymmetric epoxidation was discussed in Chapter 41, p. 1120.

Next, the piperazine fragment. This has two nucleophilic nitrogen atoms and they will both need protecting with different protecting groups to allow them to be revealed one at a time. It will also need to be made as a single enantiomer. In an early route to indinavir, this was done by resolution, but enantioselective hydrogenation provides a better alternative. Starting from a pyrazine derivative, a normal hydrogenation over palladium on charcoal could be stopped at the tetrahydropyrazine stage. The two nitrogens in this compound have different reactivities because one is conjugated with the amide while one is not (the curly arrows in the margin show this). The more nucleophilic nitrogen—the one *not* conjugated with the amide—was protected with benzyl chloroformate to give the Cbz derivative. Now the less reactive nitrogen can be protected with a Boc group, using DMAP as a base.



You met asymmetric hydrogenation using BINAP complexes of rhodium in Chapter 41 as a method for the synthesis of amino acids. The substrate and catalyst are slightly different here, but the principle is the same: the chiral ligand, BINAP, directs addition of hydrogen across one of the enantiotopic faces of the double bond with almost perfect enantioselectivity and in very high yield. A further hydrogenation step allowed selective removal of the Cbz group, preparing one of the two nitrogen atoms for alkylation.

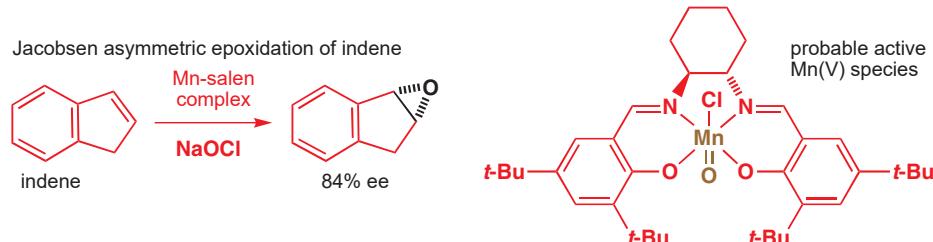


The remaining chiral fragment is a compound whose synthesis was discussed in Chapter 39. It can be made on a reasonably large scale (600 kg) in one reaction vessel, starting from indene. First, the double bond is epoxidized, not with *m*-CPBA but with the cheaper hydrogen peroxide in an acetonitrile/methanol mixture, which generates a peroxyimide acid (the C=N analogue of a peracid) as the active oxidant. Acid-catalysed opening of the epoxide leads to a cation, which takes part in a reversible Ritter reaction with the acetonitrile solvent, leading to a single diastereoisomer of a heterocyclic intermediate, which is hydrolysed to the amino-alcohol.

Turn to pp. 1066–1067 for details of the mechanisms in this reaction sequence and an explanation for its *cis* diastereoselectivity.

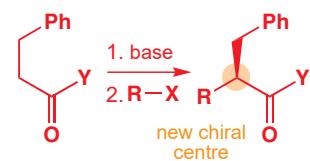


The product is, of course, racemic but, as it is an amine, resolution with an acid should be straightforward. Crystallization of its tartrate salt, for example, leads to the required single enantiomer in 99.9% ee. With such cheap starting materials, resolution is just about acceptable, even though it wastes half the material. It would be better to oxidize the indene enantioselectively, and the solution here, as you saw in Chapter 41, is to use a Jacobsen epoxidation, which gives the epoxide in 79% yield and 84% ee.

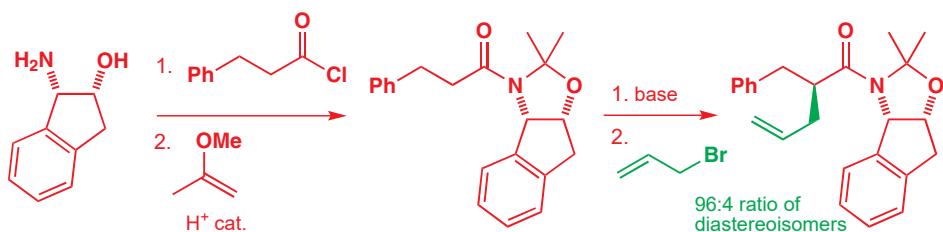
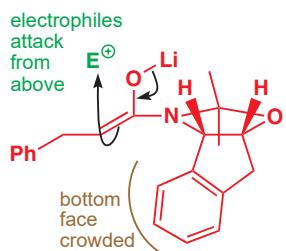
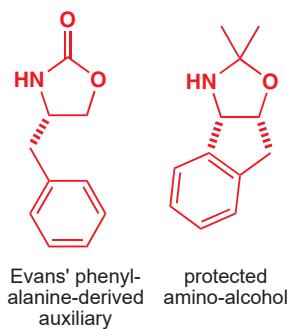


Only one, orange, stereogenic centre remains, and its stereoselective formation turns out to be the most remarkable reaction of the whole synthesis. The centre is the one created in the planned enolate alkylation step, shown in the margin. The obvious way to make this centre is to make Y a chiral auxiliary, which would direct a diastereoselective alkylation before being removed and replaced with the amino-alcohol portion.

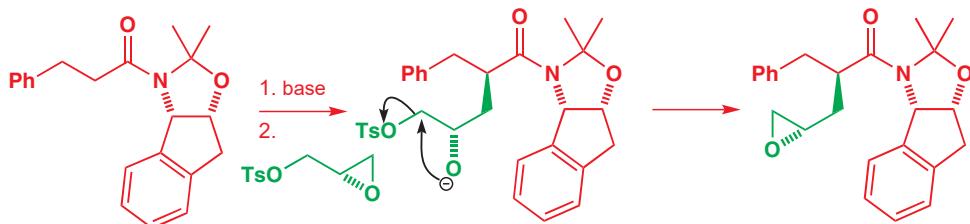
But the Merck chemists noticed that amino alcohol itself, certainly once protected, has a remarkable similarity to Evans' oxazolidinone auxiliaries anyway, and it turns out that this amino alcohol will function very successfully as a chiral auxiliary, which does not need to be removed, avoiding waste and saving steps! The amino alcohol was acylated with the acyl chloride, and the amide was protected as the nitrogen analogue of an acetonide by treating with 2-methoxypropene (the methyl enol ether of acetone) and an acid catalyst. The enolate



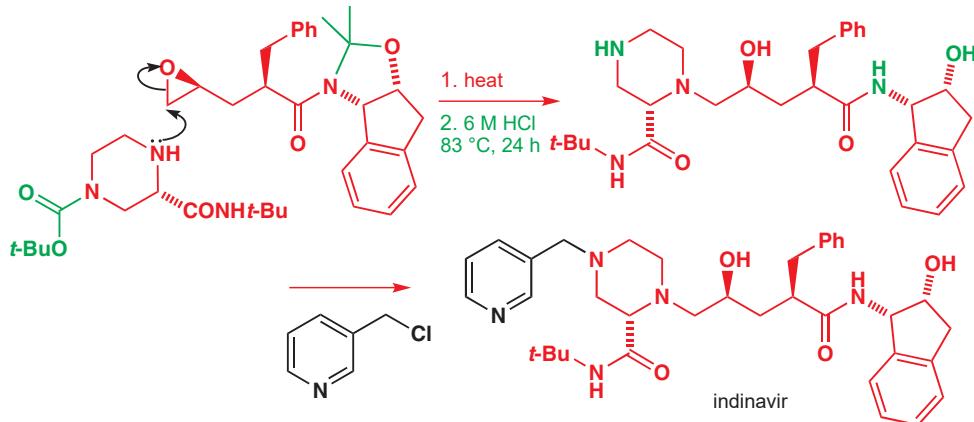
Evans auxiliary-directed alkylation is described in Chapter 41, p. 1109.



The reason for the stereoselectivity is not altogether clear, but we would expect the bulky nitrogen substituents to favour formation of the *cis* enolate. With the amino-alcohol portion arranged as shown, the top face is more open to attack by electrophiles. The enolate also reacts diastereoselectively with the epoxy-tosylate prepared earlier. The epoxide, being more electrophilic than the tosylate, is opened first, giving an alkoxide, which closes again to give a new epoxide. The absolute configuration at the stereogenic centre within the epoxide was, of course, already fixed (by the earlier enantioselective Sharpless epoxidation).



Three of the five fragments have now been assembled, and only the two amine alkylations remain. The first alkylation makes use of the epoxide to introduce the required 1,2-amino-alcohol functionality. The protected enantiomerically pure piperazine reacted with the epoxide, and the product was treated with acid to deprotect both the second piperazine nitrogen and the *gem*-dimethyl group left over from the earlier chiral auxiliary step. The newly liberated secondary amine was alkylated with the reactive electrophile 3-chloromethyl pyridine, and the final product was crystallized as its sulfate salt.



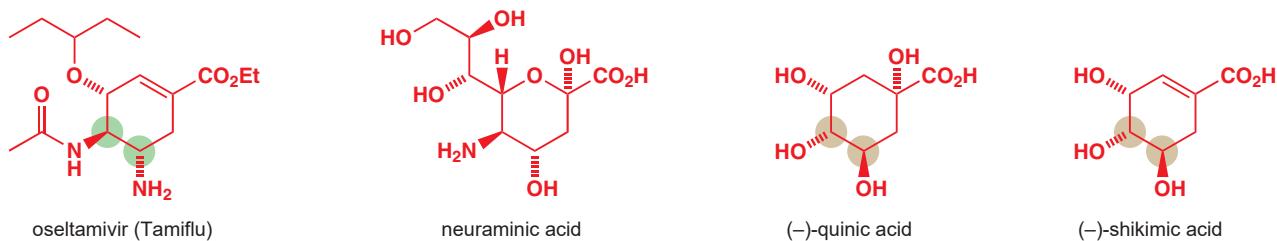
## The synthesis of oseltamivir

Our second example of the use of chemistry to save lives is more recent. Several times in the last century major epidemics of influenza have caused deaths, sometimes running into millions. Virologists tell us that a global influenza pandemic is a constant danger, and a number of times in recent years highly aggressive forms of the flu virus have found their way from other animals (often poultry or pigs) into the human population. Fortunately, at the time of writing, none has caused more than a few thousand deaths, the most serious being the swine flu pandemic of 2009–10, which claimed the lives of 18,000 people, many of them in Mexico.

To put this in context, the 1918 flu epidemic, which was caused by the same strain (H1N1) of virus, killed 50–100 million, 3% of the world's population at the time.

Vaccination can prevent the spread of flu, but influenza vaccines are slow to produce and difficult to generalize because of the rate of mutation of the virus. So the first line of defence is a class of antiviral compounds known as neuraminidase inhibitors. Neuraminidase is an enzyme used by the flu virus that targets human cell-surface carbohydrates containing neuraminic acids and allows the virus to release itself from the host cell. Inhibition of this enzyme prevents the new virus particles from spreading.

The drug oseltamivir (Tamiflu), developed by the companies Gilead and Roche, is a neuraminidase inhibitor. Like the HIV proteases described above, it has enough structural similarity with the enzyme's substrate to bind to the enzyme, but once bound it blocks the enzyme's activity. No-one knows how much oseltamivir might be needed if ever a flu pandemic took hold, but clearly the safest course of action is to stockpile the compound in readiness for such an event. The first manufacturing route to oseltamivir made use of the natural product (–)-quinic acid as a naturally derived starting material. Quinic acid is found in coffee beans, but is not available in sufficient quantities for widespread use.

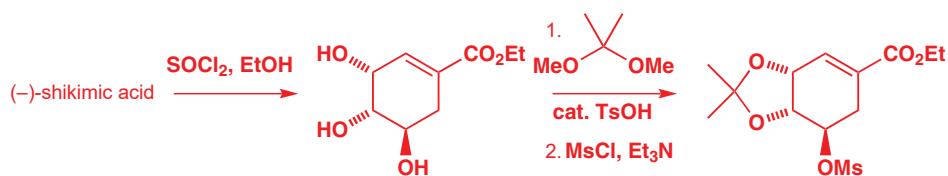


A preferable starting material, and the one that for several years now has been used as the source of the commercial drug, is (-)-shikimic acid. Shikimic acid is the plant metabolite that provides the biochemical precursor to the aromatic amino acids such as phenylalanine, tyrosine, and tryptophan. It is abundant in the spice star anise, grown in China, which can yield 3–7% of shikimic acid.

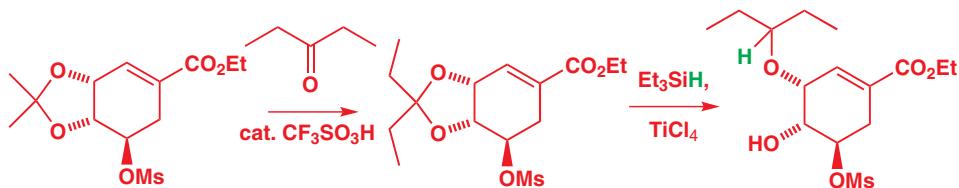
→ You met shikimic acid in Chapter 42, p. 1154.

The similarity of both quinic and shikimic acid with the target drug is obvious; what is perhaps remarkable is just how many steps it takes to get from one to the other. The majority of these steps are concerned with the introduction of the two amino substituents with inversion of stereochemistry at the coloured stereogenic centres. Chiral pool syntheses often have to take long convoluted routes to correct relatively minor ‘errors’ of structure and stereochemistry. Here this is simply the price we have to pay for a starting material that has the valuable qualities of enantiomeric purity and the right hydrocarbon skeleton.

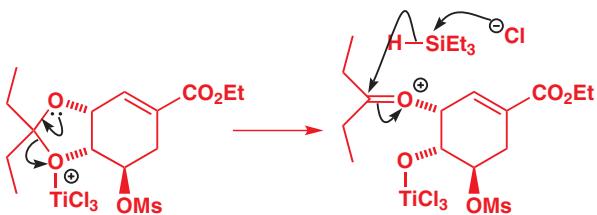
Oseltamivir is an ethyl ester, and esterification comes first, followed by selective protection of the *cis* diol (the *cis*-6,5-ring system is more stable than the alternative *trans*) and conversion of the remaining hydroxyl group to a methanesulfonate leaving group.



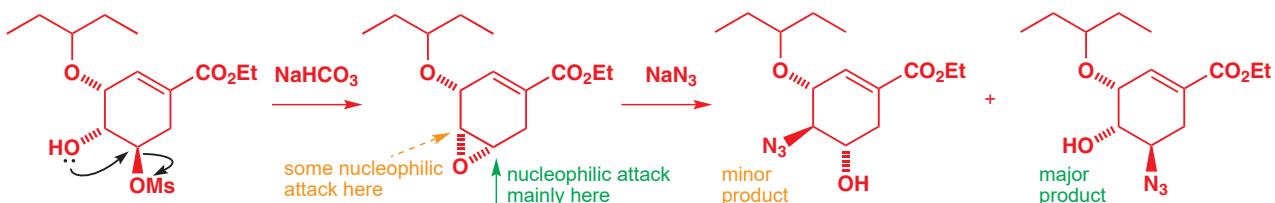
The dioxolane, which is crystalline and easily purified, is then exchanged for the acetal derived from pentan-3-one, ready for a reduction to the rather challenging hindered ether (direct alkylation with a hindered alkyl halide would struggle to avoid competing E2 elimination).



The reduction of the acetal is catalysed by a Lewis acid and goes via an oxonium ion, which collects hydride from the mild reducing agent triethylsilane. Silanes react only with cationic electrophiles. The oxonium ion could open either way, but this one is less hindered and possibly allows the titanium some favourable interaction with the mesylate substituent.

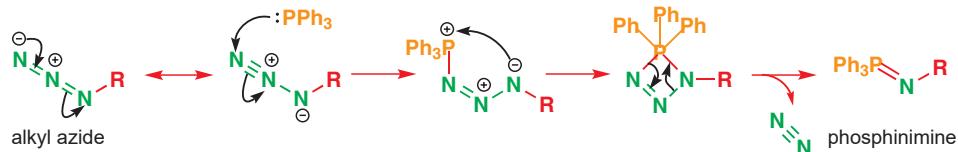


As often in the synthesis of 1,2-difunctionalized compounds, an epoxide is a key intermediate, and in this case an epoxide forms by closure of the newly revealed hydroxyl group onto the mesylate leaving group in base.

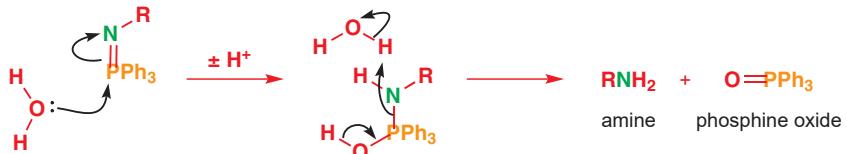


Two amino groups now need introducing with rather specific stereoselectivity, and the next key intermediate is an aziridine, the nitrogen analogue of an epoxide. Azide is not completely regioselective in opening this epoxide, but both regiosomers are formed with complete inversion of configuration.

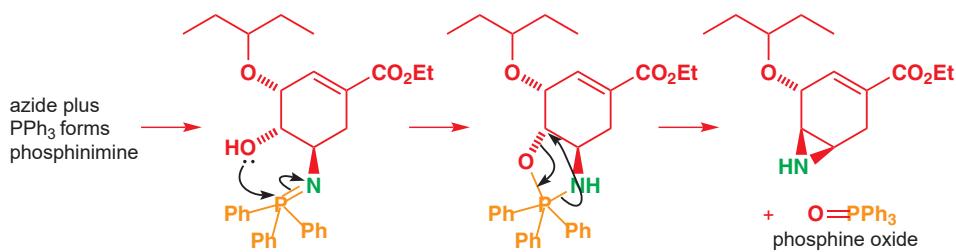
Azides may be reduced to amines with triphenylphosphine in what is known as the Staudinger reaction. The probable mechanism involves attack of triphenylphosphine on the azide and formation of a phosphoranimine via a four-membered intermediate—notice the similarity with the Wittig reaction!



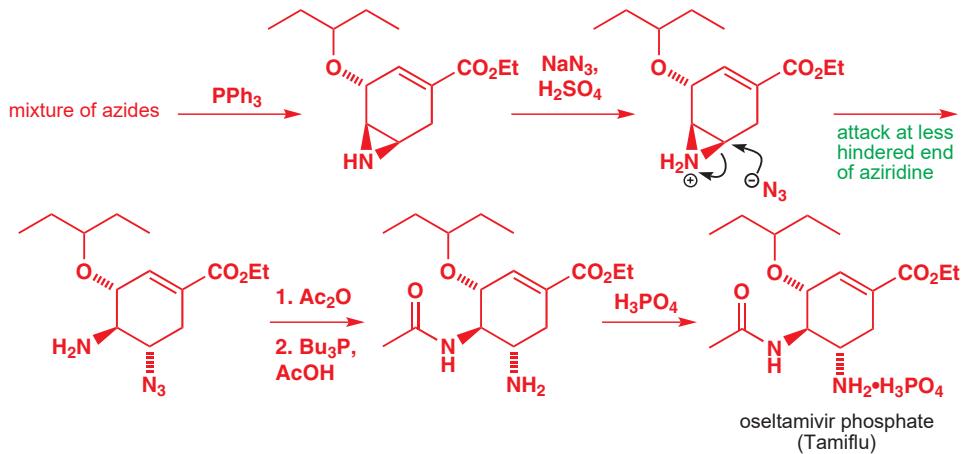
The phosphoranimine, in the presence of water, hydrolyses to an amine—overall a molecule of nitrogen is lost and a molecule of water is ‘dismembered’ and shared between the reagents.



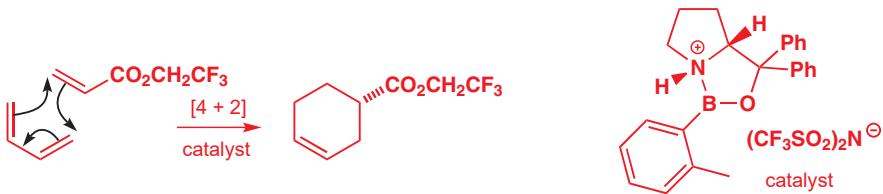
When the azide has an adjacent hydroxyl group, something more interesting happens: the phosphoranimine intermediate in the reaction is intercepted by the alcohol, which turns itself into a leaving group. Extrusion of the stable phosphine oxide gives an aziridine, with inversion of stereochemistry as the nitrogen displaces the leaving group. Here is the result with the major azide from the oseltamivir synthesis:



In this case, it doesn't matter which azide you start with: triphenylphosphine converts them both to the same aziridine. Like epoxides, aziridines open with nucleophiles under acid catalysis, and azide is used again to put in the second amino group by attack at the less hindered end of the aziridine. To get the right amino group acetylated, the amide is formed before the azide is reduced, this time with tributylphosphine. The drug is formulated as a stable phosphate salt by treatment with phosphoric acid.



This is not, by any stretch of the imagination, an efficient synthesis, not least because there are two uses of potentially explosive azides, and large amounts of waste are produced from the phosphine steps. However, for several years it was the best route available, and Roche operated it as a manufacturing process on a tonne scale. In the last few years, however, several modifications have been published, and among the most efficient of the alternatives was one devised in 2006 by the Nobel prize-winning chemist E. J. Corey. Corey's route built on the fact that oseltamivir is a cyclohexene, and as you saw in Chapter 34 cyclohexenes are made efficiently by a Diels–Alder reaction.

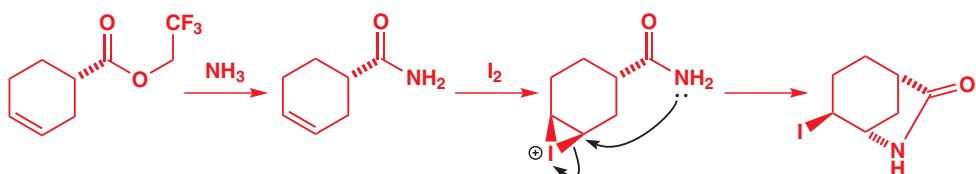


Corey's research group combined the two very cheap reagents butadiene and trifluoroethyl acrylate in the first step of their alternative synthesis: the cycloadduct already has the scaffold of oseltamivir. Not starting with a natural product has its advantages and disadvantages: no longer is supply limited by the world production of coffee beans or star anise, and no longer is there a need to make do with a compound of the wrong relative stereochemistry, wasting valuable resources inverting stereogenic centres in the course of the synthesis. However, as you know from Chapter 41, making an enantiomerically pure compound like oseltamivir *must* involve a natural compound somewhere along the line. Diels–Alder reactions are catalysed by

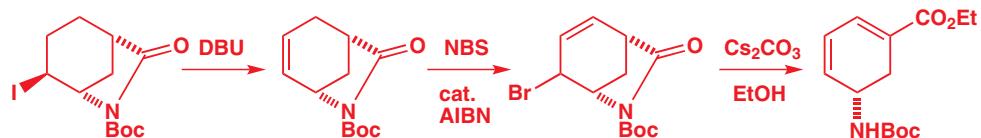
We illustrated a chiral auxiliary approach to asymmetric Diels–Alder reactions in Chapter 41, but it was clearly better to avoid the extra steps and recycling involved in large-scale synthesis with an auxiliary.

Lewis acids, and so by using a catalytic amount of the chiral Lewis acid (whose structure is evidently based on that of the CBS catalyst) it was possible to induce the cycloaddition to produce enantioselectively.

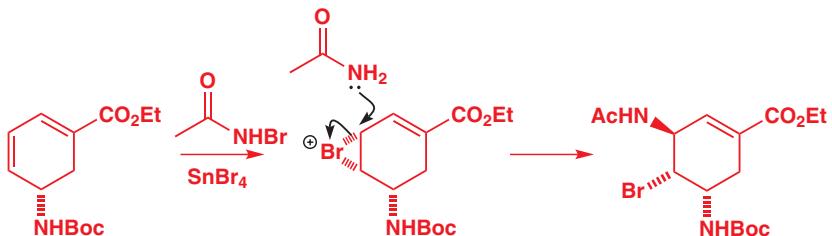
The product of the Diels–Alder reaction has the ester substituent in place, and the stereochemistry at the single chiral centre has to be used to control stereochemistry at new centres in the molecule. We discussed strategies for doing this in Chapters 32 and 33, and in this case the use of a tethered nucleophile (p. 847) allowed the first amino group to be introduced with the correct stereochemistry. Conversion of the ester to an amide followed by treatment with iodine induced in the nitrogen equivalent of an iodolactamization (an iodolactamization), placing the nitrogen *syn* to the ester and the iodide *trans*.



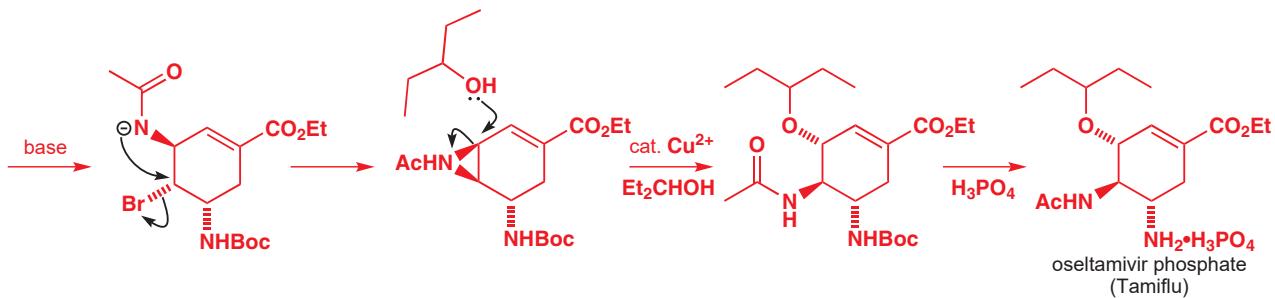
The next key intermediate is a diene, which is reached by an overall oxidation of the iodide: protection of nitrogen and elimination of the iodide gives the only possible alkene. Radical bromination with NBS followed by treatment with base in ethanol both hydrolyses the lactam and eliminates bromide to give the diene.



Now for the second nitrogen substituent. Bromination of the less electron deficient end of the diene with *N*-bromoacetamide in the presence of  $\text{SnBr}_4$  leads to an intermediate bromonium ion which is opened by the acetamide by-product at the more reactive end adjacent to the alkene, giving a *trans* diaxial product.



Treatment with base leads to cyclization to an aziridine, and this time the ether is introduced by a copper-catalysed ring opening of the aziridine with 3-pentanol. Treatment with phosphoric acid removes the Boc protecting group and converts the product to oseltamivir phosphate.



Overall, Corey's route uses just 12 steps, and gives a yield of 30%—about double that of the route from shikimic acid. But much work remains to be done: several of the steps require

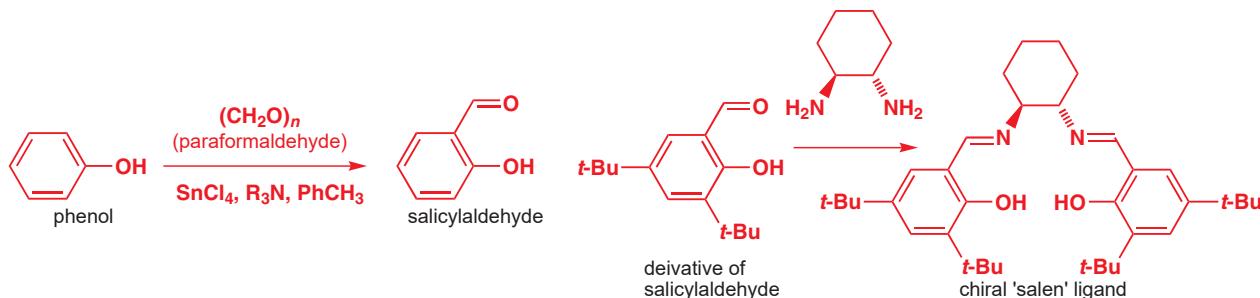
conditions or solvents (such as carbon tetrachloride) that are unsuitable for industrial use. Advances are still being made, with even shorter routes being reported since 2006. In some ways it would be best if this vital work were never made necessary, but across the world chemists are working in similar ways to relieve suffering, and potential suffering, caused by illness and disease.

## The future of organic chemistry

Not all organic chemists can be involved in such exciting projects as the launching of a life-saving antiviral drug. Some most certainly have to be: resistant bacteria are fast catching up with our current range of antibiotics, and it is teams of organic chemists, in conjunction with biologists, who will be able to erect the next line of defence against these infections. But the chemistry used in such frontline projects is often the product of work by chemists in other institutions who had no idea that it would eventually be used to make a vital drug.

Take the millions of lives saved by the synthesis of indinavir, for example. This drug would not have been possible had not the Sharpless and Jacobsen asymmetric epoxidations, the catalytic asymmetric reduction, and the stereoselective enolate alkylation, along with many of the methods tried but not used in the final synthesis, been invented and developed by organic chemists in academic and industrial research laboratories. Some of the more famous names involved, like Sharpless, Jacobsen, and Noyori, invented new methods, while others modified and optimized those methods, and still others applied the methods to new types of molecules. Yet all built on the work of other chemists.

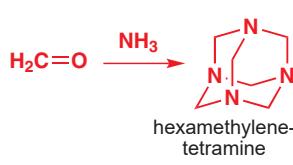
We can delve deeper into one of the steps in the indinavir synthesis. In 1980 Giovanni Casiraghi, a rather less famous chemist from the University of Parma, published a paper in the *Journal of the Chemical Society* about selective reactions between phenols and formaldehyde. He and his colleagues made the modest discovery that controlled reactions to give salicylaldehydes could be achieved in toluene with  $\text{SnCl}_4$  as catalyst. The reaction is regioselective for the *ortho* isomer and the paper described the rather precise conditions needed to get a good yield.



The reaction was also successful for substituted salicylaldehydes. When Jacobsen came to develop his asymmetric epoxidation, he chose salens as his catalysts, partly because they could be made so easily from salicylaldehydes.

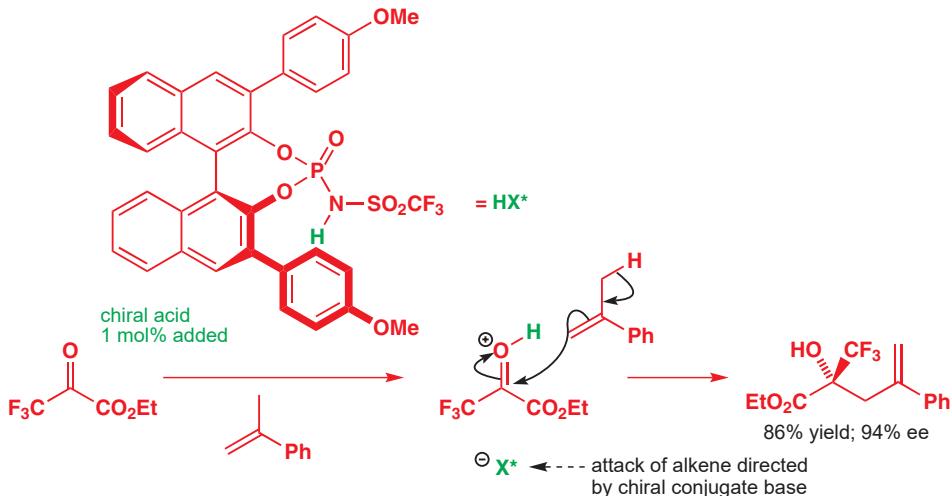
Jacobsen epoxidation turned out to be the best large-scale method for preparing the *cis*-aminoindanol for the synthesis of indinavir. This process is very much the cornerstone of the whole synthesis. It cannot have entered Casiraghi's wildest dreams that his work might someday be useful in a matter of life and death. Neither did his four co-workers nor Jacobsen's more numerous co-workers see clearly the future applications of their work. By its very nature it is impossible to predict the outcome or the applications of research. But one thing is certain: good research and exciting discoveries come from a thorough understanding of the fundamentals of organic chemistry.

When Jacobsen's epoxidation was fully described in 1998–99, the Casiraghi method was abandoned in favour of an even older method discovered in the 1930s by Duff. The remarkable Duff reaction uses hexamethylenetetramine, the oligomer of formaldehyde and ammonia, to provide the extra carbon atom. The now otherwise unknown Duff worked at Birmingham Technical College. Later in 1972, a William E. Smith, working in the GEC chemical laboratories



at Schenectady, New York, found how to make the Duff reaction more general and better yielding by using  $\text{CF}_3\text{CO}_2\text{H}$  as catalyst. Even so, this method gives a lower yield than the Casiraghi method but it uses less toxic reagents (in particular it avoids stoichiometric tin) and is more suitable for large-scale work. When Duff was inventing his reaction or Smith was modifying the conditions, asymmetric synthesis was not even a gleam in anyone's eyes. It is impossible even for the inventor to predict whether a discovery is important or not.

Where is organic chemistry going next? As we write this chapter, advances are being made in reactions which would have seemed outlandish even just ten years ago. Work published in the years since 2005 has shown, for example, that many reactions of cations can be made to form single enantiomers of products even if they take place just in the vicinity of a chiral anion. Reactions such as the one below, from 2008, promise to revolutionize, yet again, some of the ways in which chemists make chiral compounds.



Interactive mechanism for catalytic enantioselective additions controlled by chiral anions

Finding drugs is a difficult job, and the number of new drugs launched each year is dropping as it becomes harder and more expensive to advance beyond existing treatments and as demands for more stringent safety rightly increase. But new drugs are made because...they can be made! What about all those classes of molecules which have never been made, simply because they have never been needed? Among them may well be molecules that will have all the specific attributes we want a potential drug to exhibit. Techniques known as diversity orientated synthesis are now addressing this idea—how to make and study great families of fundamentally different but potentially revolutionary molecules simply and efficiently. It's too early to tell, but the hope is that these techniques will provide breakthroughs in the fight against disease by finding completely new ways to attack their causes.

Nature is a superb synthetic chemist, and organic chemists have spent the last century exploring efficient ways of building molecular structures more efficiently than nature. Nature builds molecules a certain way because there is no alternative—molecules can be biosynthesized only if the enzymes to make them exist; enzymes are only made from the same 20 amino acids; amino acids are built into proteins by the same ribosome. The ribosome is the most complex and beautiful molecular structure in the known universe, but it can make only proteins. Chemists, with the periodic table, a supply of raw materials, a laboratory, and their ingenuity can make anything. Sometimes chemists use Nature's enzymes to do a job, or even force them to evolve to do a job better. By cloning useful enzymes in bacteria and forcing them to mutate, high-speed evolution can be induced, and enzymes can be created which do a job better, faster, or at a different temperature from their original 'wild type' ancestors.

More often chemists use reactions nature can never use—Rh, Ru, Pd, or phosphine ligands for that matter have never been exploited by any known biological process. What molecules chemists will make next, and how they make them, may determine the well-being of huge numbers of people in the future, but we may well not know it until then.

That future is yours as you continue your studies in organic chemistry beyond the scope of this book, and if you do you will want to read about modern work in more specialized areas. Your university library should have a selection of books on related topics we have only touched on, such as orbitals and chemical reactions, NMR spectroscopy, molecular modelling physical organic chemistry, photochemistry, enzyme mechanisms, biosynthesis, organometallic chemistry, asymmetric synthesis, supramolecular chemistry, and polymer and materials chemistry. This book will equip you with enough fundamental organic chemistry to explore these topics with understanding and enjoyment, and, perhaps, to discover what you want to do for the rest of your life. All of the chemists mentioned in this chapter and throughout the book began their careers as students of chemistry at universities somewhere in the world. You have the good fortune to study chemistry at a time when more is understood about the subject than ever before, when information is easier to retrieve than ever before, and when organic chemistry is more interrelated with other disciplines than ever before.

## Further reading

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For an informative overview of the most important drug molecules of the 20th century, see *Chemical and Engineering News*, 2005, Jun 20 edition.

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## Check your understanding

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To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at <http://www.oxfordtextbooks.co.uk/orc/clayden2e/>

# 致谢本书插图的提供者

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# 元素周期表

	1 I	2 II	3 III	4 IV	5 V	6 VI	7 VII	8 VIII	9 VIII
<b>S</b>	3   <b>Li</b> RAM: 6.941 P: 0.98  Lithium 锂	4   <b>Be</b> RAM: 9.012182 P: 1.57  Beryllium 铍							
2									
3	11   <b>Na</b> RAM: 22.98977 P: 0.93  Sodium 钠	12   <b>Mg</b> RAM: 24.305 P: 1.31  Magnesium 镁							
4	19   <b>K</b> RAM: 39.0983 P: 0.82  Potassium 钾	20   <b>Ca</b> RAM: 40.078 P: 1  Calcium 钙	21   <b>Sc</b> RAM: 44.95591 P: 1.36  Scandium 钪	22   <b>Ti</b> RAM: 47.88 P: 1.54  Titanium 钛	23   <b>V</b> RAM: 50.9415 P: 1.63  Vanadium 钒	24   <b>Cr</b> RAM: 51.9961 P: 1.66  Chromium 钔	25   <b>Mn</b> RAM: 54.93805 P: 1.55  Manganese 锰	26   <b>Fe</b> RAM: 55.847 P: 1.83  Iron 铁	27   <b>Co</b> RAM: 58.9332 P: 1.88  Cobalt 钴
5	37   <b>Rb</b> RAM: 85.4678 P: 0.82  Rubidium 铷	38   <b>Sr</b> RAM: 87.62 P: 0.95  Strontium 钡	39   <b>Y</b> RAM: 88.90585 P: 1.22  Yttrium 钇	40   <b>Zr</b> RAM: 91.224 P: 1.33  Zirconium 钇	41   <b>Nb</b> RAM: 92.90638 P: 1.6  Niobium 钮	42   <b>Mo</b> RAM: 95.94 P: 2.16  Molybdenum 钼	43   <b>Tc</b> RAM: 98 P: 1.9  Technetium 钚	44   <b>Ru</b> RAM: 101.07 P: 2.2  Ruthenium 钇	45   <b>Rh</b> RAM: 102.9055 P: 2.28  Rhodium 钻
6	55   <b>Cs</b> RAM: 132.9054 P: 0.79  Cesium 铯	56   <b>Ba</b> RAM: 137.327 P: 0.89  Barium 钡	71   <b>Lu</b> RAM: 174.967 P: 1.27  Lutetium 镨	72   <b>Hf</b> RAM: 178.49 P: 1.3  Hafnium 钨	73   <b>Ta</b> RAM: 180.9479 P: 1.5  Tantalum 钨	74   <b>W</b> RAM: 183.85 P: 2.36  Tungsten 钨	75   <b>Re</b> RAM: 186.207 P: 1.9  Rhenium 镍	76   <b>Os</b> RAM: 190.2 P: 2.2  Osmium 镍	77   <b>Ir</b> RAM: 192.22 P: 2.2  Iridium 镍
7	87   <b>Fr</b> RAM: 223 P: 0.7  Francium 钇	88   <b>Ra</b> RAM: 226.0254 P: 0.9  Radium 镭	103   <b>Lr</b> RAM: 260 P:  Lawrencium 长	104   <b>Rf</b> RAM: 261 P:  Rutherfordium 长	105   <b>Db</b> RAM: 262 P:  Dubnium 长	106   <b>Sg</b> RAM: 263 P:  Seaborgium 长	107   <b>Bh</b> RAM: 262 P:  Bohrium 长	108   <b>Hs</b> RAM: 265 P:  Hassium 长	109   <b>Mt</b> RAM: 266 P:  Meitnerium 长
			57   <b>La</b> RAM: 138.9055 P: 1.1  Lanthanum 镧	58   <b>Ce</b> RAM: 140.115 P: 1.12  Cerium 钆	59   <b>Pr</b> RAM: 140.9077 P: 1.13  Praseodymium 镧	60   <b>Nd</b> RAM: 144.24 P: 1.14  Neodymium 镧	61   <b>Pm</b> RAM: 145 P: 1.13  Promethium 镧	62   <b>Sm</b> RAM: 150.36 P: 1.17  Samarium 镧	63   <b>Eu</b> RAM: 151.965 P: 1.2  Europium 镧
			89   <b>Ac</b> RAM: 227 P: 1.1  Actinium 镧	90   <b>Th</b> RAM: 232.0381 P: 1.3  Thorium 钍	91   <b>Pa</b> RAM: 213.0359 P: 1.5  Protactinium 镧	92   <b>U</b> RAM: 238.0289 P: 1.38  Uranium 钔	93   <b>Np</b> RAM: 237.0482 P: 1.36  Neptunium 镧	94   <b>Pu</b> RAM: 244 P: 1.28  Plutonium 镧	95   <b>Am</b> RAM: 243 P: 1.3  Americium 镧

图例	元素符号
原子序数	.....00   Xx
相对原子质量	.....RAM: 0.000
电负性 (Pauling)	.....P: 0.0
元素名称	Name 名称

10	11	12	13	14	15	16	17	18							
I	II		III	IV	V	VI	VII	VIII							
<b>p</b>															
5   <b>B</b> RAM: 10.811 P: 2.04	6   <b>C</b> RAM: 12.011 P: 2.55	7   <b>N</b> RAM: 14.00674 P: 3.04	8   <b>O</b> RAM: 15.9994 P: 3.44	9   <b>F</b> RAM: 18.9984 P: 3.98	10   <b>Ne</b> RAM: 20.1797 P: 0										
Boron 硼	Carbon 碳	Nitrogen 氮	Oxygen 氧	Fluorine 氟	Neon 氖										
13   <b>Al</b> RAM: 26.98154 P: 1.61	14   <b>Si</b> RAM: 28.0855 P: 1.9	15   <b>P</b> RAM: 30.97376 P: 2.19	16   <b>S</b> RAM: 32.066 P: 2.58	17   <b>Cl</b> RAM: 35.4527 P: 3.16	18   <b>Ar</b> RAM: 39.948 P: 0										
Aluminium 铝	Silicon 硅	Phosphorus 磷	Sulfur 硫	Chlorine 氯	Argon 氩										
28   <b>Ni</b> RAM: 58.6934 P: 1.91	29   <b>Cu</b> RAM: 63.546 P: 1.9	30   <b>Zn</b> RAM: 65.39 P: 1.65	31   <b>Ga</b> RAM: 69.723 P: 1.81	32   <b>Ge</b> RAM: 72.61 P: 2.01	33   <b>As</b> RAM: 74.92159 P: 2.18	34   <b>Se</b> RAM: 78.96 P: 2.55	35   <b>Br</b> RAM: 79.904 P: 2.96	36   <b>Kr</b> RAM: 83.8 P: 0							
Nickel 镍	Copper 铜	Zinc 锌	Gallium 镊	Germanium 镉	Arsenic 砷	Selenium 硒	Bromine 溴	Krypton 氖							
46   <b>Pd</b> RAM: 106.42 P: 2.2	47   <b>Ag</b> RAM: 107.8682 P: 1.93	48   <b>Cd</b> RAM: 112.411 P: 1.69	49   <b>In</b> RAM: 114.82 P: 1.78	50   <b>Sn</b> RAM: 118.71 P: 1.96	51   <b>Sb</b> RAM: 121.757 P: 2.05	52   <b>Te</b> RAM: 127.6 P: 2.1	53   <b>I</b> RAM: 126.9045 P: 2.66	54   <b>Xe</b> RAM: 131.29 P: 0							
Palladium 钯	Silver 银	Cadmium 镉	Indium 钨	Tin 锡	Antimony 钻	Tellurium 硒	Iodine 碘	Xenon 氙							
78   <b>Pt</b> RAM: 195.08 P: 2.28	79   <b>Au</b> RAM: 196.9665 P: 2.54	80   <b>Hg</b> RAM: 200.59 P: 2	81   <b>Tl</b> RAM: 204.3833 P: 2.04	82   <b>Pb</b> RAM: 207.2 P: 2.33	83   <b>Bi</b> RAM: 208.9804 P: 2.02	84   <b>Po</b> RAM: 209 P: 2	85   <b>At</b> RAM: 210 P: 2.2	86   <b>Rn</b> RAM: 222 P: 0							
Platinum 铂	Gold 金	Mercury 汞	Thallium 铋	Lead 铅	Bismuth 铑	Polonium 钍	Astatine 砹	Radon 氪							

还有一些已被分离的人造元素，  
但它们对有机化学家来说没有实质帮助。

64   <b>Gd</b> RAM: 157.25 P: 1.2	65   <b>Tb</b> RAM: 158.9253 P: 1.2	66   <b>Dy</b> RAM: 162.5 P: 1.22	67   <b>Ho</b> RAM: 164.9303 P: 1.23	68   <b>Er</b> RAM: 167.26 P: 1.24	69   <b>Tm</b> RAM: 168.9342 P: 1.25	70   <b>Yb</b> RAM: 173.04 P: 1.1
Gadolinium 钇	Terbium 钔	Dysprosium 镨	Holmium 钕	Erbium 钕	Thulium 钕	Ytterbium 钇
96   <b>Cm</b> RAM: 247 P: 1.3	97   <b>Bk</b> RAM: 247 P: 1.3	98   <b>Cf</b> RAM: 251 P: 1.3	99   <b>Es</b> RAM: 252 P: 1.3	100   <b>Fm</b> RAM: 257 P: 1.3	101   <b>Md</b> RAM: 258 P: 1.3	102   <b>No</b> RAM: 259 P: 1.3
Curium 钆	Berkelium 钔	Californium 镨	Einsteinium 镔	Fermium 镔	Mendelevium 钍	Nobelium 镔

### 镧系元素 Lanthanides

### 锕系元素 Actinides

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# Index

3TC *see* Lamivudine

## A

*A* value 375  
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