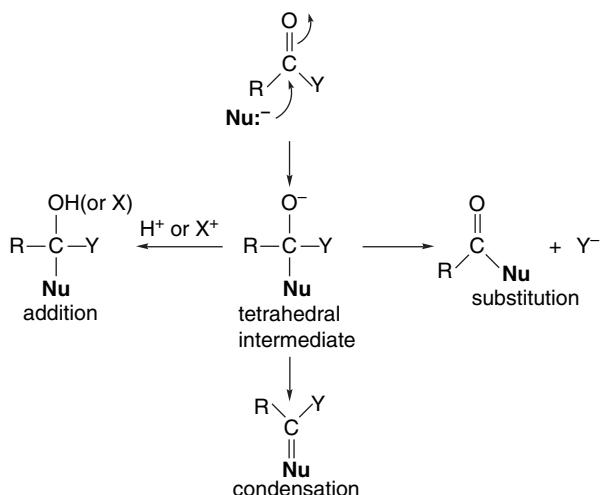


Addition, Condensation and Substitution Reactions of Carbonyl Compounds

Introduction

The carbonyl group is one of the most prevalent of the functional groups and is involved in many synthetically important reactions. Reactions involving carbonyl groups are also particularly important in biological processes. Most of the reactions of aldehydes, ketones, esters, carboxamides, and the other carboxylic acid derivatives directly involve the carbonyl group. We discussed properties of enols and enolates derived from carbonyl compounds in Chapter 6. In the present chapter, the primary topic is the mechanisms of addition, condensation and substitution reactions at carbonyl centers. We deal with the use of carbonyl compounds to form carbon-carbon bonds in synthesis in Chapters 1 and 2 of Part B.

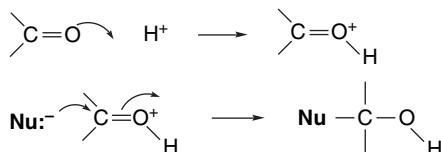
In many reactions at carbonyl groups, a key step is the addition of a nucleophile, which generates a tetracoordinate carbon atom. The overall course of the reaction is then determined by the fate of this tetrahedral intermediate. *Addition* occurs when the tetrahedral intermediate goes directly on to product. *Condensation* occurs if the carbonyl oxygen is eliminated and a double bond is formed. *Substitution* results when one of the groups is eliminated from the tetrahedral intermediate to re-form a carbonyl group.



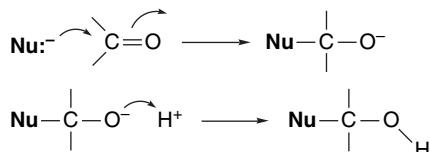
The reaction patterns of the specific classes of carbonyl compounds are related by the decisive importance of tetrahedral intermediates, and differences in reactivity can often be traced to structural features present in those intermediates. In Section 3.4.4, we considered some of the fundamental substituent effects on the stability of both carbonyl compounds and tetrahedral intermediates. These relationships will be important as we discuss the reactions in this chapter.

In broad terms, there are three possible mechanisms for addition of a nucleophile and a proton to give a tetrahedral intermediate in a carbonyl addition reaction.

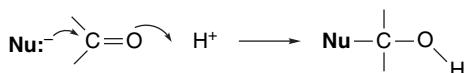
(a) Protonation followed by nucleophilic attack on the protonated carbonyl group:



(b) Nucleophilic addition at the carbonyl group followed by protonation:



(c) Concerted proton transfer and nucleophilic attack:

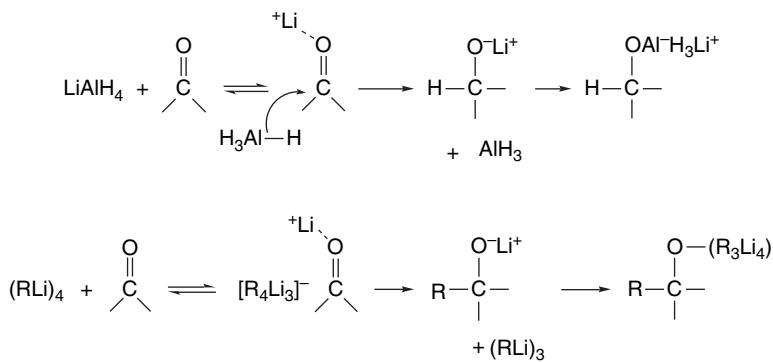


The nucleophile is shown as an anion, but can also be a neutral species, in which case a proton is subsequently lost.

There are carbonyl addition reactions that are examples of each of the general mechanisms, and a two-dimensional potential energy diagram provides a useful framework within which to consider specific addition reactions. The breakdown of a tetrahedral intermediate involves the same processes but operates in the opposite direction, so the principles that are developed also apply to the reactions of the tetrahedral intermediates. Let us examine the three general mechanistic cases in relation to the energy diagram in Figure 7.1.

Case (a) is favored for weak nucleophiles. The protonated carbonyl compound is more reactive toward such nucleophiles. The nucleophile may be neutral or a weakly basic anion. This mechanism is most likely to operate in relatively acidic conditions. Case (b) is favored for strongly basic nucleophiles. For example, carbanions cannot generally exist under acidic conditions, so carbanion additions occur under strongly basic conditions. These nucleophiles are more basic than carbonyl oxygens and are protonated in preference to the carbonyl group. In such systems, proton donors diminish the overall reaction rate by decreasing the amount of anionic nucleophile that is available for reaction. The concerted mechanism, case (c), is observed for less basic nucleophiles. The simultaneous transfer of the proton at the carbonyl oxygen facilitates addition by species that are not sufficiently nucleophilic to react by mechanism (b). The general pattern is that the weaker and less basic the nucleophile, the more important the partial or complete protonation of the carbonyl group. If we consider the reverse process, the same general relationships will hold. Good leaving groups (which are poor nucleophiles) can be expected to follow path (a); poor leaving groups will follow path (b); and intermediate cases are likely to react by the concerted mechanism (c).

Metal cations and other Lewis acids can replace protons as reagents/catalysts for carbonyl addition reactions. Metal cations, for example, are involved in hydride and organometallic addition reactions. Metal cations and Lewis acids are also key reagents in the aldol-type reactions that are considered in Section 7.7.



It is useful to recognize that the dissociation of tetrahedral intermediates in carbonyl chemistry is closely related to the generation of carbocations by ionization processes. The protonated carbonyl compounds or iminium ions that

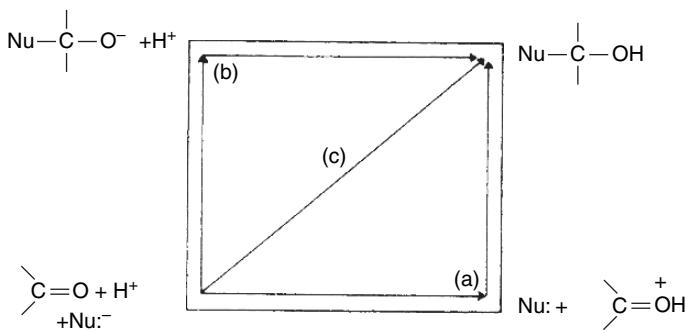
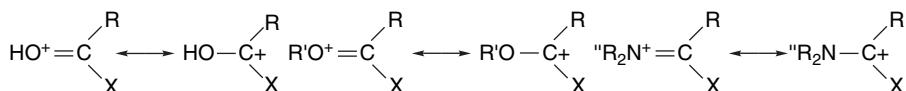


Fig. 7.1. Two-dimensional potential energy diagram for addition of a proton and nucleophile to a carbonyl group. (a) Proton transfer complete before nucleophilic addition begins; (b) nucleophilic addition complete before proton transfer begins; (c) concerted proton transfer and nucleophilic addition.

are generated by breakdown of tetrahedral intermediates are resonance-stabilized carbocations.

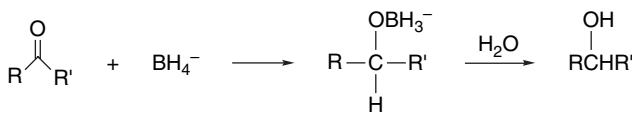


The question of which substituent on a tetrahedral intermediate is the best leaving group is similar to comparing S_N1 reactants on the basis of leaving-group ability. Poorer leaving groups such as alkoxides can function as leaving groups in the case of tetrahedral intermediates because of the assistance provided by the remaining oxygen or nitrogen substituents. Keeping these relationships in mind should be helpful in understanding the reactivity of tetrahedral intermediates.

7.1. Reactivity of Carbonyl Compounds toward Addition

At this point we consider some general relationships concerning the reactivity of carbonyl compounds toward addition of nucleophiles. Several factors influence the overall rate of a reaction under various conditions. Among the crucial factors are: (1) structural features of the carbonyl compound; (2) the role of protons or other Lewis acids in activating the carbonyl group toward nucleophilic attack; (3) the reactivity of the nucleophilic species and its influence on subsequent steps; and (4) the stability of the tetrahedral intermediate and the extent to which it proceeds to product rather than reverting to starting material.

We focus first on the inherent reactivity of the carbonyl compound itself. An irreversible process in which the addition product is stable is the most direct means of comparing the reactivity of carbonyl compounds. In these circumstances, the relative rate of reaction of different carbonyl compounds can be directly compared. One such reaction is hydride reduction. In particular, reductions by sodium borohydride in protic



The reaction is second-order overall, with the rate equal to $k[\text{R}_2\text{C}=\text{O}][\text{NaBH}_4]$. The interpretation of the rates is complicated somewhat by the fact that the alkoxyborohydrides produced by the first addition can also function as reducing agents by successive hydride transfers, but this has little apparent effect on the relative reactivity of the carbonyl compounds. Table 7.1 presents some of the rate data obtained from these studies.

Reductions by NaBH_4 are characterized by low enthalpies of activation (8 to 13 kcal/mol) and large negative entropies of activation (-28 to -40 eu). These data suggest an early TS with considerable organization. Aldehydes are substantially more reactive than ketones, as can be seen by comparing benzaldehyde and acetophenone. This relative reactivity is characteristic of nearly all carbonyl addition reactions. The lower reactivity of ketones is due primarily to steric effects. Not only does the additional substituent increase the steric restrictions to approach of the nucleophile, but it also causes greater steric interaction in the tetrahedral adduct as the hybridization changes from trigonal to tetrahedral. Alkyl substituents also act as electron donors toward carbonyl groups by hyperconjugation (see Section 2.2.1).

Among the cyclic ketones shown in Table 7.1, the reactivity of cyclobutanone is enhanced because of the strain of the four-membered ring, which is decreased on going from sp^2 to sp^3 hybridization. The higher reactivity of cyclohexanone compared to cyclopentanone is quite general for carbonyl addition reactions. The major factor responsible for the difference in this case is the change in torsional strain as addition occurs. As the hybridization goes from sp^2 to sp^3 , the torsional strain is *increased* in cyclopentanone. The opposite is true for cyclohexanone. The

Table 7.1. Rates of Reduction of Aldehydes and Ketones by Sodium Borohydride

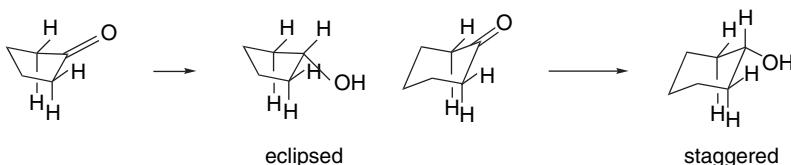
Carbonyl compound	$k \times 10^4 M^{-1} s^{-1}$
Benzaldehyde	12,400 ^b
Benzophenone	1.9
Acetophenone	2.0
Acetone	15.1
Cyclobutanone	264
Cyclopentanone	7
Cyclohexanone	161

a. In isopropanol at 0°C.

b. Extrapolated from data at lower temperatures.

¹. H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron*, **1**, 214 (1957); H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957).

equatorial hydrogens are nearly eclipsed with the carbonyl oxygen in cyclohexanone, but the chair structure of cyclohexanol allows all bonds to attain staggered arrangements.



The borohydride reduction rate data are paralleled by many other carbonyl addition reactions. In fact, for a series of ketones, most of which are cyclic, a linear free-energy correlation of the form

$$\log k = A \log k_0 + B$$

exists for nucleophiles such as NH_2OH , CN^- , $\text{HOCH}_2\text{CH}_2\text{S}^-$, and HSO_3^- .² These nucleophiles span a wide range of reactivity and include nitrogen, carbon, and sulfur nucleophiles. This free-energy relationship implies that in this series of ketones the same structural features govern reactivity toward each of the nucleophiles. To a good approximation the parameter $A = 1$, which reduces the correlation to

$$\log (k/k_0) = B$$

This equation implies that the *relative reactivity is independent of the specific nucleophile* and is insensitive to changes in position of the transition state. Table 7.2 lists some of the B values for some representative ketones. The parameter B indicates relative reactivity on a log scale. Cyclohexanone is seen to be a particularly reactive ketone, being almost as reactive as cyclobutanone and more than ten times as reactive as acetone.

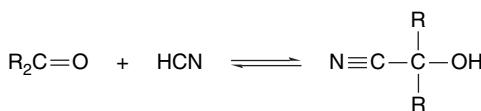
The same structural factors come into play in determining the position of equilibria in reversible additions to carbonyl compounds. An example of such equilibrium processes is the addition of cyanide to give cyanohydrins.

Table 7.2. Relative Reactivity of Some Ketones toward Addition of Nucleophiles

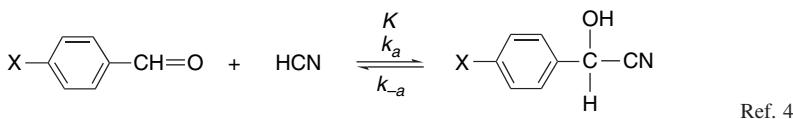
Ketone	B^a
Cyclobutanone	0.09
Cyclohexanone	0.00
4- <i>t</i> -Butylcyclohexanone	-0.008
Adamantanone	-0.46
Cycloheptanone	-0.95
Cyclopentanone	-1.18
Acetone	-1.19
Norbornan-2-one	-1.48
3,3,5,5-Tetramethylcyclohexanone	-1.92

a. A. Finiels and P. Geneste, *J. Org. Chem.*, **44**, 1577 (1979); reactivity relative to cyclohexanone.

² A. Finiels and P. Geneste, *J. Org. Chem.*, **44**, 1577 (1979).



The equilibrium constants in Table 7.3 illustrate some of the broad trends in carbonyl group reactivity. Alkyl substitution decreases the extent of addition. Aromatic carbonyl compounds are somewhat less reactive toward addition than similar alkyl compounds because the carbonyl group is stabilized by conjugation with the aromatic ring. Strong electron-attracting groups, such as trifluoromethyl, favor addition by enhancing the electrophilicity of the carbonyl group. For cyclopentanone, cyclohexanone, and cycloheptanone the K 's for addition of CN^- are 48, 1000, and $8 M^{-1}$, respectively.³ For aromatic aldehydes, the equilibria are affected by the electronic nature of the aryl substituent. Electron donors disfavor addition by stabilizing the aldehyde, whereas electron-accepting substituents have the opposite effect. The Hammett correlation with σ^+ gives $\rho = +1.01$.



There are large differences in the reactivity of the various carboxylic acid derivatives, such as amides, esters, and acyl chlorides. One important factor is the resonance stabilization provided by the heteroatom substituent, which is in the order $\text{N} > \text{O} > \text{Cl}$. Electron delocalization reduces the electrophilicity of the carbonyl group and the corresponding stabilization is lost in the tetrahedral intermediate.

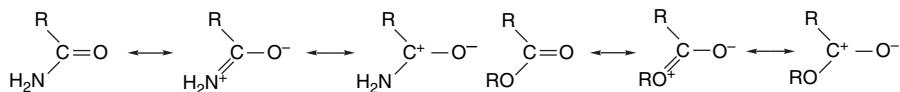


Table 7.3. Equilibrium Constants for Cyanohydrin Formation^a

$\text{R}_2\text{C}=\text{O}$	$\log K$
$\text{CH}_2=\text{O}$	7.48
$\text{CH}_3\text{CH}=\text{O}$	2.29
$(\text{CH}_3)_2\text{C}=\text{O}$	-1.84
$\text{PhCH}=\text{O}$	0.74 ^b
PhCOCF_3	3.98 ^c

a. Except where otherwise noted the data are from G. Schlesinger and S. L. Miller, *J. Am. Chem. Soc.*, **85**, 3729 (1973).

b. W. M. Ching and R. G. Kallen, *J. Am. Chem. Soc.*, **100**, 6119 (1978).

c. C. D. Ritchie, *J. Am. Chem. Soc.*, **106**, 7087 (1984).

³. V. Prelog and M. Kobelt, *Helv. Chim. Acta*, **32**, 1187 (1949).

⁴. W.-M. Ching and R. G. Kallen, *J. Am. Chem. Soc.*, **100**, 6119 (1978); V. Gold and W. N. Wassef, *J. Chem. Soc., Perkin Trans. 2*, 1431 (1984).

The high reactivity of the acyl chlorides also reflects the polar electron-withdrawing effect of the chlorine, which more than outweighs its small π -donor effect. Another factor that strongly affects the reactivity of these carboxylic acid derivatives is the leaving-group ability of the substituents. The order is $\text{Cl} > \text{OAr} > \text{OR} > \text{NR}_2 > \text{O}^-$ so that not only is it easier to form the tetrahedral intermediate in the order $\text{Cl} > \text{OAr} > \text{OR} > \text{NR}_2 > \text{O}^-$, but the tendency for subsequent elimination to occur is also in the same order. As the two factors work together, there are large differences in reactivity toward the nucleophiles. (See Scheme 3.3 for some specific data.)

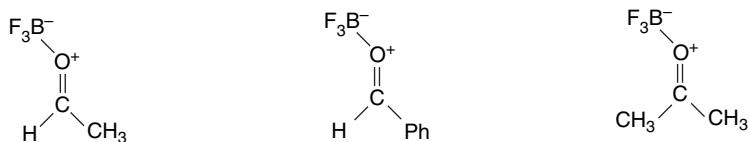
**Approximate Relative Reactivity toward
Hydrolysis**

RCOCl	10^{11}
$\text{RCO}_2\text{R}'$	1
RCONR'_2	10^{-3}
RCO_2^-	$<< 1$

Many carbonyl addition and substitution reactions are carried out under acidic conditions or in the presence of Lewis acids. Qualitatively, protonation or complexation increases the electrophilicity of the carbonyl group. The structural effects of protonation have been examined for formaldehyde, acetaldehyde, acetone, formamide, and formyl fluoride. These effects should correspond to those in more complex carbonyl compounds. Protonation results in a substantial lengthening of the $\text{C}=\text{O}$ bond.⁵ The calculated [B3LYP/ 6-31++G(*d, p*)] gas phase proton affinities reflect the trend of increasing basicity with donor groups (CH_3 , NH_2) and decreased basicity for fluorine.

	$\text{CH}_2=\text{O}$	$\text{CH}_3\text{CH}=\text{O}$	$(\text{CH}_3)_2\text{C}=\text{O}$	$\text{H}_2\text{NCH}=\text{O}$	$\text{FCH}=\text{O}$
$r_{\text{C}=\text{O}}$	1.209	1.214	1.219	1.219	1.186
$r_{\text{C}=\text{OH}^+}$	$\text{CH}_2=\text{O}^+\text{H}$ 1.252	$\text{CH}_3\text{CH}=\text{O}^+\text{H}$ 1.270	$(\text{CH}_3)_2\text{C}=\text{O}^+\text{H}$ 1.282	$\text{H}_2\text{NCH}=\text{O}^+\text{H}$ 1.294	$\text{FCH}=\text{O}^+\text{H}$ 1.252
PA in kcal/mol	168.9	184.4	195.7	198.0	156.2

The effect of Lewis acids has also been examined computationally. In agreement with crystal structure determinations,⁶ Lewis acids such as BF_3 normally adopt an *anti* structure for aldehydes. Despite the unfavorable steric effect in acetone, the calculated (MP2/6-31G) energy of complexation with BF_3 is nearly as high as for acetaldehyde, presumably owing to the additional electron donation by the methyl groups.⁷



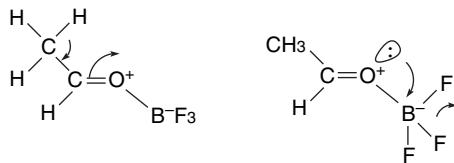
ΔE **-11.9** **-13.0** **-10.3**

⁵. A. K. Chandra, M. T. Nguyen, and T. Zeegers-Huyskens, *Chem. Phys.*, **255**, 149 (2000).

⁶. M. T. Reetz, M. Hullmann, W. Massa, S. Berger, P. Rademacher, and P. Heymanns, *J. Am. Chem. Soc.*, **108**, 2405 (1986).

⁷. B. W. Gung and M. A. Wolf, *J. Org. Chem.*, **57**, 1370 (1992).

It is believed that two significant hyperconjugative effects result from complexation with a Lewis acid. The donor effect of alkyl substituents is enhanced by the greater electrophilicity of the carbonyl oxygen. There is also believed to be an interaction of the remaining unshared oxygen electrons with the σ^* orbital of the B–F bond. The interaction lowers the energy of both the π and π^* orbitals and enhances the reactivity toward nucleophiles, as indicated in Figure 7.2.⁸



Several factors, then, are important in assessing relative reactivity of carbonyl compounds. Electronegative substituents enhance reactivity by a polar effect, but if they are also π donors, there is a resonance effect in the opposite direction. Alkyl and aryl substituents decrease reactivity relative to hydrogen by a combination of steric and electronic effects. Protonation or complexation with a Lewis acid at the carbonyl oxygen enhances reactivity.

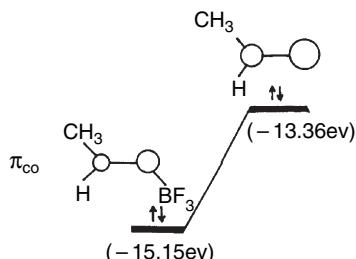
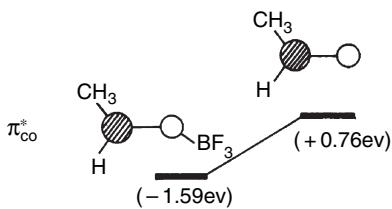


Fig. 7.2. Effect of BF_3 complexation of HOMO and LUMO in acetaldehyde. From MNDO calculations, *J. Am. Chem. Soc.*, **108**, 2405 (1986).

⁸. K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, **95**, 4094 (1973).

7.2. Hydration and Addition of Alcohols to Aldehydes and Ketones

The reactivity of carbonyl compounds toward hydration parallels the order indicated in Section 7.1. For most carbonyl compounds, the equilibrium constant for addition of water to the carbonyl group is unfavorable.



Formaldehyde is an exception and is nearly completely hydrated in aqueous solution. Unhindered aliphatic aldehydes are approximately 50% hydrated in water. Aryl groups disfavor hydration by conjugative stabilization of the carbonyl group. Ketones are much less extensively hydrated than aldehydes. Aldehydes and ketones with highly electronegative substituents such as trichloroacetaldehyde and hexafluoroacetone are extensively hydrated. α -Dicarbonyl compounds, such as biacetyl and ethyl pyruvate, are also significantly hydrated. Table 7.4 gives the K_{hydr} for a number of carbonyl compounds. Data on other compounds are available in Table 3.23.

Although the equilibrium constant for hydration is usually unfavorable, the equilibrium between an aldehyde or ketone and its hydrate is established rapidly and can be detected by isotopic exchange, using water labeled with ^{17}O , for example.⁹ For

Table 7.4. Equilibrium Constants for Hydration of Carbonyl Compounds

Carbonyl compound	K (in water, 25°C) ^a
CH_2O	2.28×10^3 ^b
CH_3CHO	1.06 ^b
$\text{CH}_3\text{CH}_2\text{CHO}$	0.85 ^b
$(\text{CH}_3)_2\text{CHCHO}$	0.61 ^b
$(\text{CH}_3)_3\text{CCCHO}$	0.23 ^b
CF_3CHO	2.9×10^4 ^b
$\text{C}_6\text{H}_5\text{CHO}$	8×10^{-3} ^c
CH_3COCH_3	1.4×10^{-3} ^b
$\text{FCH}_2\text{COCH}_3$	0.11 ^c
$\text{ClCH}_2\text{COCH}_3$	0.11 ^b
CF_3COCH_3	35 ^b
CF_3COCF_3	1.2×10^6 ^b
$\text{C}_6\text{H}_5\text{COCH}_3$	9.3×10^{-6} ^c
$\text{C}_6\text{H}_5\text{COCF}_3$	78 ^b
$\text{CH}_3\text{COCOCH}_3$	0.6 ^d
$\text{CH}_3\text{COCO}_2\text{CH}_3$	0.8 ^d

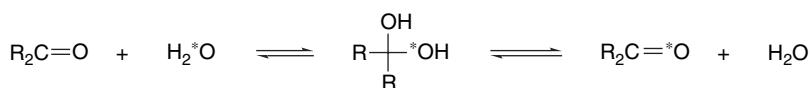
a. $K = [\text{hydrate}]/[\text{carbonyl}] = K_{\text{eq}}[\text{H}_2\text{O}] = 55.5 K_{\text{eq}}$

b. J. P. Guthrie, *Can. J. Chem.*, **53**, 898 (1975).

c. J. P. Guthrie, *Can. J. Chem.*, **56**, 962 (1978).

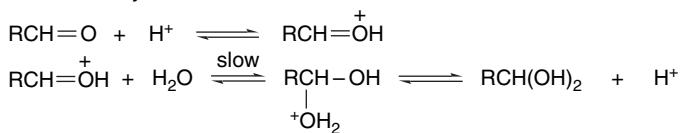
d. T. J. Burkey and R. C. Fahey, *J. Am. Chem. Soc.*, **105**, 868 (1983).

⁹. P. Greenzaid, Z. Luz, and D. Samuel, *Trans. Faraday Soc.*, **64**, 2780, 2787 (1968).

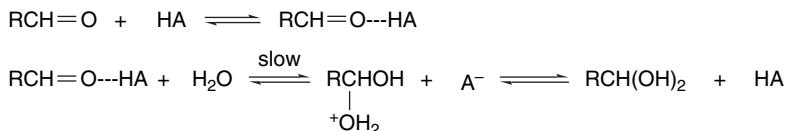


acetaldehyde, the half-life of the exchange reaction is on the order of 1 min under neutral conditions, but is considerably faster in acidic or basic solution. The second-order rate constant for acid-catalyzed hydration of acetaldehyde is about $500 \text{ M}^{-1}\text{s}^{-1}$.¹⁰

Specific acid-catalyzed mechanism

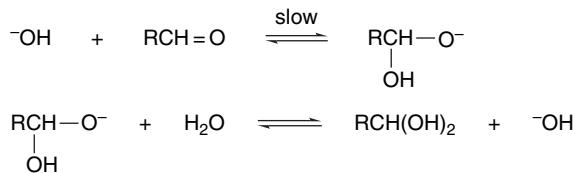


General acid-catalyzed hydration

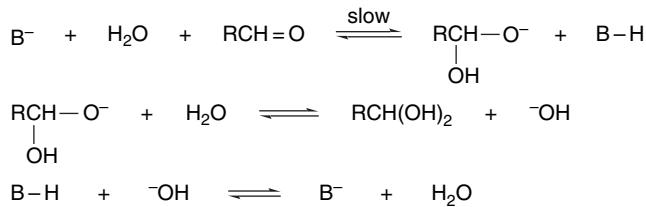


Hydroxide ion addition results in specific base-catalyzed hydration. General base catalysts function by deprotonating water to give the more nucleophilic hydroxide ion.

Specific base-catalyzed hydration



General base-catalyzed hydration

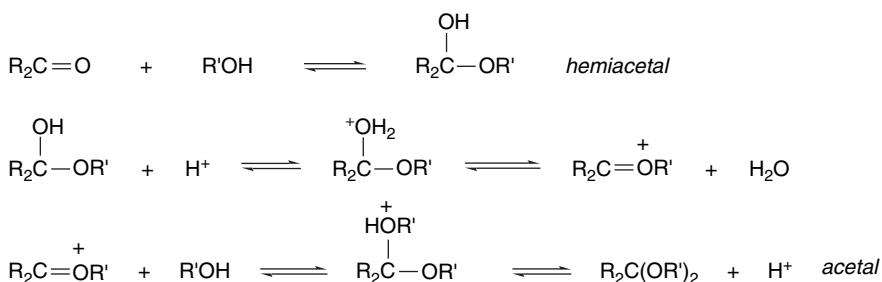


¹⁰ P. Greenzaid, Z. Luz, and D. Samuel, *J. Am. Chem. Soc.*, **89**, 756 (1967).

¹¹ R. P. Bell, *Adv. Phys. Org. Chem.*, **4**, 1 (1966); W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).

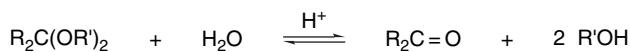
¹² L. H. Funderburk, L. Aldwin, and W. P. Jencks, *J. Am. Chem. Soc.*, **100**, 5444 (1978); R. A. McClelland and M. Coe, *J. Am. Chem. Soc.*, **105**, 2718 (1983).

Aldehydes and ketones undergo reversible addition reactions with alcohols. The product of addition of one molecule of alcohol to an aldehyde or ketone is referred to as a *hemiacetal*. Dehydration followed by addition of a second molecule of alcohol gives an *acetal*.¹³ This second phase of the process can be catalyzed only by acids because a necessary step is elimination of hydroxide (as water) from the tetrahedral intermediate. There is no low-energy mechanism for base assistance of this elimination step, so acetals are stable toward hydrolysis in alkaline aqueous solution but are hydrolyzed rapidly in acidic solution.



The equilibrium constants for addition of alcohols to carbonyl compounds to give hemiacetals show the same response to structural features as the hydration reaction. Equilibrium constants for addition of methanol to acetaldehyde in both water and chloroform solution are near $0.8 M^{-1}$. The structural effects of the alcohol group have been examined.¹⁴ Steric effects result in an order of $\text{CH}_3 \sim \text{C}_2\text{H}_5 > (\text{CH}_3)_2\text{CH} > (\text{CH}_3)_3\text{C}$ for acetaldehyde hemiacetals. EWG substituents in the alcohol disfavor hemiacetal formation and this trend is believed to reflect the decreasing $n \rightarrow \sigma^*$ hyperconjugation (anomeric effect, see Topic 1.2) as the substituents become more electron withdrawing.

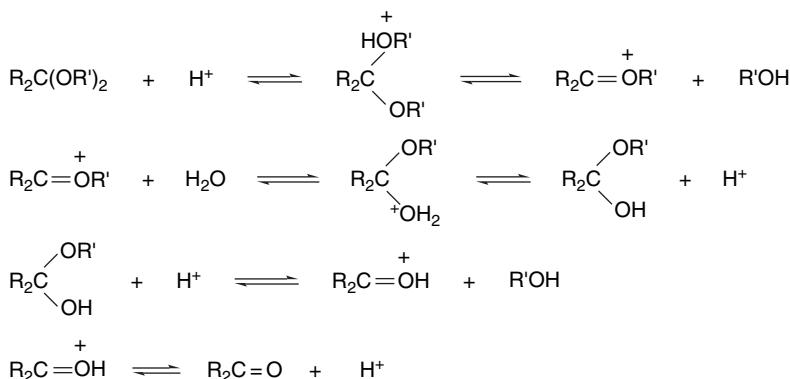
The overall equilibrium constant for formation of the dimethyl acetal of acetaldehyde is $1.58 M^{-1}$. The comparable value for the addition of water is about $0.02 M^{-1}$.¹⁵ Because the position of the equilibrium does not strongly favor product, the synthesis of acetals is carried out in such a way as to drive the reaction to completion. One approach is to use a dehydrating reagent or azeotropic distillation so that the water that is formed is irreversibly removed from the system. Because of the unfavorable equilibrium constant and the relative facility of the hydrolysis, acetals are rapidly converted back to aldehydes and ketones in acidic aqueous solution. The facile hydrolysis makes acetals useful carbonyl protecting groups (see Part B, Section 3.5.3).



¹³ Sometimes these derivatives of ketones are called hemiketals and ketals, respectively.

¹⁴ Y.-H. Fan and J. Haseltine, *Tetrahedron Lett.*, **37**, 9279 (1996).

¹⁵ R. Bone, P. Cullis, and R. Wolfenden, *J. Am. Chem. Soc.*, **105**, 1339 (1983).



Some of the evidence that has helped to establish the general mechanism is as follows:

1. Isotopic-labeling experiments have established that C–O bond rupture occurs between the carbonyl carbon and oxygen; substitution at the alcohol C–O bond is not involved.
2. For most acetals, the reaction is *specific acid catalyzed*, which is consistent with the existence of a preequilibrium in which the acetal is protonated. The proton assists the departure of the alkoxy group by converting it to a better leaving group. In essence, this cleavage step is an S_N1 reaction with the remaining alkoxy group stabilizing the carbocation formed by ionization.
3. Hammett treatments show good correlations with large negative ρ values for the hydrolysis of acetals of aromatic aldehydes, which is consistent with the development of a positive charge at the carbonyl center in the rate-determining step.
4. Solvent isotope effects are usually in the range $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}} = 2\text{--}3$. These values reflect the greater equilibrium acidity of deuterated acids (see Section 3.7.1.1) and indicate that the initial protonation is a fast preequilibrium.

Acetal hydrolyses usually exhibit specific acid catalysis, in agreement with a mechanism involving rate-determining cleavage of the conjugate acid of the reactant. However, general acid catalysis is observed in certain acetals and ketals in which special structural features reduce the energy required for C–O bond cleavage.¹⁷ Thus, hydrolysis of each of the acetals shown in Scheme 7.1 exhibits general acid catalysis, and each acetal has a structural feature that facilitates C–O bond heterolysis. Reducing the energy requirement for C–O bond cleavage permits the proton transfer step to become partially rate determining and results in the observation of general acid catalysis.

¹⁶ E. H. Cordes and H. G. Bull, *Chem. Rev.*, **74**, 581 (1974).

¹⁷ T. H. Fife, *Acc. Chem. Res.*, **5**, 264 (1972).

Scheme 7.1. Acetals that Exhibit General Acid Catalysis in Hydrolysis

	Acetal	Structural feature promoting hydrolysis
1 ^a		Very stable oxonium ion intermediate; stabilized by aromaticity.
2 ^b		Resonance-stabilized phenolic leaving group.
3 ^c		Especially acidic alcohol is good leaving group.
4 ^d		Ring strain is relieved in bond-breaking step
5 ^e	$(Ar)_2C(OC_2H_5)_2$	Aryl substituents stabilize oxonium ion.
6 ^f	$PhCH[OC(CH_3)_3]_2$	Aryl stabilization of oxonium ion and relief of steric strain.

- a. E. Anderson and T. H. Fife, *J. Am. Chem. Soc.*, **91**, 7163 (1969).
 b. T. H. Fife and L. H. Brod, *J. Am. Chem. Soc.*, **92**, 1681 (1970).
 c. J. L. Jensen and W. B. Wuhrman, *J. Org. Chem.*, **48**, 4686 (1983).
 d. R. F. Atkinson and T. C. Bruice, *J. Am. Chem. Soc.*, **96**, 819 (1974).
 e. R. H. DeWolfe, K. M. Ivanetich, and N. F. Perry, *J. Org. Chem.*, **34**, 848 (1969).
 f. E. Anderson and T. H. Fife, *J. Am. Chem. Soc.*, **93**, 1701 (1971).

Two-dimensional potential energy diagrams can be used to evaluate structural effects on the reactivity of carbonyl compounds and the tetrahedral intermediates. These reactions involve the formation or breaking of two separate bonds. This is the case in the first stage of acetal hydrolysis, which involves both a proton transfer and breaking of a C–O bond. The overall reaction might take place in several ways, but there are two stepwise mechanistic extremes.

1. The proton can be completely transferred and then the departing alcohol molecule can leave to form a carbocation in a distinct second step. This is the specific acid-catalyzed mechanism.
2. The acetal can undergo ionization with formation of an alkoxide ion and a carbocation. The alkoxide is protonated in a second step. This mechanism is very unlikely, because an alkoxide ion is a poor leaving group.
3. An alternative mechanism involves general acid catalysis, in which the proton transfer and the C–O bond rupture occur as a *concerted process*. The concerted process need not be perfectly synchronous; that is, proton transfer might be

more complete at the TS than C–O rupture, or vice-versa. These ideas are represented in the two-dimensional energy diagram in Figure 7.3.

The two paths around the edge of the diagram represent the stepwise processes described as the mechanistic extremes 1 and 2. We know that Process 2 represented by path (a) is a high-energy process so the upper-left corner of the diagram would have a very high energy. The lines designated (b) and (c) indicate concerted but nonsynchronous mechanisms in which there is both partial proton transfer and partial C–O bond rupture at the transition state. In path (b) C–O cleavage is more complete than proton transfer at the transition state, whereas the reverse is true for path (c). Both these paths represent concerted, general acid-catalyzed processes. Path (d) represents the specific acid-catalyzed process in which proton transfer precedes C–O cleavage.

If it is possible to estimate or calculate the energy of the reacting system at various stages, the energy dimension can be added as in Figure 7.4 and can be shown as contours. The actual mechanism is the process that proceeds over the lowest energy barrier. The diagram in Figure 7.4 shows the initial ionization to an alkoxide and carbocation as very high in energy. The stepwise path of protonation followed by ionization is shown with smaller barriers with the protonated ketal as an intermediate. The lowest energy path is shown as a concerted process represented by the dashed line. The TS, which lies at the highest energy point on this line, would exhibit more complete proton transfer than C–O cleavage.

Structural and substituent effects can be discussed by considering how they affect the position of the TS on the potential energy surface. The stepwise path via the protonated acetal is preferred in the case of alcohols that are poor leaving groups. If the alcohol is more acidic, its conjugate base is a better leaving group and the TS shifts to a point where C–O bond breaking begins before proton transfer is complete. This means that the mechanism is concerted, although the TS still has much of the character of a carbocation. Two-dimensional reaction energy diagrams can be used to describe how structural changes affect the nature of the TS. Just as potential energy diagrams give

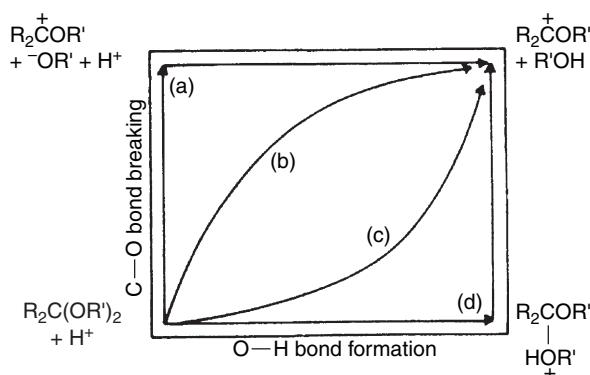


Fig. 7.3. Representation of mechanism for the first stage of acetal hydrolysis: (a) stepwise mechanism with initial C–O bond breaking; (b) concerted mechanism with C–O bond breaking leading O–H bond formation; (c) concerted mechanism with proton transfer leading C–O bond breaking; and (d) stepwise mechanism with initial proton transfer.

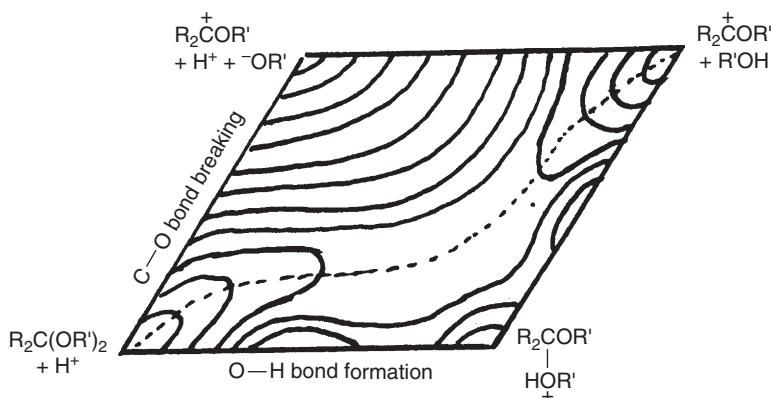
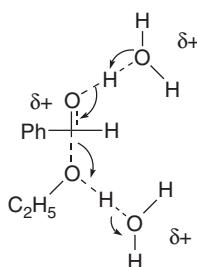


Fig. 7.4. Contour plot showing a favored concerted mechanism for the first step in acetal hydrolysis, with proton transfer more advanced at the transition state than C–O bond breaking.

meaning to such phrases as an “early” or a “late” TS, the two-dimensional diagrams are illustrative of statements such as “C–O cleavage is more advanced than proton transfer.”

Consideration of the types of acetals shown in Scheme 7.1, which exhibit general acid catalysis, indicates why the concerted mechanism operates in these molecules. The developing aromatic character of the cation formed in the case of Entry 1 lowers the energy requirement for C–O bond rupture. The bond can begin to break before protonation is complete. Entries 2 and 3 are cases where a better leaving group reduces the energy requirement for C–O bond cleavage. In Entry 4, the four-membered ring is broken in the reaction. Cleavage in this case is facilitated by release of strain energy. Entries 5 and 6 are similar to Entry 1 because the aryl groups provide stabilization for developing cationic character.

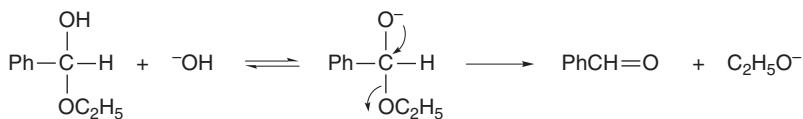
The second step in acetal hydrolysis is conversion of the hemiacetal to the carbonyl compound. The mechanism of this step is similar to that of the first step. Usually the second step is faster than the initial one.¹⁸ Hammett $\sigma-\rho$ plots and solvent isotope effects both indicate that the TS has less cationic character than is the case for the first step. These features of the mechanism suggest that a concerted removal of the proton at the hydroxy group occurs as the alcohol is eliminated.



¹⁸. Y. Chiang and A. J. Kresge, *J. Org. Chem.*, **50**, 5038 (1985); R. A. McClelland, K. M. Engell, T. S. Larsen, and P. O. Sorensen, *J. Chem. Soc., Perkin Trans. 2*, 2199 (1994).

The positive charge is dispersed over several atoms and this diminishes the sensitivity of the reaction to substituent effects. The ρ values that are observed are consistent with this interpretation. Whereas ρ is -3.25 for hydrolysis of aryl acetals, it is only -1.9 for hemiacetal hydrolysis.¹⁹

In contrast to acetals, which are base stable, hemiacetals undergo base-catalyzed hydrolysis. In the alkaline pH range the mechanism shifts toward a base-catalyzed elimination.



There are two opposing substituent effects on this reaction. Electron-attracting aryl substituents favor the deprotonation but disfavor the elimination step. The observed substituent effects are small, and under some conditions the Hammett plots are nonlinear.²⁰

7.3. Condensation Reactions of Aldehydes and Ketones with Nitrogen Nucleophiles

The mechanistic pattern of hydration and alcohol addition reactions of ketones and aldehydes is followed in reactions of carbonyl compounds with amines and related nitrogen nucleophiles. These reactions involve addition and elimination steps proceeding through tetrahedral intermediates. These steps can be either acid catalyzed or base catalyzed. The rates of the reactions are determined by the energy and reactivity of the tetrahedral intermediates. With primary amines, C=N bond formation ultimately occurs. These reactions are reversible and the position of the overall equilibrium depends on the nitrogen substituents and the structure of the carbonyl compound.



Scheme 7.2 lists some familiar types of such reactions. In general, these reactions are reversible and mechanistic information can be obtained by study of either the forward or the reverse process.

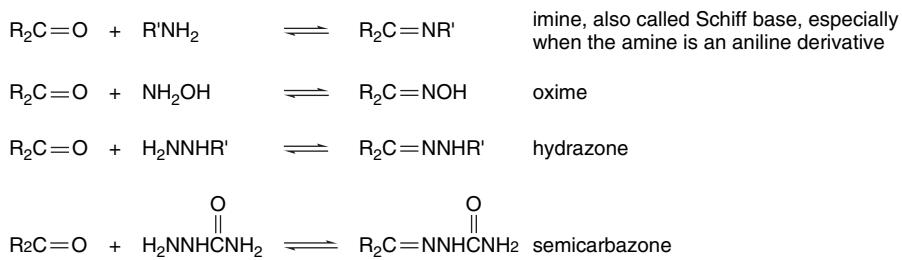
¹⁹. T. J. Przystas and T. H. Fife, *J. Am. Chem. Soc.*, **103**, 4884 (1981).

²⁰. R. L. Finley, D. G. Kubler, and R. A. McClelland, *J. Org. Chem.*, **45**, 644 (1980).

Scheme 7.2. Addition-Elimination Reactions of Aldehydes and Ketones

CHAPTER 7

Addition, Condensation
and Substitution
Reactions of Carbonyl
Compounds



For simple alkyl amines, the K for imine formation in aqueous solution is defined as

$$K = \frac{[\text{imine}][\text{H}_2\text{O}]}{[\text{aldehyde}][\text{amine}]}$$

The value of K has been measured for several amines with 2-methylpropanal.²¹ The effect of the structure of the alkyl group is quite small, although the trifluoroethyl group significantly reduces imine stability.

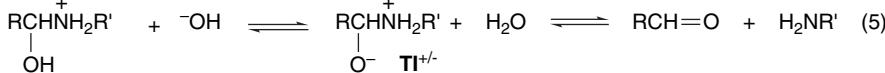
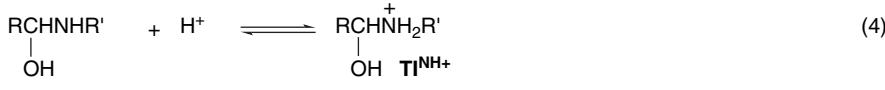
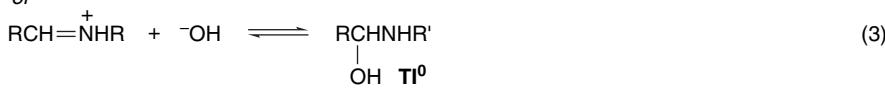
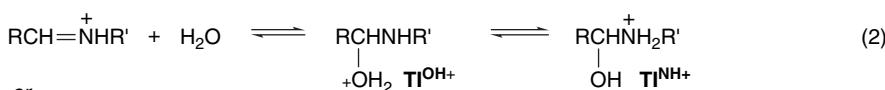
**Equilibrium Constants for Imines
Formation with 2-Methylpropanal**

Amine	K
CH_3NH_2	4.98×10^3
$\text{CH}_3\text{CH}_2\text{NH}_2$	3.49×10^3
$\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2$	4.18×10^3
$(\text{CH}_3)_2\text{CHNH}_2$	1.84×10^3
PhCH_2NH_2	2.50×10^3
$\text{CF}_3\text{CH}_2\text{NH}_2$	2.38×10^2
$\text{CH}_3\text{OCH}_2\text{CH}_2\text{NH}_2$	2.06×10^3

The hydrolysis of simple imines occurs readily in aqueous acid, and has been studied in detail by kinetic methods. The precise mechanism is a function of the reactant structure and the pH of the solution. The overall mechanism consists of an addition of water to the $\text{C}=\text{N}$ bond, followed by expulsion of the amine from a tetrahedral intermediate.²² There are at least four variants of the tetrahedral intermediate that differ in the extent and site of protonation. In the general mechanism below, the neutral intermediate is labeled TI^0 and the zwitterionic form is labeled $\text{TI}^{+/-}$. There are two possible monoprotonated forms, one protonated on oxygen ($\text{TI}^{\text{OH}+}$) and one protonated on nitrogen ($\text{TI}^{\text{NH}+}$).

²¹. J. Hine and C. Y. Yeh, *J. Am. Chem. Soc.*, **89**, 2669 (1967); J. Hine, C. Y. Yeh, and F. C. Schmalstieg, *J. Org. Chem.*, **35**, 340 (1970).

²². (a) J. Hine, J. C. Craig, Jr., J. G. Underwood, II, and F. A. Via, *J. Am. Chem. Soc.*, **92**, 5194 (1970); (b) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **85**, 2843 (1963).



The rates of the various steps are a function of the pH of the solution, the basicity of the imine, and the reactivity of the aldehyde. Imine protonation enhances reactivity toward either water or hydroxide ion as nucleophiles. *N*-Protonation in the tetrahedral intermediate makes the amine a better leaving group. The zwitterionic intermediate $\text{Ti}^{+/-}$ is more reactive toward elimination of the amine than $\text{Ti}^{\text{NH}+}$ because of the assistance of the anionic oxygen. In the alkaline range, the rate-determining step is usually nucleophilic attack by hydroxide ion on the protonated C=N bond (Step 3). At intermediate pH values, water replaces hydroxide as the dominant nucleophile (Step 2). In acidic solution, the rate-determining step is the breakdown of the tetrahedral intermediate (Step 5). A mechanism of this sort, in which the observed rate is sensitive to pH, can be usefully studied by constructing a pH-rate profile, which is a plot of the observed rate constants versus pH. (See Section 3.7.1.4 to review pH-rate profiles.) Figure 7.5 is an example of the pH-rate profile for hydrolysis of a series of imines derived from substituted aromatic aldehydes and *t*-butylamine. The form of pH-rate profiles can be predicted on the basis of the detailed mechanism of the reaction. The value of the observed rates can be calculated as a function of pH if a sufficient number of the individual rate constants and the acid dissociation constants of the participating species are known. Agreement between the calculated and observed pH-rate profiles serves as a sensitive test of the adequacy of the postulated mechanism. Alternatively, one may begin with the experimental pH-rate profile and deduce details of the mechanism from it.

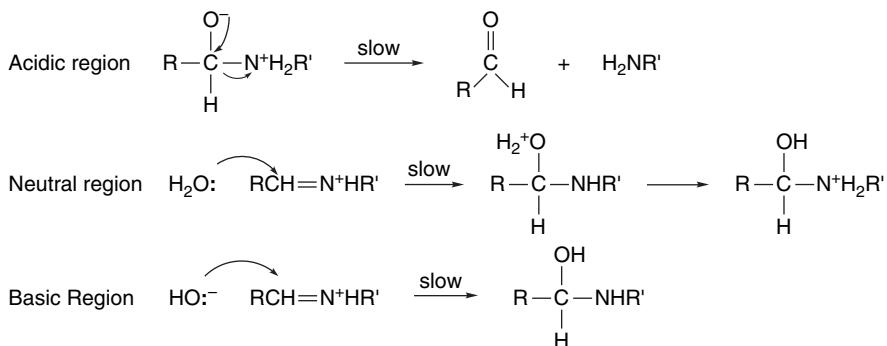
Complete understanding of the shape of the curves in Figure 7.5 requires a kinetic expression somewhat more complicated than we wish to deal with here. However, the nature of the extremities of the curve can be understood on the basis of qualitative arguments. The rate decreases with pH in the acidic region because formation of the zwitterionic tetrahedral intermediate $\text{Ti}^{+/-}$ is required for expulsion of the amine (Step 5). The concentration of the zwitterionic species decreases with increasing acidity, since its concentration is governed by an acid-base equilibrium.

$$K = \frac{[\text{H}^+][\text{Ti}^{+/-}]}{[\text{Ti}^{\text{NH}+}]}$$

Note also that in the acidic region, EWG substituents accelerate the reaction, owing to a more favorable equilibrium for the hydration step. In the alkaline region, the rate is pH independent. In this region, the rate-controlling step is attack of the

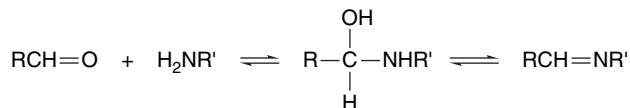
hydroxide ion on the protonated imine (Step 3). The concentration of both of these species is pH dependent, but in opposite, compensating, ways. The overall rate is therefore pH independent in the alkaline range. (Work problem 7.26 to establish that this is so.) Note that in this region the substituent effect is considerably smaller and is in the opposite sense from the acidic portion of the profile. This is due to the enhanced basicity of the ERG-substituted imines. At any given pH, more of the protonated imine is present for the ERG substituents.

The pH-rate profile for the hydrolysis of the *N*-methylimine of 2-methylpropanal is shown in Figure 7.6. The curve is similar to that for aromatic ketones with EWG substituents. The rate increases in the pH range 0–4.5, where decomposition of the zwitterionic intermediate is rate controlling. In the pH range 4.5–8, the rate decreases and then levels off. This corresponds to the transformation of the protonated imine to the less reactive neutral form. Above pH 8, the rate is again constant, as the increase in $[\text{OH}]$ is compensated by the decrease in the amount of protonated imine.



G2 computations have been used to model the formation of the imine between methylamine and formaldehyde and to study the effect of water on the process.²³ The computations lead to the TS structures and energy profiles shown in Figure 7.7. The results point to the importance of the proton transfer steps in the overall energy requirement of the reaction. The inclusion of one or two water molecules leads to cyclic TS for proton transfer. This corresponds to concerted addition and elimination of water through six- and eight-membered cyclic hydrogen-bonded structures. The addition of water molecules substantially lowers the energy of the TS for each step of the reaction, while having relatively modest effects on the energy of the products. This is because the TSs involve considerably more charge separation than the products.

The formation of imines takes place by a mechanism that is the reverse of hydrolysis. Preparative procedures often ensure completion of the reaction by removing water by azeotropic distillation or by the use of an irreversible dehydrating agent.



The other C=N systems included in Scheme 7.2 are more stable to aqueous hydrolysis than the imines. The equilibrium constants for oxime formation are high, even in

²³ N. E. Hall and B. I. Smith, *J. Phys. Chem. A*, **102**, 4930 (1998).

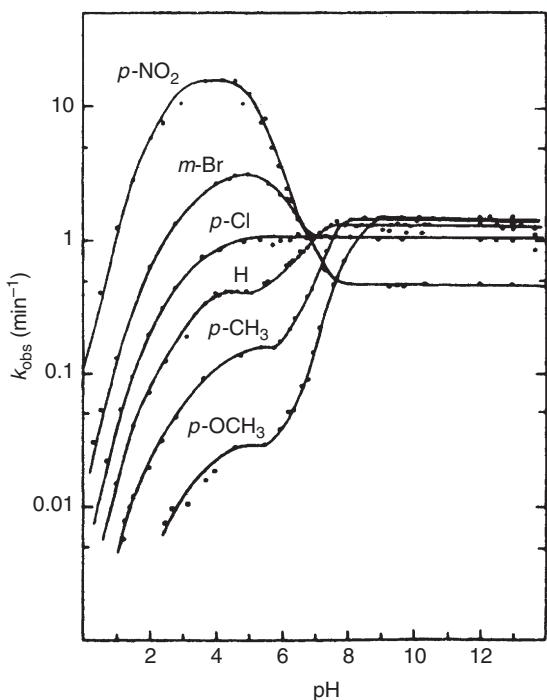


Fig. 7.5. pH-Rate profile for the hydrolysis of substituted benzylidene-1,1-dimethylethylamines. Reproduced from *J. Am. Chem. Soc.*, **85**, 2843 (1963), by permission of the American Chemical Society.

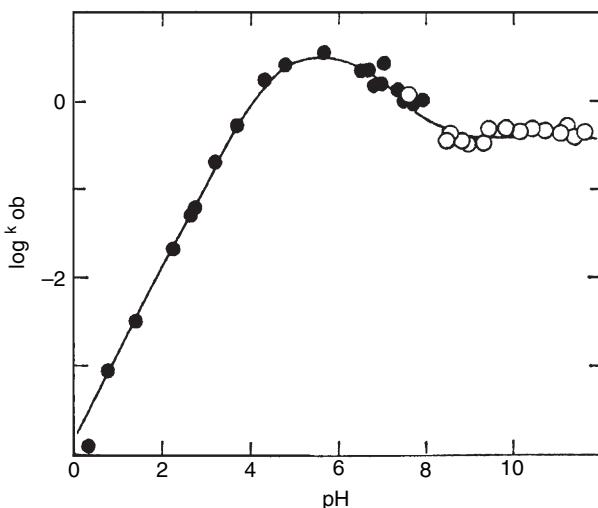


Fig. 7.6. pH-Rate profile for hydrolysis of *N*-methyl-2-methylpropanimine in water at 35°C. Solid points are from the hydrolysis reaction and open points are from the formation of the imine. Reproduced from *J. Am. Chem. Soc.*, **92**, 5194 (1970), by permission of the American Chemical Society.

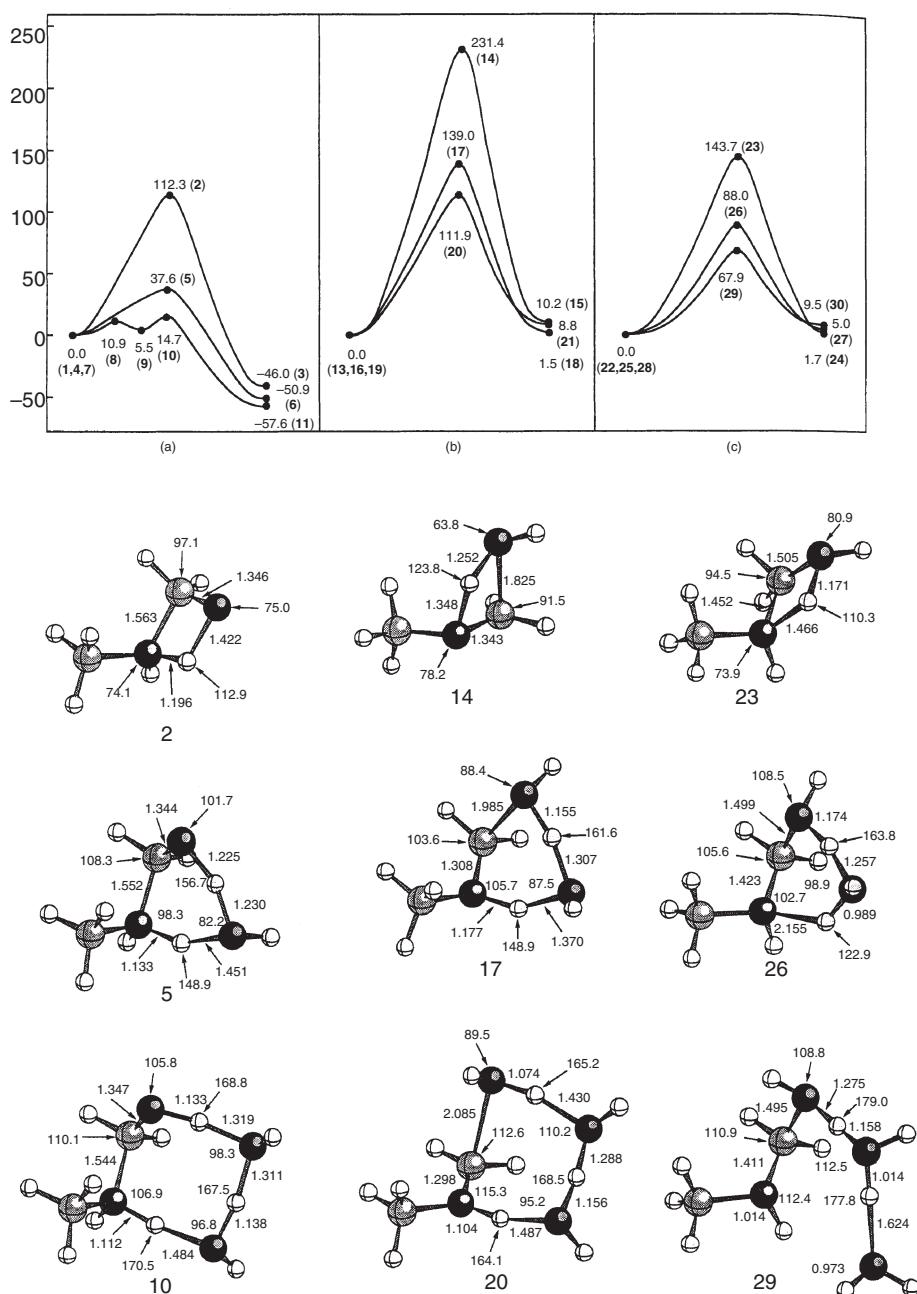


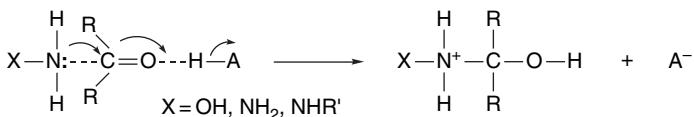
Fig. 7.7. Upper panel: Energy profiles in kJ/mol from G2 computations for: (a) carbinolamine formation, (b) imine formation, and (c) iminium ion formation with zero, one, and two water molecules. Lower panel: Transition structures for carbinolamine, imine, and iminium ion formation with zero, one, and two water molecules and showing selected bond lengths and angles. Reproduced from *J. Phys. Chem. A*, **102**, 4930 (1998), by permission of the American Chemical Society.

aqueous solution. For example, the values for acetone ($4.7 \times 10^5 M^{-1}$), 3-pentanone ($7.7 \times 10^4 M^{-1}$), and cyclopentanone ($4.0 \times 10^5 M^{-1}$) have been measured.²⁴ Traditionally, the additional stability was attributed to the participation of the atom adjacent to the nitrogen in delocalized bonding.

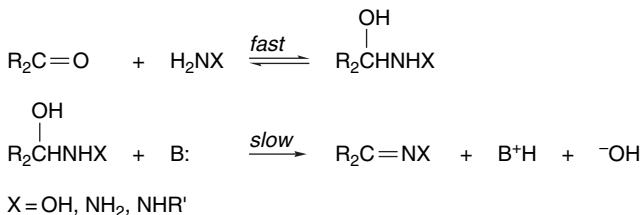


However, analysis based on HF/6-31G* computations suggests that reduction of the lone pair repulsions that are present in hydroxylamine and hydrazine reactants may be more important.²⁵

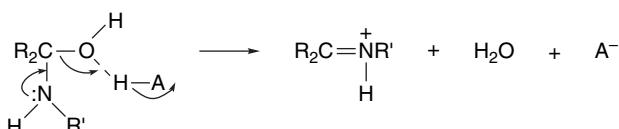
The formation of oximes and hydrazones is usually catalyzed by both general acids and general bases. The acid-catalyzed addition step can be depicted as concerted proton transfer and nucleophilic addition.²⁶



General base catalysis of dehydration of the tetrahedral intermediate involves nitrogen deprotonation concerted with elimination of hydroxide ion.²⁷



General acid catalysis of the breakdown of the carbinolamine intermediate occurs by assistance of the expulsion of water.



As with imines, the identity of the rate-limiting step changes with solution pH. As the pH decreases, the rate of addition decreases because protonation of the amino compound reduces the concentration of the nucleophilic unprotonated form. Thus, while the dehydration step is normally rate determining in neutral and basic solutions, addition becomes rate determining in acidic solutions. Figure 7.8 shows the pH-rate profiles for oximation of benzaldehyde and acetone. The acetone profile shows a region from pH 8 to 10 that is pH independent and corresponds to catalysis by water. The profile for benzaldehyde shows only a very slight contribution from a pH-independent reaction.

²⁴ J. Hine, J. P. Zeigler, and M. Johnston, *J. Org. Chem.*, **44**, 3540 (1979).

²⁵ K. B. Wiberg and R. Glaser, *J. Am. Chem. Soc.*, **114**, 841 (1992).

²⁶ C. G. Swain and J. C. Worosz, *Tetrahedron Lett.*, 3199 (1965).

²⁷ W. P. Jencks, *Prog. Phys. Org. Chem.*, **2**, 63 (1964); J. M. Sayer, M. Peskin, and W. P. Jencks, *J. Am. Chem. Soc.*, **95**, 4277 (1973).

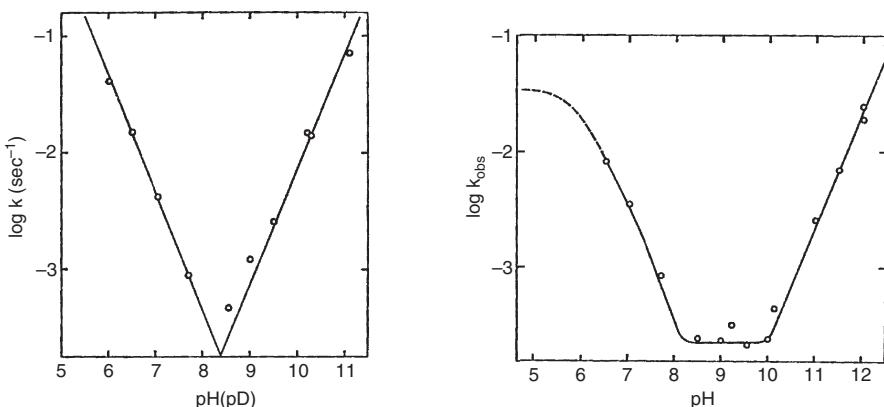


Fig. 7.8. pH-*Rate* profiles for formation of oximes of benzaldehyde (left) and acetone (right). The solid lines are the theoretical lines of slope -1 , 0 , and $+1$. Reproduced from *J. Am. Chem. Soc.*, **88**, 2508 (1966), by permission of the American Chemical Society.

The ρ values for both the addition and elimination steps in oxime formation of aromatic aldehydes have been determined.²⁸ For addition, ρ is $+1.21$ (and the best correlation is with σ^+). This is due to the decreased reactivity of aldehydes having direct conjugation with donor substituents. For the dehydration step, ρ is -0.85 , which is the result of stabilization of the developing C=N bond by conjugation with donor substituents.

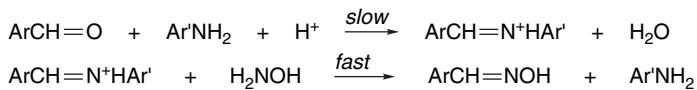
The mechanism of semicarbazone formation is similar to that for oximes.²⁹ The rate-limiting step at neutral pH is acid-catalyzed dehydration of the tetrahedral intermediate. Comparison of the semicarbazone and oxime formation reactions with those for imines has shown that there are differences in the details, such as the pH ranges associated with the different steps. The less basic amines, including aromatic amines and semicarbazide, undergo the addition step through concerted general acid catalysis. That is, the activation of the carbonyl group by simultaneous interaction with a proton donor is important.³⁰ For the more nucleophilic primary amines and hydroxylamine, the proton transfer associated with the addition step can be accomplished by the solvent, without an external proton source. Note that this relationship between amine nucleophilicity and the nature of proton transfer are consistent with the broad concepts indicated in Figure 7.1.

Certain reactions between carbonyl compounds and nucleophiles are catalyzed by amines. Some of these reactions are of importance for forming carbon-carbon bonds and these are discussed in Section 2.2.3 of Part B. The mechanistic principle can be illustrated by considering the catalysis of the reaction between ketones and hydroxylamine by aniline derivatives.³¹



- ²⁸. M. Calzadilla, A. Malpica, and T. Cordova, *J. Phys. Org. Chem.*, **12**, 708 (1999).
²⁹. W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959); B. M. Anderson and W. P. Jencks, *J. Am. Chem. Soc.*, **82**, 1773 (1960).
³⁰. R. B. Martin, *J. Phys. Chem.*, **68**, 1369 (1964).
³¹. E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 826 (1962); J. Hine, R. C. Dempsey, R. A. Evangelista, E. T. Jarvi, and J. M. Wilson, *J. Org. Chem.*, **42**, 1593 (1977).

Analysis of the kinetics of this catalysis points to the protonated imine as the key reactant.

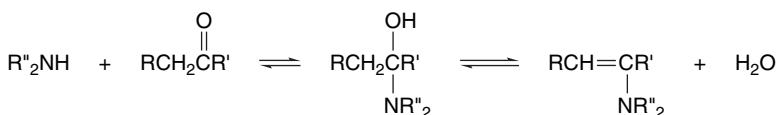


Because the imine nitrogen is much more basic than the carbonyl oxygen, it is more extensively protonated than the aldehyde at any given pH. The protonated imine is also more reactive as an electrophile than the neutral aldehyde. There are four possible electrophiles in the system.

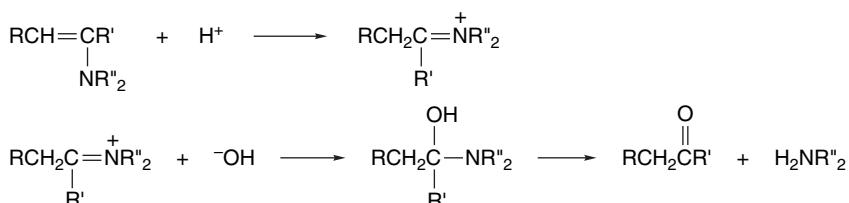


The protonated imine is the dominant reactive form. Although the protonated aldehyde is more reactive, its concentration is very low, because it is much less basic than the imine or the reactant hydroxylamine. On the other hand, even though the aldehyde may be present in a greater concentration than the protonated imine, its reactivity is sufficiently less that the iminium ion is the major reactant.

Secondary amines cannot form imines, and dehydration proceeds to give a carbon–carbon double bond bearing an amino substituent (enamine). Enamines were mentioned in Chapter 6 as examples of nucleophilic carbon species, and their synthetic utility is discussed in Section 1.3 of Part B. The equilibrium for the reaction between secondary amines and carbonyl compounds ordinarily lies to the left in aqueous solution, but the reaction can be driven forward by dehydration methods.



The mechanism of hydrolysis of enamines has been studied kinetically over a range of pH. In alkaline solution, rate-determining C-protonation is followed by attack of hydroxide ion on the resulting iminium ion. The carbinolamine intermediate then breaks down as in imine hydrolysis. In the neutral and weakly acidic pH range, water attack on the C-protonated enamine becomes rate limiting. As in imine hydrolysis, decomposition of the tetrahedral intermediate becomes rate limiting in strongly acidic solutions.³²



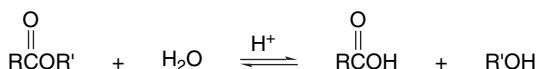
³² P. Y. Sollenberger and R. B. Martin, *J. Am. Chem. Soc.*, **92**, 4261 (1970); W. Maas, M. J. Janssen, E. J. Stamhuis, and H. Wynberg, *J. Org. Chem.*, **32**, 1111 (1967); E. J. Stamhuis and W. Maas, *J. Org. Chem.*, **30**, 2156 (1965).

7.4. Substitution Reactions of Carboxylic Acid Derivatives

Substitution reactions of carboxylic acid derivatives are among the most fundamental reactions in organic chemistry. The most common derivatives include acyl halides, anhydrides, esters, and carboxamides. Both synthesis and hydrolysis of esters and amides are examples of these substitution reactions. Most of these substitution reactions involve the formation and breakdown of a tetrahedral intermediate. The structural features of the carboxylic acid derivatives and related tetrahedral intermediates are discussed in Section 3.4.4. The fundamental difference in the chemistry of the carboxylic acid derivatives, as compared to ketones and aldehydes, is the presence of a potential leaving group at the carbonyl carbon. The order of reactivity as leaving groups is $\text{Cl}, \text{Br} > \text{O}_2\text{CR} > \text{OR} > \text{NHR} > \text{O}^- > \text{N}^-\text{R}$. The broad reactivity trends among the carboxylic acid derivatives can be recognized by taking account of the *effect of the substituents on the stability of the carbonyl center and the ability of the various substituents to act as leaving groups from the tetrahedral intermediate*. The detailed mechanisms of these reactions also depend on the site and extent of protonation in the tetrahedral intermediate.

7.4.1. Ester Hydrolysis and Exchange

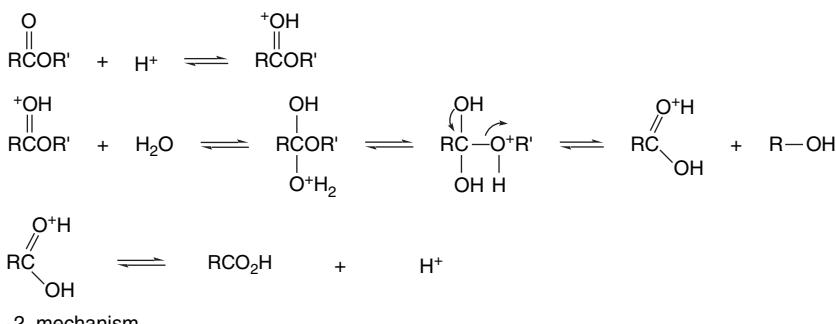
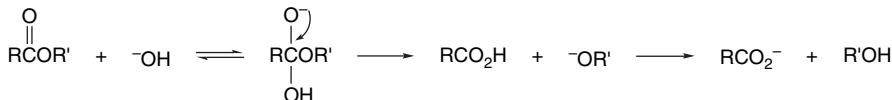
Esters can be hydrolyzed in either basic or acidic solution. In acidic solution, the reaction is reversible. The position of the equilibrium depends on the relative concentration of water and the alcohol. In aqueous solution, hydrolysis occurs. In alcoholic solution, the equilibrium is shifted in favor of the ester.



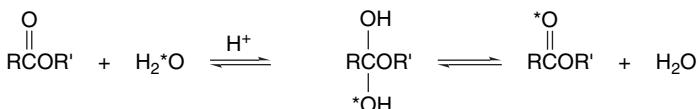
In alkaline aqueous solution, ester hydrolysis is essentially irreversible.



The carboxylic acid is converted to its anion under these conditions, and the position of the equilibrium lies far to the right. The mechanistic designations $A_{AC}2$ and $B_{AC}2$ are given to the acid- and base-catalyzed hydrolysis mechanisms, respectively. The A denotes acid catalysis and B indicates base catalysis. The subscript AC designation indicates that acyl-oxygen bond cleavage occurs. The digit 2 has its usual significance, indicating the bimolecular nature of the rate-determining step.

A_{AC2} mechanism**B_{AC2}** mechanism

Esters without special structural features can hydrolyze by either of these mechanisms. Among the evidence supporting these mechanisms are kinetic studies that show the expected dependence on hydrogen ion or hydroxide ion concentration and isotopic-labeling studies that prove it is the acyl-oxygen bond, not the alkyl-oxygen bond, that is cleaved during hydrolysis.³³ Acid-catalyzed hydrolysis of esters is accompanied by some exchange of oxygen from water into the carbonyl group. This exchange occurs by way of the tetrahedral intermediate because loss of water is competitive with expulsion of the alcohol.



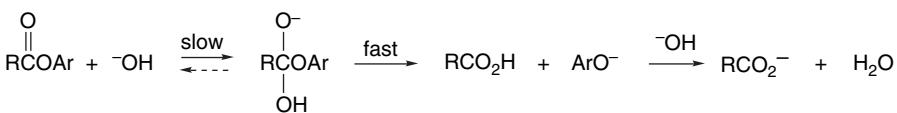
Alkyl benzoate esters give only a small amount of exchange under basic hydrolysis conditions. This means that reversal of the hydroxide addition must be slow relative to the forward breakdown of the tetrahedral intermediate.³⁴

Substituent effects come into play at several points in the ester hydrolysis mechanism. In the base-catalyzed reaction, EWG substituents in either the acyl or alkoxy group facilitate hydrolysis. If the carbonyl group is conjugated with an ERG, reactivity is decreased by ground state stabilization. Since the rate-determining tetrahedral intermediate is negatively charged, the corresponding TS is stabilized by an EWG. The partitioning of the tetrahedral intermediate between reversion to starting material by loss of hydroxide ion and formation of product by expulsion of the alkoxide is strongly affected by substituents in the alkoxy group. An EWG on the alkoxy group shifts the partitioning to favor loss of the alkoxide and accelerates hydrolysis. For this reason, exchange of carbonyl oxygen with solvent does not occur in basic hydrolyses when the alkoxy group is a good leaving group. This has been demonstrated, for example, for esters of phenols. As phenols are stronger acids than alcohols,

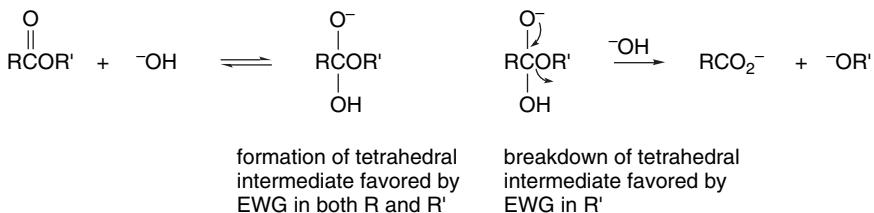
³³. M. I. Bender, *Chem. Rev.*, **60**, 53 (1960); S. L. Johnson, *Adv. Phys. Org. Chem.*, **5**, 237 (1967); D. P. N. Satchell and R. S. Satchell, in *Chemistry of Carboxylic Acid Derivatives*, Vol. 2, Part 1, S. Patai, ed., Wiley, New York, 1992, pp. 747–802.

³⁴. R. A. McClelland, *J. Am. Chem. Soc.*, **106**, 7579 (1984).

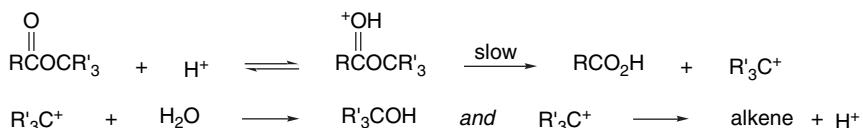
their conjugate bases are better leaving groups than alkoxide ions. Aryl esters are hydrolyzed faster than alkyl esters, without observable exchange of carbonyl oxygen with solvent.



These substituent effects can be summarized for the $\text{B}_{\text{AC}2}$ mechanism by noting the effect of substituents on each step of the mechanism.



Structural changes in the reactant can shift ester hydrolysis away from the usual $\text{A}_{\text{AC}2}$ or $\text{B}_{\text{AC}2}$ mechanisms. When the ester is derived from a tertiary alcohol, acid-catalyzed hydrolysis often occurs by a mechanism involving *alkyl oxygen fission*. The change in mechanism is due to the stability of the tertiary carbocation that can be formed by alkyl-oxygen cleavage.³⁵ When this mechanism occurs, alkenes as well as alcohols are produced, because the carbocation can react by either substitution or elimination. This mechanism is referred to as $\text{A}_{\text{AL}1}$, indicating the cleavage of the alkyl-oxygen bond and the unimolecular character of the rate-determining step.

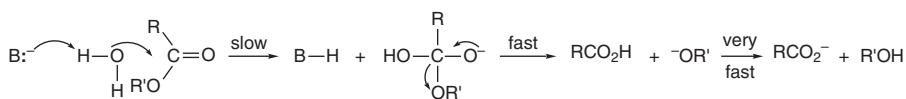


The facile $\text{A}_{\text{AL}1}$ mechanism of tertiary alkyl esters is valuable in synthetic methodology because it permits tertiary esters to be hydrolyzed selectively. The usual situation involves the use of *t*-butyl esters, which can be cleaved to carboxylic acids by the action of acids such as *p*-toluenesulfonic acid or trifluoroacetic acid under anhydrous conditions where other esters are stable.

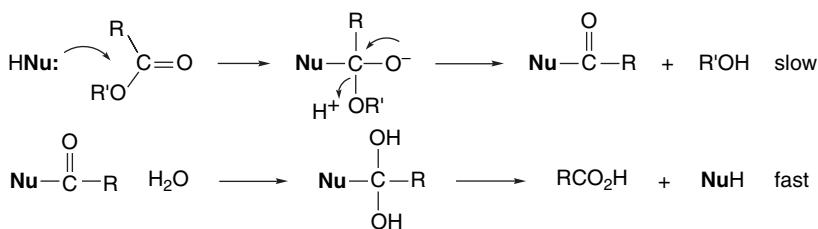
The ester hydrolysis mechanisms discussed in the preceding paragraphs pertains to aqueous solutions of strong acids and strong bases, in which specific acid or base catalysis is dominant. In media where other acids or bases are present, general acid-catalyzed and general base-catalyzed hydrolysis can occur. General base catalysis has been observed in the case of esters in which the acyl group carries EWG substituents.³⁶ The TS for esters undergoing hydrolysis by a general base-catalyzed mechanism involves partial proton transfer from the attacking water molecule to the general base during formation of the tetrahedral intermediate.

³⁵ A. G. Davies and J. Kenyon, *Q. Rev. Chem. Soc.*, **9**, 203 (1955).

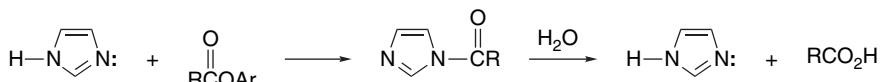
³⁶ W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **83**, 1743 (1961); D. Stefanidis and W. P. Jencks, *J. Am. Chem. Soc.*, **115**, 6045 (1993).



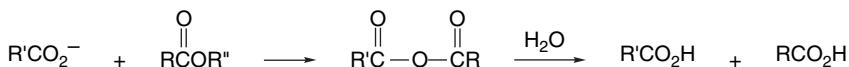
Ester hydrolysis can also occur by *nucleophilic catalysis*. If a component of the reaction system is a more effective nucleophile toward the carbonyl group than water under a given set of conditions, an acyl transfer reaction can take place to form the acyl derivative of the catalytic nucleophile. If this acyl intermediate, in turn, is more rapidly attacked by water than the original ester, the overall reaction will be faster in the presence of the nucleophile than in its absence. These are the requisite conditions for nucleophilic catalysis.



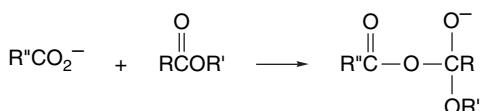
Esters of relatively acidic alcohols (in particular phenols) are hydrolyzed by the nucleophilic catalysis mechanism in the presence of imidazole.³⁷ The acylimidazolides are inherently quite reactive and protonation of the second nitrogen can facilitate the hydrolysis.



Carboxylate anions can also serve as nucleophilic catalysts.³⁸ In this case, an anhydride is the reactive intermediate.



The nucleophilic catalysis mechanism only operates when the alkoxy group being hydrolyzed is not substantially more basic than the nucleophilic catalyst. This requirement can be understood by considering the tetrahedral intermediate generated by attack of the potential catalyst on the ester.



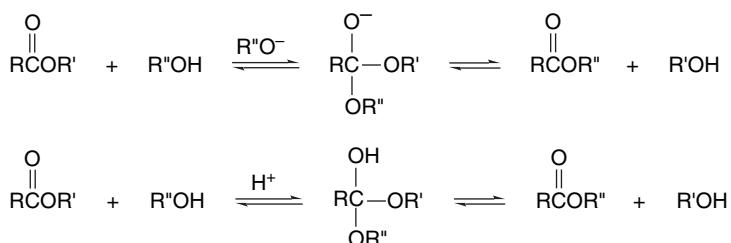
The relative leaving-group abilities of $\text{R}'\text{O}^-$ and $\text{R}'\text{CO}_2^-$ are strongly correlated with the basicity of the two anions. If $\text{R}'\text{CO}_2^-$ is a much better leaving group than $\text{R}'\text{O}^-$, it will be eliminated preferentially from the tetrahedral intermediate and no catalysis will occur.

³⁷ T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, **79**, 1663 (1967); M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1652, 1656 (1957); P. Menegheli, J. P. S. Farah, and O. A. El Seoud, *Ber. Bunsenges. Phys. Chem.*, **95**, 1610 (1991).

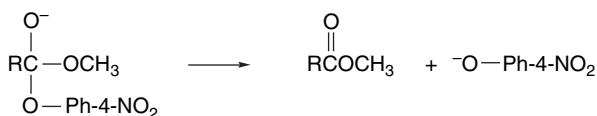
³⁸ V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc., Perkin Trans. B*, 515 (1968).

The preceding discussion has touched on the most fundamental aspects of ester hydrolysis mechanisms. Much effort has been devoted to establishing some of the finer details, particularly concerning proton transfers during the formation and breakdown of the tetrahedral intermediates. These studies have been undertaken in part because of the importance of hydrolytic reactions in biological systems, which are catalyzed by enzymes. The detailed mechanistic studies of ester hydrolysis laid the groundwork for understanding the catalytic mechanisms of the hydrolytic enzymes. Discussions of the biological mechanisms and their relationship to the fundamental mechanistic studies are available in several books that discuss enzyme catalysis in terms of molecular mechanisms.³⁹

Esters react with alcohols in either acidic or basic solution to exchange alkoxy groups (ester interchange) by a mechanism that parallels hydrolysis. The alcohol or alkoxide acts as the nucleophile.



As in the case of hydrolysis, there has been a good deal of study of substituent effects, solvent effects, isotopic exchange, kinetics, and the catalysis of these processes.⁴⁰ In contrast to hydrolysis, the alcoholysis reaction is reversible in both acidic and basic solutions. The key intermediate is the tetrahedral adduct. Its fate is determined mainly by the relative basicity of the two alkoxy groups. A tetrahedral intermediate generated by addition of methoxide ion to a *p*-nitrophenyl ester, for example, breaks down exclusively by elimination of the much less basic *p*-nitrophenoxide ion.

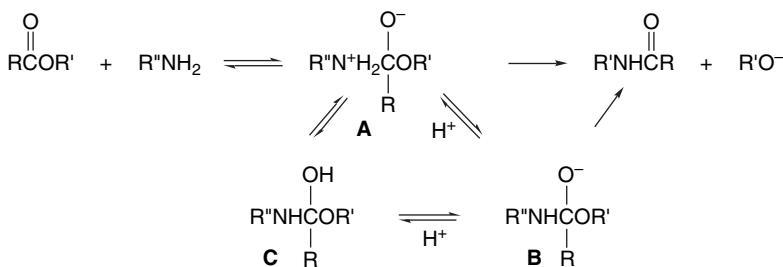


In general, the equilibrium in a base-catalyzed alcohol exchange reaction lies in the direction of incorporation of the less acidic alcohol in the ester. This is a reflection both of the kinetic factor, the more acidic alcohol being a better leaving group, and the greater stabilization provided to the carbonyl group by the more electron-rich alkoxy substituent.

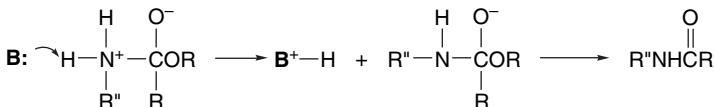
³⁹. T. C. Bruice and S. J. Benkovic, *Bioorganic Mechanisms*, Vol. 1, W. A. Benjamin, New York, 1966, pp. 1–258; W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, 1969; M. L. Bender, *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley-Interscience, New York, 1971; C. Walsh, *Enzymatic Reaction Mechanisms*, W. H. Freeman, San Francisco, 1979; A. Fersht, *Enzyme Structure and Mechanism*, 2nd Edition, W. H. Freeman, New York, 1985.

⁴⁰. C. G. Mitton, R. L. Schowen, M. Gresser, and J. Shapely, *J. Am. Chem. Soc.*, **91**, 2036 (1969); C. G. Mitton, M. Gresser, and R. L. Schowen, *J. Am. Chem. Soc.*, **91**, 2045 (1969).

Esters react with ammonia and amines to give amides. The mechanism involves nucleophilic attack of the amine at the carbonyl group, followed by expulsion of the alkoxy group from the tetrahedral intermediate. The identity of the rate-determining step depends primarily on the leaving-group ability of the alkoxy group.⁴¹ With relatively good leaving groups such as phenols or trifluoroethanol, the slow step is expulsion of the oxygen leaving group from a zwitterionic tetrahedral intermediate **A**. With poorer leaving groups, breakdown of the tetrahedral intermediate occurs only after formation of the anionic species **B**.



Aminolysis of esters often exhibits general base catalysis in the form of reaction rate terms that are second order in the amine. The amine is believed to assist deprotonation of the zwitterionic tetrahedral intermediate.⁴² Deprotonation of the nitrogen facilitates breakdown of the tetrahedral intermediate because the increased electron density at nitrogen favors expulsion of an alkoxide ion.

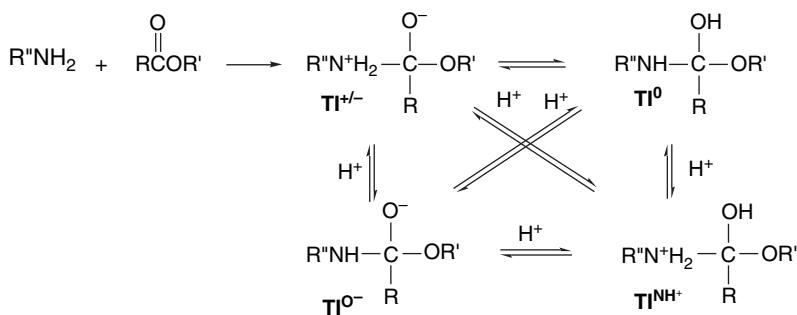


Detailed mechanistic studies have been carried out on aminolysis of substituted aryl acetates and aryl carbonates.⁴³ Aryl esters are considerably more reactive than alkyl esters because phenoxide ions are better leaving groups than alkoxide ions. The tetrahedral intermediate formed in aminolysis can exist in several forms that differ in the extent and the site of protonation.

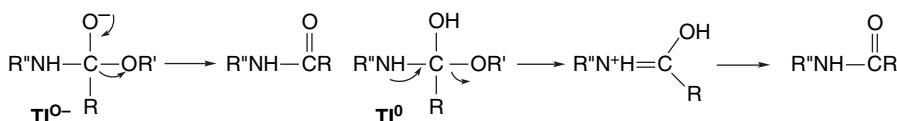
⁴¹ F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, **94**, 3824 (1972); A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7018 (1974).

⁴² W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **88**, 104 (1966); J. F. Kirsch and A. Kline, *J. Am. Chem. Soc.*, **91**, 1841 (1969); A. S. Shawali and S. S. Biechler, *J. Am. Chem. Soc.*, **89**, 3020 (1967); J. F. Bennett and G. T. Davis, *J. Am. Chem. Soc.*, **82**, 665 (1961).

⁴³ W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **90**, 2622 (1968); A. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7018 (1974); A. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7031 (1974); M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 6970 (1977).

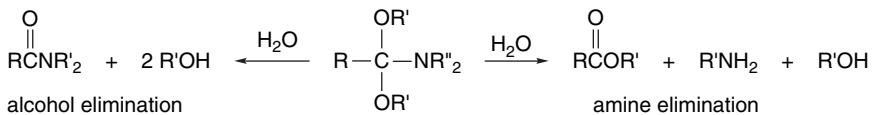


In $\text{TI}^{+/-}$ and TI^{NH+} , the best leaving group is the neutral amine, whereas in TI^{0-} and TI^0 the group $\text{R}'\text{O}^-$ is a better leaving group than R''NH^- . Furthermore, in TI^{0-} and TI^0 the unshared pair on nitrogen can assist in elimination. In $\text{TI}^{+/-}$ the negatively charged oxygen also has increased capacity to “push” out the leaving group, with reformation of the carbonyl group. Precisely how the intermediate proceeds to product depends upon pH and the identity of the groups R''NH_2 and $\text{R}'\text{O}^-$. When $\text{R}'\text{O}^-$ is a relatively poor leaving group, as in the case for alkyl esters, reaction usually occurs through TI^{0-} or TI^0 .

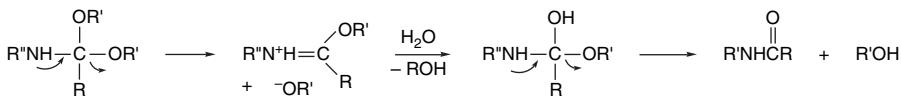


When the leaving group is better, breakdown can occur directly from $\text{TI}^{+/-}$. This is the case when $\text{R}'\text{O}^-$ is a phenolate anion. The mechanism also depends upon the pH and the presence of general acids and bases because the position of the equilibria among the tetrahedral intermediates and rates of breakdown are determined by these factors.

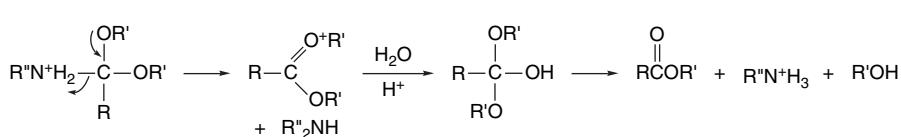
Insight into the factors that govern breakdown of tetrahedral intermediates has been gained by studying the hydrolysis of amide acetals. If the amine is expelled, an ester is formed, whereas elimination of an alcohol gives an amide.



The pH of the solution is of overwhelming importance in determining the course of these hydrolyses.⁴⁴ In basic solution, oxygen elimination is dominant, because the unprotonated nitrogen substituent is a very poor leaving group and is also more effective at facilitating the alkoxide elimination by electron donation.

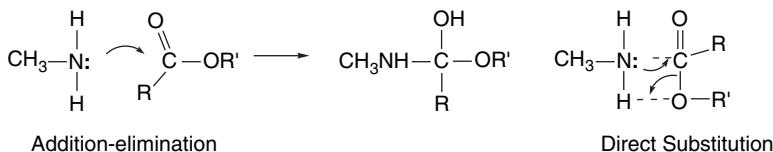


⁴⁴. R. A. McClelland, *J. Am. Chem. Soc.*, **100**, 1844 (1978).



In analyzing the behavior of these types of tetrahedral intermediates, it should be kept in mind that proton transfer reactions are usually fast relative to other steps. This circumstance permits the possibility that a minor species in equilibrium with the major species may be the kinetically dominant intermediate. Detailed studies of kinetics, solvent isotope effects, and catalysis are the best tools for investigating the various possibilities.

Recent computational work has suggested the existence of a mechanism for aminolysis that bypasses the tetrahedral intermediates. Transition structures corresponding to both stepwise addition-elimination through a tetrahedral intermediate and direct substitution were found for the reaction of methylamine with methyl acetate and phenyl acetate.⁴⁵ There is considerable development of charge separation in the direct displacement mechanism because proton transfer lags rupture of the C–O bond.



The direct substitution reaction becomes progressively more favorable as the alcohol becomes a better leaving group. According to the computations, the two mechanisms are closely competitive for alkyl esters, but the direct substitution mechanism is favored for aryl esters. These results refer to the gas phase.

Computed Activation Energy (kcal/mol)

	Addition-elimination	Direct substitution
$\text{CH}_3\text{CO}_2\text{CH}_3$	35.5	36.2
$\text{CH}_3\text{CO}_2\text{C}_6\text{H}_5$	32.1	26.6
$\text{CH}_3\text{CO}_2\text{C}_6\text{H}_4\text{NO}_2$		~1.7

A direct substitution mechanism was indicated for the 2-pyridone catalysis of aminolysis of methyl acetate by methylamine.⁴⁶ This mechanism is represented in Figure 7.9. It avoids a tetrahedral intermediate and describes a concerted displacement process that is facilitated by proton transfer involving 2-pyridone. Two very closely related TSs involving either the 2-hydroxypyridine or 2-pyridone tautomers were found. These TSs show extensive cleavage of the C–O bond (2.0–2.2 Å) and formation

⁴⁵. H. Zipse, L.-h. Wang, and K. N. Houk, *Liebigs Ann.*, 1511 (1996).

⁴⁶. L.-h. Wang and H. Zipse, *Liebigs Ann.*, 1501 (1996).

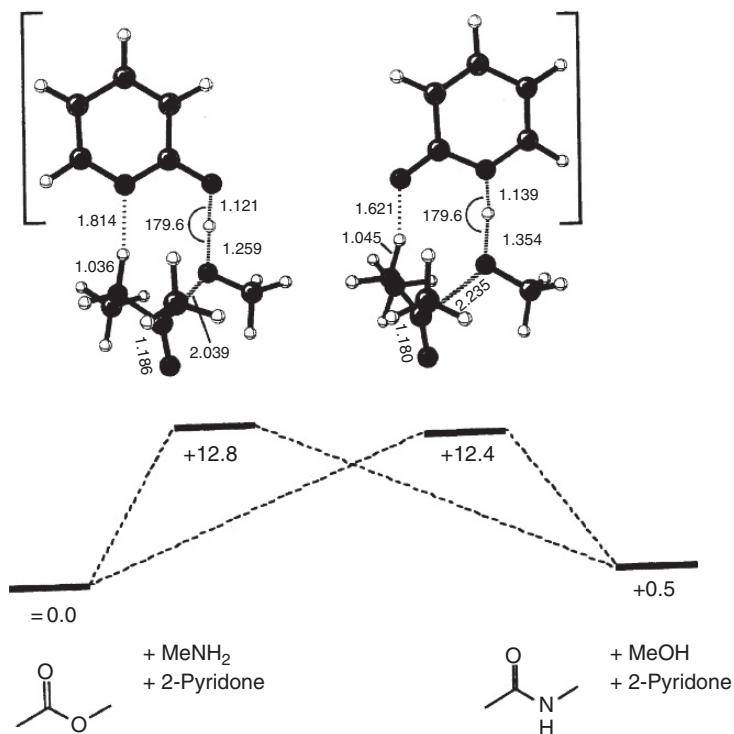
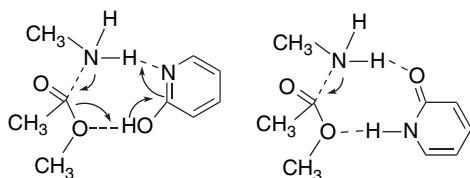


Fig. 7.9. Concerted mechanism for 2-pyridone-catalyzed reaction of methylamine with methyl acetate. TS energies (kcal/mol) are from B3LYP/6-31G** calculations. Reproduced from *Liebigs Ann.*, 1501 (1996), by permission of Wiley-VCM.

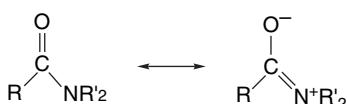
of the C–N bond. O-Protonation is also advanced, but N-deprotonation is minimal. Experimentally, it was found that catalytic efficiency could be improved by a factor of about 2500 by use of the more acidic 4-cyano-2-pyridone.



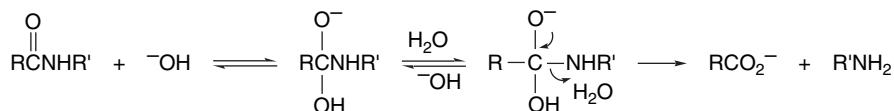
7.4.3. Amide Hydrolysis

The hydrolysis of amides to carboxylic acids and amines requires considerably more vigorous conditions than ester hydrolysis.⁴⁷ The reason is that the electron-releasing nitrogen imparts a very significant ground state stabilization that is lost in the TS leading to the tetrahedral intermediate.

⁴⁷ C. O'Connor, *Q. Rev. Chem. Soc.*, **24**, 553 (1970).

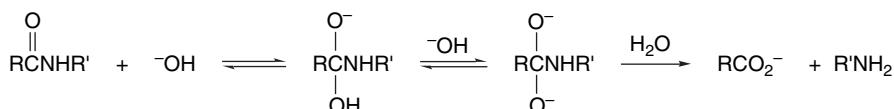


In basic solution, a $B_{AC}2$ mechanism similar to the that for ester hydrolysis is believed to operate.⁴⁸



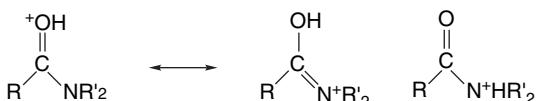
The principal difference lies in the poorer ability of amide anions to act as leaving groups, compared to alkoxides. As a result, protonation at nitrogen is required for dissociation of the tetrahedral intermediate. Exchange between the carbonyl oxygen and water is extensive because reversal of the tetrahedral intermediate to reactants is faster than decomposition to products.

In some amide hydrolyses, the rupture of the tetrahedral intermediate in the forward direction requires formation of a dianion.⁴⁹



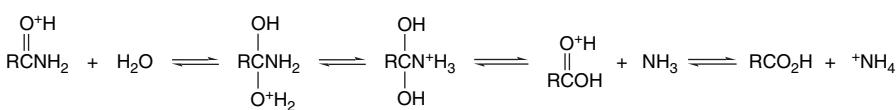
This variation from the ester hydrolysis mechanism also reflects the poorer leaving ability of amide ions, as compared to alkoxide ions. The evidence for the involvement of the dianion comes from kinetic studies and from solvent isotope effects that suggest that a rate-limiting proton transfer is involved.⁵⁰ The reaction is also higher than first order in hydroxide ion under these circumstances, which is consistent with the dianion mechanism.

The mechanism for acid-catalyzed hydrolysis of amides involves attack by water on the protonated amide. Amides are weak bases with pK_a values in the range from 0 to -2 .⁵¹ An important feature of the chemistry of amides is that the most basic site is the carbonyl oxygen. Very little of the N-protonated form is present.⁵² The major factor that favors the O-protonated form is the retention of π -electron delocalization over the O–C–N system. No such delocalization is possible in the N-protonated form.



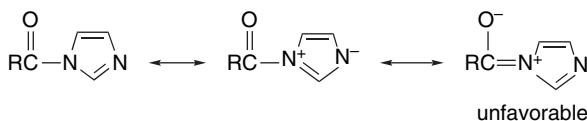
- ⁴⁸. M. L. Bender and R. J. Thomas, *J. Am. Chem. Soc.*, **83**, 4183 (1961); R. S. Brown, A. J. Bennet, and H. Slebocka-Tilk, *Acc. Chem. Res.*, **25**, 481 (1992).
- ⁴⁹. R. M. Pollack and M. L. Bender, *J. Am. Chem. Soc.*, **92**, 7190 (1970).
- ⁵⁰. R. L. Schowen, H. Jayaraman, L. Kershner, and G. W. Zuorick, *J. Am. Chem. Soc.*, **88**, 4008 (1966).
- ⁵¹. R. A. Cox, L. M. Druet, A. E. Klausner, T. A. Modro, P. Wan, and K. Yates, *Can. J. Chem.*, **59**, 1568 (1981); A. Bagno, G. Lovato, and G. Scorrano, *J. Chem. Soc., Perkin Trans. 2*, 1091 (1993).
- ⁵². R. J. Gillespie and T. Birchall, *Can. J. Chem.*, **41**, 148, 2642 (1963); A. R. Fersht, *J. Am. Chem. Soc.*, **93**, 3504 (1971); R. B. Martin, *J. Chem. Soc., Chem. Commun.*, 793 (1972); A. J. Kresge, P. H. Fitzgerald, and Y. Chiang, *J. Am. Chem. Soc.*, **96**, 4698 (1974).

The usual hydrolysis mechanism in strongly acidic solutions involves addition of water to the O-protonated amide followed by dissociation of the tetrahedral intermediate.



There is almost no exchange of oxygen with water during acid-catalyzed hydrolysis of amides.⁵³ Since a tetrahedral intermediate is involved, the lack of exchange means that it must react exclusively by elimination of the nitrogen substituent. This result is reasonable, because the amino group is the most basic site and is the preferred site of protonation in the tetrahedral intermediate. The protonated amine is a much better leaving group than the hydroxide ion.

Acylimidazoles and related amides in which the nitrogen atom is part of an aromatic ring hydrolyze much more rapidly than aliphatic amides. A major factor is the decreased resonance stabilization of the carbonyl group, which is opposed by the participation of the nitrogen lone pair in the aromatic sextet.

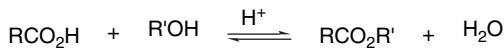


The acid-catalyzed hydrolysis of imidazolides is accelerated by protonation of N(3), which increases the leaving-group ability of the ring,⁵⁴ and accumulation of additional nitrogens in the ring (triazoles, tetrazoles) further increased that ability.⁵⁵

7.4.4. Acylation of Nucleophilic Oxygen and Nitrogen Groups

The conversion of alcohols to esters by O-acylation and of amines to amides by N-acylation are fundamental organic reactions that are the reverse of the hydrolyses discussed in the preceding sections. In Section 3.4 of Part B we discuss these reactions from the point of view of synthetic applications and methods.

Although the previous two sections of this chapter emphasized hydrolytic processes, two mechanism that led to O or N-acylation were considered. In the discussion of acid-catalyzed ester hydrolysis, it was pointed out that this reaction is reversible (p. 654). Thus it is possible to acylate alcohols by acid-catalyzed reaction with a carboxylic acid. This is called the *Fischer esterification* method. To drive the reaction forward, the alcohol is usually used in large excess, and it may also be necessary to remove water as it is formed. This can be done by azeotropic distillation in some cases.



⁵³. R. A. McClelland, *J. Am. Chem. Soc.*, **97**, 5281 (1975); For cases in which some exchange does occur, see H. Slebocka-Tilk, R. S. Brown, and J. Olekszyk, *J. Am. Chem. Soc.*, **109**, 4620 (1987); A. J. Bennet, H. Slebocka-Tilk, R. S. Brown, J. P. Guthrie, and A. J. Jodhan, *J. Am. Chem. Soc.*, **112**, 8497 (1990).

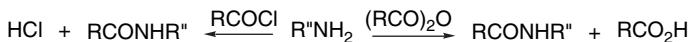
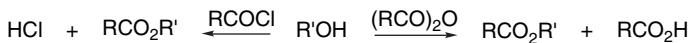
⁵⁴. T. H. Fife, *Acc. Chem. Res.*, **26**, 325 (1993).

⁵⁵. J. F. Patterson, W. P. Huskey, and J. L. Hoggs, *J. Org. Chem.*, **45**, 4675 (1980); B. S. Jursic and Z. Zdravkovski, *Theochem*, **109**, 177 (1994).

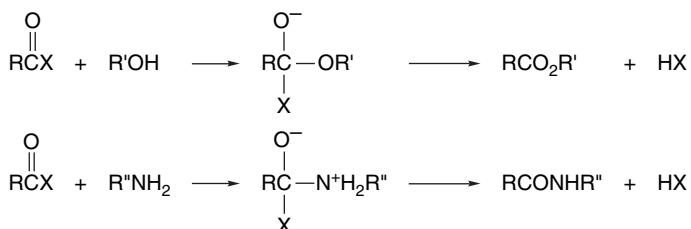
The second reaction that should be recalled is the aminolysis of esters (p. 659), which leads to the formation of amides by N-acylation. The equilibrium constant for this reaction is ordinarily favorable, but the reactions are rather slow.



The most common O- and N-acylation procedures use acylating agents that are more reactive than carboxylic acids or their esters. Acyl chlorides and anhydrides react rapidly with most unhindered alcohols and amines to give esters and amides, respectively.

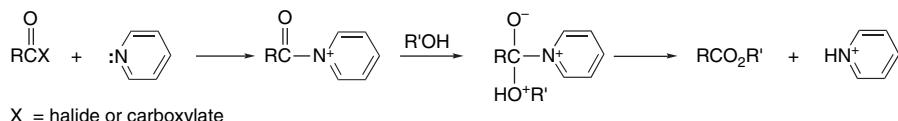


The general features of the mechanisms are well established.⁵⁶ The nucleophilic species undergoes addition at the carbonyl group, followed by elimination of the halide or carboxylate group. Acyl halides and anhydrides are reactive acylating reagents because of a combination of the polar effect of the halogen or oxygen substituent, which enhances the reactivity of the carbonyl group, and the ease with which the tetrahedral intermediate can expel these relatively good leaving groups.



X = halide or carboxylate

Acylation of alcohols is often performed in the presence of an organic base such as pyridine. The base serves two purposes: it neutralizes the protons generated in the reaction and prevents the development of high acid concentrations. Pyridine also becomes directly involved in the reaction as a *nucleophilic catalyst* (see p. 657).



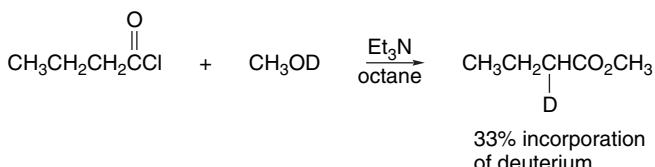
X = halide or carboxylate

Pyridine is more nucleophilic than an alcohol toward the carbonyl center of an acyl chloride. The product that results, an acylpyridinium ion, is, in turn, more reactive toward an alcohol than the original acyl chloride. The conditions required for nucleophilic catalysis therefore exist, and acylation of the alcohol by acid chloride is faster in the presence of pyridine than in its absence. Among the evidence that supports this

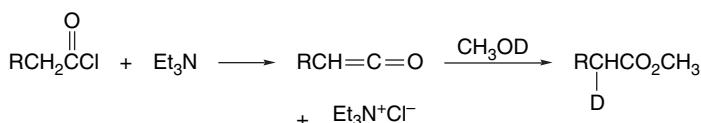
⁵⁶ D. P. N. Satchell, *Q. Rev. Chem. Soc.*, **17**, 160 (1963).

mechanism is spectroscopic observation of the acetylpyridinium ion intermediate.⁵⁷ An even more effective catalyst is 4-dimethylaminopyridine (DMAP), which functions in the same way, but is more reactive because of the ERG dimethylamino substituent.⁵⁸

With more strongly basic tertiary amines such as triethylamine, another mechanism can come into play. It has been found that when methanol deuterated on oxygen reacts with acyl chlorides in the presence of triethylamine, some deuterium is introduced α to the carbonyl group in the ester.

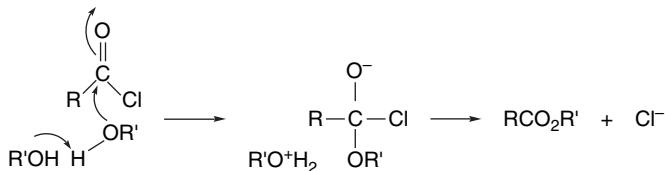


This finding suggests that some of the ester is formed via a ketene intermediate.⁵⁹



Ketenes undergo rapid addition by nucleophilic attack at the *sp*-carbon atom. The reaction of tertiary amines and acyl halides in the absence of nucleophiles is a general preparation for ketenes for other purposes.⁶⁰

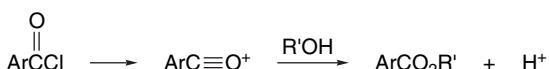
Kinetic studies of the reaction of alcohols with acyl chlorides in polar solvents in the absence of basic catalysts generally reveal terms of both first and second order in alcohol.⁶¹ Transition structures in which the second alcohol molecule acts as a proton acceptor have been proposed.



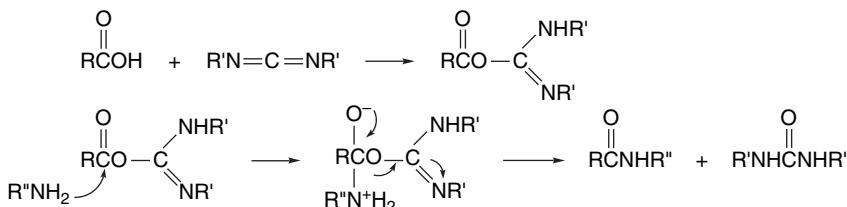
There is an alternative to the addition-elimination mechanism for nucleophilic substitution of acyl chlorides. Certain acyl chlorides react with alcohols by a dissociative mechanism in which *acylium ions* are intermediates. This mechanism is observed with aryl halides having ERG substituents.⁶² Other acyl halides show

- ^{57.} A. R. Fersht and W. P. Jencks, *J. Am. Chem. Soc.*, **92**, 5432, 5442 (1970).
- ^{58.} E. F. V. Scriven, *Chem. Soc. Rev.*, **12**, 129 (1983).
- ^{59.} W. E. Truce and P. S. Bailey, *J. Org. Chem.*, **34**, 1341 (1969).
- ^{60.} R. N. Lacey, in *The Chemistry of Alkenes*, S. Patai, ed., Interscience Publishers, New York, 1964, pp. 1168–1170; W. E. Hanford and J. C. Sauer, *Org. React.*, **3**, 108 (1947).
- ^{61.} D. N. Kevill and F. D. Foss, *J. Am. Chem. Soc.*, **91**, 5054 (1969); S. D. Ross, *J. Am. Chem. Soc.*, **92**, 5998 (1970).
- ^{62.} M. L. Bender and M. C. Chen, *J. Am. Chem. Soc.*, **85**, 30 (1963); T. W. Bentley, H. C. Harris, and I. S. Koo, *J. Chem. Soc., Perkin Trans. 2*, 783 (1988); B. D. Song and W. P. Jencks, *J. Am. Chem. Soc.*, **111**, 8470 (1989).

reactivity indicative of mixed or borderline mechanisms.⁶³ The existence of the S_N1-like dissociative mechanism reflects the relative stability of acylium ions.

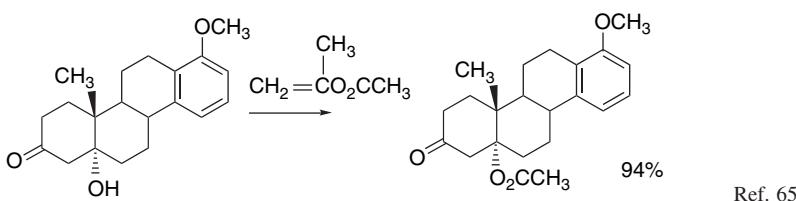


In addition to acyl chlorides and acid anhydrides, there are a number of other types of compounds that are reactive acylating agents. Many have been developed to facilitate the synthesis of polypeptides, for which mild conditions and high selectivity are required (see Part B, Section 3.4). The carbodiimides, such as dicyclohexylcarbodiimide, make up an important group of reagents for converting carboxylic acids to active acylating agents. The mechanism for carbodiimide-promoted amide bond formation is shown below.



The first step is addition of the carboxylic acid to the C=N bond of the carbodiimide, which generates an O-acylated urea derivative. This is a reactive acylating agent because there is a strong driving force for elimination of the very stable urea carbonyl group.⁶⁴ The amine reacts with the active acylating agent. In the absence of an amine, the acid is converted to the anhydride, with a second molecule of the carboxylic acid serving as the nucleophile.

Enol esters are another type of acylating agent. The acetate of the enol form of acetone, isopropenyl acetate, is the most commonly used example. In the presence of an acid catalyst, they act as acylating agents and are reactive toward weak nucleophiles such as hindered hydroxy groups.

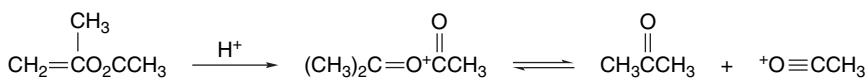


The active acylating agent is presumably the C-protonated enol ester. This species is highly reactive owing to the presence of a positively charged oxygen. An alternative possibility is that the protonated enol ester dissociates to acetone and the acetylum ion, which then acts as the acylating agent.

⁶³. T. W. Bentley, I. S. Koo, and S. J. Norman, *J. Org. Chem.*, **56**, 1604 (1991); T. W. Bentley and B. S. Shim, *J. Chem. Soc., Perkin Trans. 2*, 1659 (1993).

⁶⁴. D. F. DeTar and R. Silverstein, *J. Am. Chem. Soc.*, **88**, 1013, 1020 (1966).

⁶⁵. W. S. Johnson, J. Ackerman, J. F. Eastham, and H. A. DeWalt, Jr., *J. Am. Chem. Soc.*, **78**, 6302 (1956).

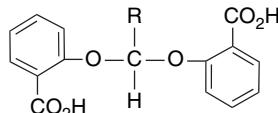


Other examples of synthetically useful acylating reagents are given in Section 3.4 of Part B.

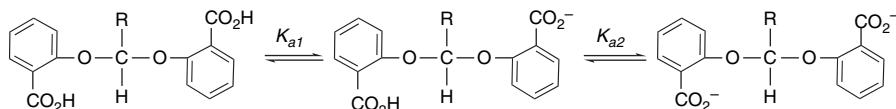
7.5. Intramolecular Catalysis of Carbonyl Substitution Reactions

The reactions of carbonyl compounds have provided an important testing ground for developing an understanding of *intramolecular catalysis*, which is a neighboring-group interaction that accelerates a reaction. Studies in intramolecular catalysis have been designed to determine how much more efficiently a given functional group can act as a catalyst when it is part of the reacting molecule and located in a position that enables an encounter between the catalytic group and the reaction center. These studies are relevant to understanding biological mechanisms, because enzymes achieve exceedingly efficient catalysis by bringing together at the “active site” combinations of basic, acidic, and nucleophilic groups in a geometry that is particularly favorable for reaction. The present section illustrates some of the facts that have emerged from these studies and the mechanistic conclusions that have been drawn.

It was pointed out in the mechanistic discussion concerning acetal hydrolysis that general acid catalysis occurs only for acetals having special structural features (see p. 641) Usually, specific acid catalysis operates. The question of whether general acid catalysis can be observed in intramolecular reactions has been of interest because intramolecular general acid catalysis is thought to play a part in the mechanism of action of the enzyme lysozyme, which hydrolyzes the acetal linkage present in certain polysaccharides. One group of molecules that has been examined as a model system are acetals derived from *o*-hydroxybenzoic acid (salicylic acid).⁶⁶



The pH-rate profile for hydrolysis of the benzaldehyde acetal (see Figure 7.10) indicates that of the species that are available, the *monoanion* of the acetal is the most reactive. The reaction is fastest in the pH range where the concentration of the monoanion is at a maximum. The neutral molecule decreases in concentration with increasing pH and the converse is true for the dianion.



⁶⁶ E. Anderson and T. H. Fife, *J. Am. Chem. Soc.*, **95**, 6437 (1973).

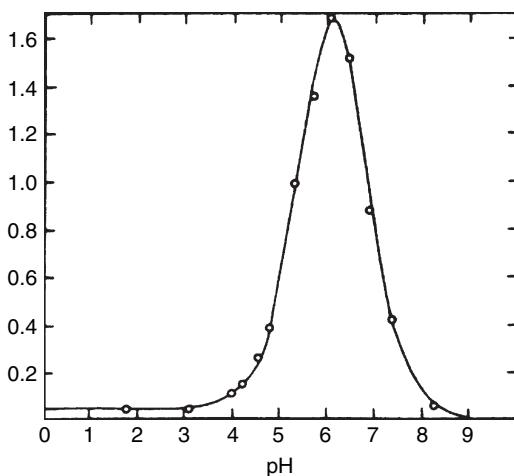
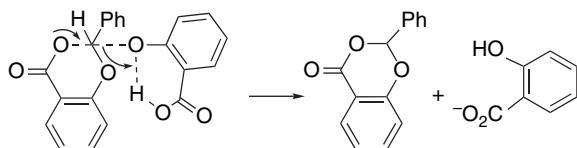
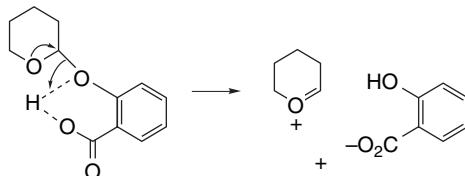


Fig. 7.10. pH-Rate profile for release of salicylic acid from benzaldehyde disalicyl acetal. Reproduced from *J. Am. Chem. Soc.*, **95**, 6437 (1973), by permission of the American Chemical Society.

The TS for the rapid hydrolysis of the monoanion is depicted as involving an intramolecular general acid catalysis by the carboxylic acid group, with participation by the anionic carboxylate group, which becomes bound at the developing electrophilic center. The un-ionized carboxylic acid group acts as a *general acid catalyst* and the carboxylate as a *nucleophilic catalyst*.



A mixed acetal of benzaldehyde, tetrahydropyranol, and salicylic acid has also been studied.⁶⁷ It, too, shows a marked rate enhancement attributable to intramolecular general acid catalysis. In this case the pH-rate profile (Figure 7.11) shows a plateau in the region pH 2–5. As the carboxy group becomes protonated below pH 6, it provides an increment owing to intramolecular general acid catalysis.



The case of intramolecular carboxylate participation in ester hydrolysis has been extensively studied using acetylsalicylic acid (aspirin) and its derivatives. The kinetic data show that the anion is hydrolyzed more rapidly than the neutral species, indicating

⁶⁷ T. H. Fife and E. Anderson, *J. Am. Chem. Soc.*, **93**, 6610 (1971).

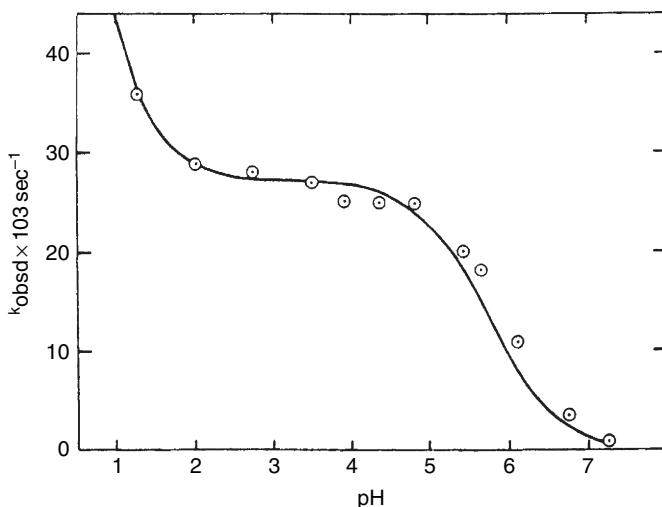
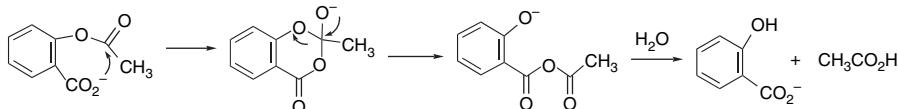


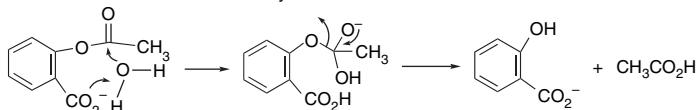
Fig. 7.11. pH-Rate profile for hydrolysis of 2-(*o*-carboxyphenoxy)tetrahydropyran in 50% dioxane-water at 15°C. Reproduced from *J. Am. Chem. Soc.*, **93**, 6610 (1971), by permission of the American Chemical Society.

that the carboxylate group becomes involved in the reaction in some way. Three mechanisms can be considered.

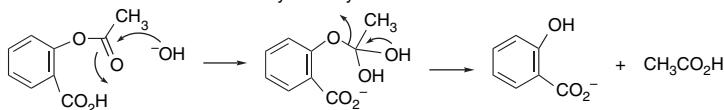
Mechanism I. Nucleophilic Catalysis



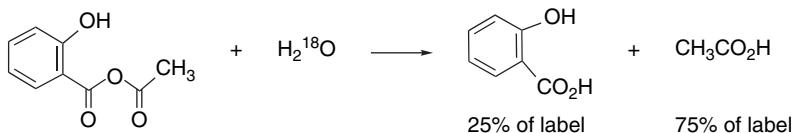
Mechanism II. General Base Catalysis of Water Attack



Mechanism III. General Acid Catalysis of Hydroxide Ion Attack



Mechanism I was ruled out by an isotopic-labeling experiment. The mixed anhydride of salicylic acid and acetic acid is an intermediate if nucleophilic catalysis occurs by Mechanism I. This molecule, which can be prepared independently, hydrolyzes in water with about 25% incorporation of solvent water into the salicylic acid.



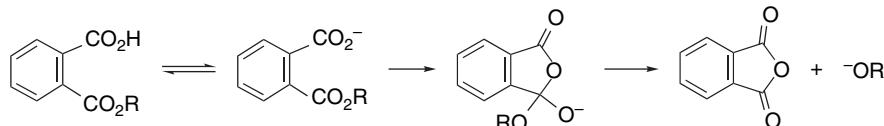
Hydrolysis of aspirin in H_2^{18}O does not lead to incorporation of ^{18}O into the product salicylic acid, ruling out the anhydride as an intermediate and thereby excluding

Mechanism I.⁶⁸ Mechanism III cannot be distinguished from the first two on the basis of kinetics alone, because the reactive species shown is in rapid equilibrium with the anion and therefore equivalent to it in terms of reaction kinetics. The general acid catalysis of Mechanism III can be eliminated on the basis of failure of other nucleophiles to show evidence for general acid catalysis by the neighboring carboxylic acid group. Since there is no reason to believe hydroxide should be special in this way, Mechanism III is ruled out. Thus Mechanism II, general base catalysis of water attack, is believed to be the correct description of the hydrolysis of aspirin.

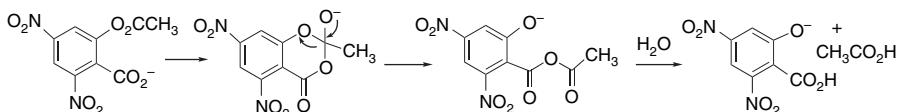
The extent to which intramolecular nucleophilic catalysis of the type depicted in Mechanism I is important is a function of the leaving ability of the alkoxy group. This has been demonstrated by the study of the hydrolysis of a series of monoesters of phthalic acid.



Nucleophilic participation is important only for esters of alcohols that have $pK_a < 13$. Specifically, phenyl and trifluoroethyl esters exhibit nucleophilic catalysis, but methyl and 2-chloroethyl esters do not.⁶⁹ This result reflects the fate of the tetrahedral intermediate that results from nucleophilic participation. For relatively acidic alcohols, the alkoxide group can be eliminated, leading to hydrolysis via nucleophilic catalysis.



For less acidic alcohols, nucleophilic participation is ineffective because of the low tendency of such alcohols to function as leaving groups. The tetrahedral intermediate formed by intramolecular addition simply returns to starting material because the carboxylate is a much better leaving group than the alkoxide. A similar observation is made for salicylate esters. In contrast to aspirin itself, acetyl salicylates with EWG groups (*o*- and *p*-nitro analogs) hydrolyze via the nucleophilic catalysis mechanism in which the phenolates act as leaving groups from the cyclic intermediate.⁷⁰ The difference, in comparison with aspirin, is the improved leaving group capacity of the phenolate.



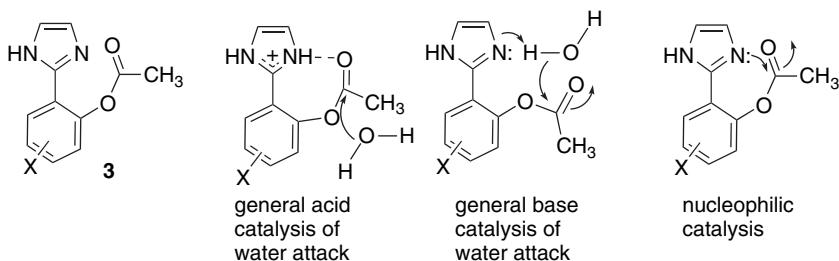
Intramolecular catalysis of ester hydrolysis by nitrogen nucleophiles is also important. The role of imidazole rings in intramolecular catalysis has received particularly close scrutiny. There are two reasons for this. One is that the imidazole ring of

⁶⁸ A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, **89**, 4857 (1967).

⁶⁹ J. W. Thanassi and T. C. Bruice, *J. Am. Chem. Soc.*, **88**, 747 (1966).

⁷⁰ A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, **89**, 5960 (1967); *J. Am. Chem. Soc.*, **90**, 5818 (1968).

the histidine residue in proteins is involved in enzyme-catalyzed hydrolyses. Secondly, the imidazole ring has several possible catalytic functions, which include acting as a general acid in the protonated form, acting as a general base, or acting as a nucleophile in the neutral form. A study of a number of derivatives of Structure **3** was undertaken to distinguish between these various possible mechanisms as a function of pH.⁷¹



The relative importance of the potential catalytic mechanisms depends on pH, which also determines the concentration of the other participating species such as water, hydronium ion, and hydroxide ion. The change in mechanism with pH gives rise to the pH-rate profile shown in Figure 7.12.

The rates at the extremities $\text{pH} < 2$ and $\text{pH} > 9$ are proportional to $[\text{H}^+]$ and $[\text{OH}^-]$, respectively, and represent the specific proton-catalyzed and hydroxide-catalyzed mechanisms. In the absence of an intramolecular catalytic mechanisms, the H^+ - and OH^- -catalyzed reactions would decrease in proportion to the concentration of the catalytic species and intersect at a minimum value representing the “uncatalyzed water hydrolysis.” An estimate of the effectiveness of the intramolecular mechanisms can be made by extrapolating the lines that are proportional to $[\text{H}^+]$ and $[\text{OH}^-]$. The extent to which the actual rate lies above these extrapolated lines in the pH range 2–8 represents the contribution from the intramolecular catalysis. The region at pH 2–4 is the area where intramolecular general acid catalysis operates. Comparison with similar systems where intramolecular proton transfer is not available suggests a 25–100 fold rate enhancement. At pH 6–8 the intramolecular general base catalysis mechanism is

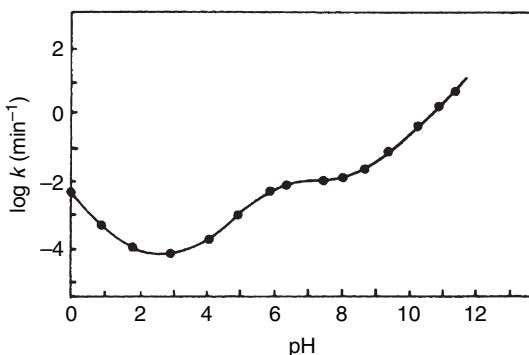
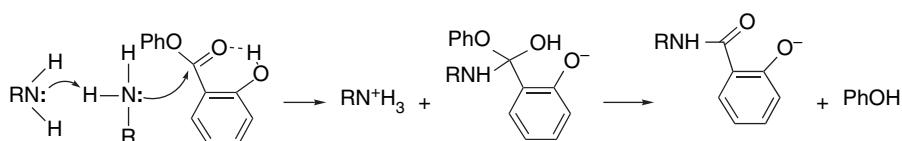


Fig. 7.12. pH-rate profile for hydrolysis of Compound **3**. Reproduced from *J. Am. Chem. Soc.*, **96**, 2463 (1974), by permission of the American Chemical Society.

⁷¹ G. A. Rogers and T. C. Bruice, *J. Am. Chem. Soc.*, **96**, 2463 (1974).

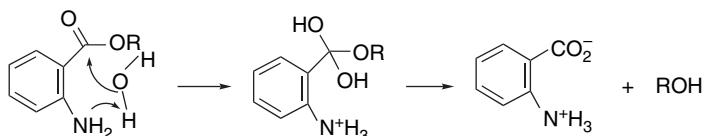
dominant. Analysis of the kinetic data indicates an acceleration of about 10^4 . Although the nucleophilic catalysis mechanism was not observed in the parent compound, it did occur in certain substituted derivatives.

Intramolecular participation of the *o*-hydroxy group in aminolysis of phenyl salicylate has been established by showing that such compounds are more reactive than analogs lacking the hydroxy substituent. This reaction exhibits overall third-order kinetics, second order in the reacting amine. Similar kinetics are observed in the aminolysis of simple esters (see p. 659) Both intermolecular general base catalysis (by the second amine molecule) and intramolecular general acid catalysis (by the hydroxyl group) apparently occur.⁷²

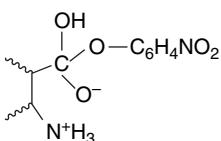


This mechanism can reduce the overall activation energy of the reaction in at least two ways. The partial transfer of a proton to the carbonyl oxygen increases its electrophilicity. Likewise, partial deprotonation of the amino group increases its nucleophilicity.

Intramolecular general base-catalyzed water attack has also been observed for phenyl 2-aminobenzoate.⁷³



Similar results have been obtained with β -aminoalkyl 4-nitrophenolates, with observed rate enhancements of $\sim 10^4$.⁷⁴ Besides the general base-catalyzed mechanism, it has been suggested that the kinetically equivalent electrostatic stabilization of the tetrahedral intermediate by the protonated amino group might be involved.



Neither of these systems is likely to react by direct nucleophilic catalysis, because that would require formation of a four-membered ring. The pH-rate profiles for these reactions are shown in Figure 7.13. Note that the plateau region for the aromatic amines occurs at lower pH than for the alkylamines, reflecting the difference in the basicity of the two types of amino groups.

Certain molecules that can permit concerted proton transfers are efficient catalysts for reaction at carbonyl centers. An example is the catalytic effect that 2-pyridone

⁷². F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, **91**, 5346 (1969).

⁷³. T. H. Fife, R. Singh, and R. Bembi, *J. Org. Chem.*, **67**, 3179 (2002).

⁷⁴. M. I. Page, D. Pender, and G. Bernath, *J. Chem. Soc., Perkin Trans. 2*, 867 (1986).

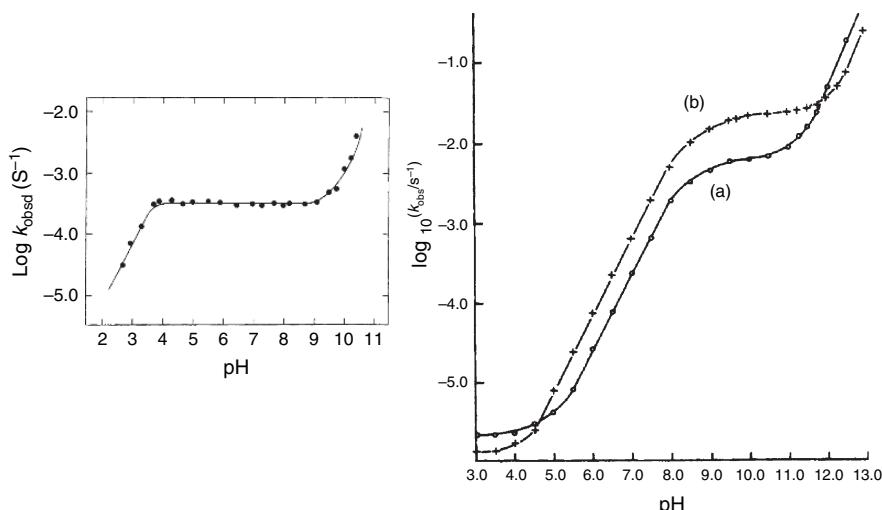
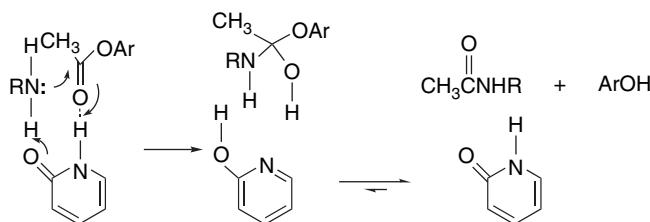
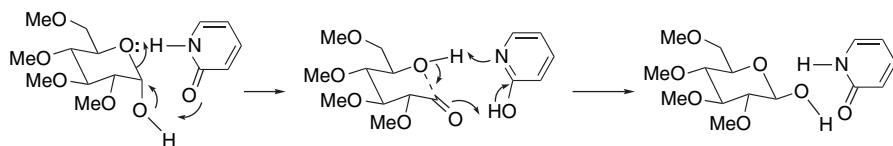


Fig. 7.13. pH-Rate profiles for phenyl *o*-aminobenzoates (left, 50°C) and β -aminoalkyl 4-nitrophenolates (right, 30°C). Reproduced from *J. Org. Chem.*, **67**, 3179 (2002) and *J. Chem. Soc., Perkin Trans.*, **2**, 867 (1986), respectively, by permission of the American Chemical Society and the Royal Society of Chemistry.

has on the aminolysis of esters (see also p. 661–662). Although neither a strong base ($\text{p}K_{\text{aH+}} = 0.75$) nor a strong acid ($\text{p}K_a = 11.6$), 2-pyridone is an effective catalyst of the reaction of *n*-butylamine with 4-nitrophenyl acetate.⁷⁵ The overall rate is more than 500 times greater when 2-pyridone acts as the catalyst than when a second molecule of butylamine (acting as a general base) is present in the TS. 2-Pyridone has been called a *tautomeric catalyst* to emphasize its role in proton transfer. Such molecules are also called *bifunctional catalysts*, since two atoms in the molecule are involved in the proton transfer process.



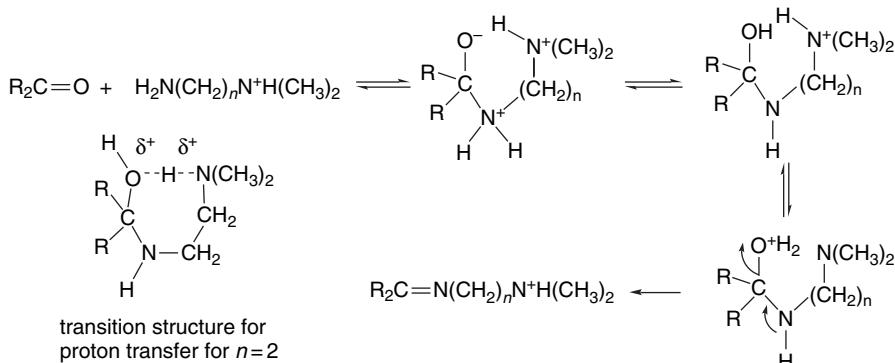
2-Pyridone also catalyzes epimerization of the anomeric position of the tetramethyl ether of glucose. The mechanism involves two double-proton transfers. The first leads to a ring-opened intermediate and the second results in ring closure to the isomerized product.



⁷⁵. P. R. Rony, *J. Am. Chem. Soc.*, **91**, 6090 (1969).

Other compounds such as benzoic acid and pyrazole, which can effect similar concerted proton transfer and avoid charged species, also catalyze this and related reactions.⁷⁶

Another type of bifunctional catalysis has been noted with α , ω -diamines in which one of the amino groups is primary and the other tertiary. These substituted diamines are from several times to as much as 1000 times more reactive toward imine formation than monofunctional amines.⁷⁷ This is attributed to a catalytic intramolecular proton transfer.



The rate enhancement is greatest for $n = 2$ (1000) but still significant for $n = 3$ (a factor of 10). As the chain is lengthened to $n = 4$ and $n = 5$, the rate enhancement, if any, is minor. This relationship reflects the fact that when $n = 4$ or 5, the TS for the intramolecular proton transfer would have to involve rings of nine and ten atoms, respectively, which is not structurally advantageous. The particularly rapid reaction when $n = 2$ corresponds to the possibility of a proton transfer via a seven-membered cyclic TS. If the assumption is that the proton is transferred in a colinear fashion through a hydrogen bond, this represents a favorable TS geometry.

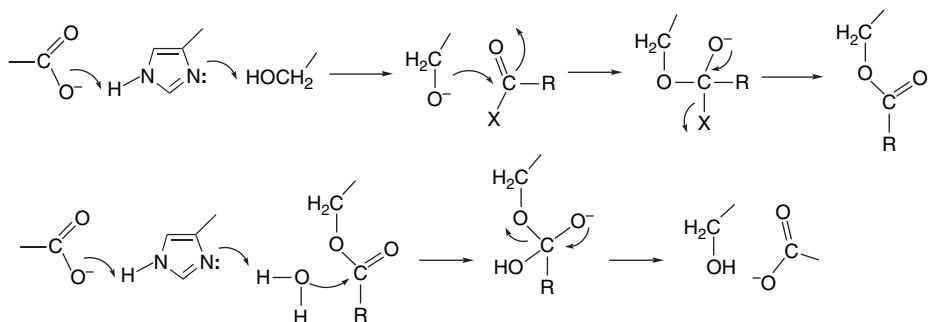
These examples serve to illustrate the concept of intramolecular catalysis and the idea that favorable juxtaposition of acidic, basic, or nucleophilic sites can markedly accelerate some of the common reactions of carbonyl compounds. Nature has used optimal placement of functional groups to achieve the catalytic activity of enzymes. The functional groups employed to accomplish this are those present on the amino acid residues found in proteins. The acidic sites available include phenolic (tyrosine) or carboxylic acid groups (glutamic acid and aspartic acid). Basic sites include the imidazole ring (histidine) and the ϵ -amino group of lysine. This latter group and the guanidine group in arginine are normally protonated at physiological pH and can stabilize nearby anionic centers by electrostatic effects. Thiol (cysteine) and hydroxy (threonine and serine) groups and the deprotonated carboxy groups of glutamic and aspartic acids are potential nucleophilic sites.

A good example of an enzyme active site is the “catalytic triad” found in various hydrolytic enzymes. The active sites of these enzymes contain a hydroxy group (from serine), a carboxylate group (from glutamic or aspartic acid), and an imidazole ring (from histidine). The three groups are aligned in such a way that the carboxylate group assists a proton transfer from the serine hydroxy to the imidazole. This enhances the nucleophilicity of the serine toward the carbonyl group of the substrate undergoing

⁷⁶. P. R. Rony, *J. Am. Chem. Soc.*, **90**, 2824 (1968).

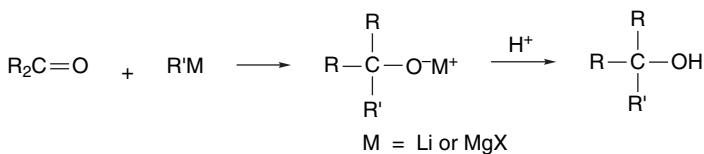
⁷⁷. J. Hine, R. C. Dempsey, R. A. Evangelista, E. T. Jarvi, and J. M. Wilson, *J. Org. Chem.*, **42**, 1593 (1977); J. Hine and Y. Chou, *J. Org. Chem.*, **46**, 649 (1981).

hydrolysis. The acyl group is transferred to the serine through a tetrahedral intermediate. Breakdown of the tetrahedral intermediate is accompanied by transfer of a proton back to the leaving group. Subsequently, a water molecule is activated by the same mechanism to cleave the acyl enzyme intermediate.⁷⁸

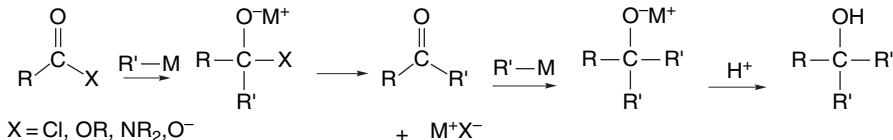


7.6. Addition of Organometallic Reagents to Carbonyl Groups

The addition of carbon nucleophiles, such as organometallic compounds, to carbonyl groups is one of the main methods of formation of carbon-carbon bonds. Such reactions are extremely important in synthesis and are discussed extensively in Chapter 7 of Part B. Here, we examine some of the fundamental mechanistic aspects of the addition of organometallic reagents to carbonyl groups. Organolithium and organomagnesium reagents are highly reactive toward most carbonyl compounds. With aldehydes and ketones, the tetrahedral adduct is stable and alcohols are isolated after protonation of the adduct.



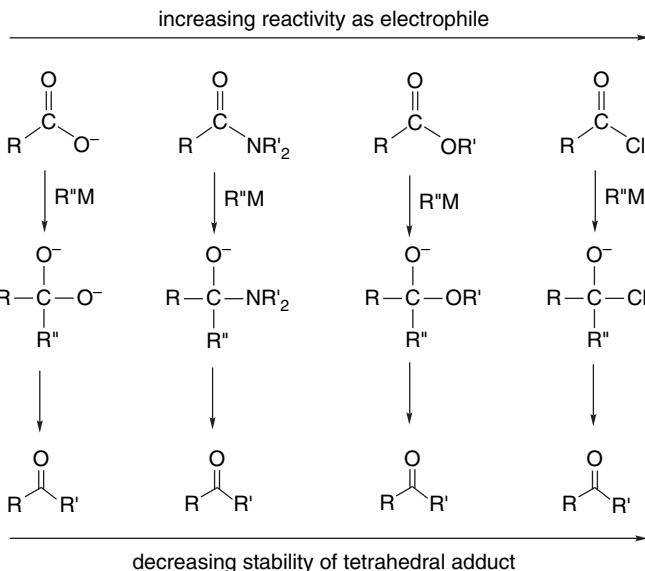
For acyl chlorides, anhydrides, esters, carboxamides, and carboxylate anions, the tetrahedral adduct can undergo elimination. The elimination forms a ketone, permitting a second addition step to occur.



The rate at which dissociation of the tetrahedral adduct occurs depends on the reactivity of the heteroatom substituent as a leaving group. The order of stability of the tetrahedral

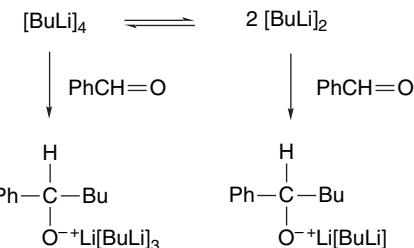
⁷⁸. D. M. Blow, *Acc. Chem. Res.*, **9**, 145 (1976); R. M. Garavito, M. G. Rossman, P. Argos, and W. Eventoff, *Biochemistry*, **16**, 5065 (1977); M. L. Bender, R. J. Bergeron, and M. Komiyama, *The Bioorganic Chemistry of Enzymatic Catalysis*, Wiley, New York, 1984, pp. 121–123; C.-H. Hu, T. Brinck, and K. Hult, *Int. J. Quantum Chem.*, **69**, 89 (1998).

adducts is shown in the diagram below. In some cases, the product can be controlled by the choice of reaction conditions. Ketones are isolated under conditions where the tetrahedral intermediate is stable until hydrolyzed, whereas tertiary alcohols are formed when the tetrahedral intermediate decomposes while unreacted organometallic reagent remains. Ketones can also be obtained with certain organometallic reagents that react only with acyl halides.



7.6.1. Kinetics of Organometallic Addition Reactions

The reactions of organolithium reagents with simple carbonyl compounds are very fast and there is relatively little direct kinetic evidence concerning the details of the reaction. It is expected that one important factor in determining reactivity is the degree of aggregation of the organolithium reagent (see p. 588). It is possible to follow the reaction of benzaldehyde with *n*-butyllithium at -85°C, using NMR techniques that are capable of monitoring fast reactions. The reaction occurs over a period of 50–300 ms. It has been concluded that the dimer of *n*-butyllithium is more reactive than the tetramer by a factor of about 10. As the reaction proceeds, the product alkoxide ion is incorporated into butyllithium aggregates, which gives rise to additional species with different reactivities.⁷⁹



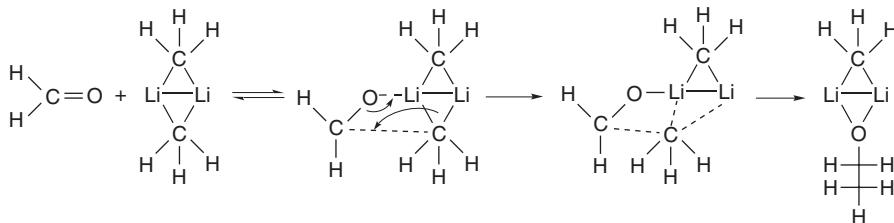
⁷⁹. J. F. McGarrity, C. A. Ogle, Z. Brich, and H.-R. Loosli, *J. Am. Chem. Soc.*, **107**, 1810 (1985).

The rates for the reaction of several aromatic ketones with alkylolithium reagents have been examined. The reaction of 2,4-dimethyl-4'-(methylthio)benzophenone with methyl lithium in ether exhibits the rate expression

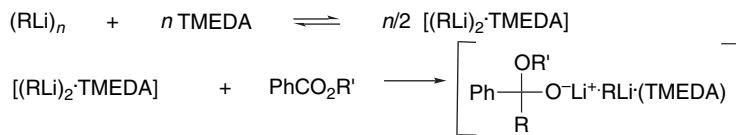
$$\text{Rate} = k[\text{MeLi}]^{1/4} [\text{ketone}]$$

This is consistent with a mechanism in which monomeric methyllithium, in equilibrium with the tetramer, is the reactive nucleophile.⁸⁰ Most other studies have indicated considerably more complex behavior. The rate data for reaction of 3-methyl-1-phenyl-1-butanone with *s*-butyllithium and *n*-butyllithium in cyclohexane can be fit to a mechanism involving product formation both through a complex of the ketone with alkylolithium aggregate and by reaction with dissociated alkylolithium.⁸¹ Initial formation of a complex is indicated by a shift in the carbonyl absorption band in the infrared spectrum. Complex formation presumably involves a Lewis acid-base interaction between the lithium ions and carbonyl oxygen in the alkylolithium cluster. In general terms, it appears likely that alkylolithium reagents have the possibility of reacting through any of several aggregated forms.

MO modeling (HF/3-21G) of the reaction of organolithium compounds with carbonyl groups has examined the interaction of formaldehyde with the dimer of methyllithium. The reaction is predicted to proceed by initial complexation of the carbonyl group at lithium, followed by a rate-determining formation of the new carbon-carbon bond. The cluster then reorganizes to incorporate the newly formed alkoxide ion.⁸² The TS is reached very early in the second step with only slight formation of the C–C bond. This feature is consistent with the fast and exothermic nature of the addition step.



The kinetics of addition of alkylolithium reagents to esters has been studied using a series of ethyl benzoates.⁸³ The rates show a rather complex dependence on both alkyl-lithium concentration and the nature of aryl substituents. The rapid formation of an initial ester-alkylolithium complex can be demonstrated. It is believed that product can be formed by reaction with aggregated or monomeric alkylolithium reagent. *N,N,N,N*-Tetramethylethylenediamine greatly accelerates the reaction, presumably by dissociating the organometallic aggregate (see Section 6.1).



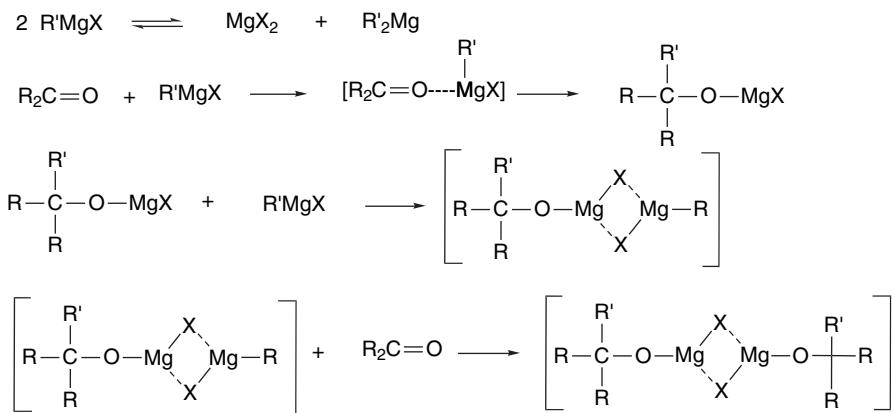
⁸⁰ S. G. Smith, L. F. Charbonneau, D. P. Novak, and T. L. Brown, *J. Am. Chem. Soc.*, **94**, 7059 (1972).

⁸¹ M. A. Al-Aseer and S. G. Smith, *J. Org. Chem.*, **49**, 2608 (1984).

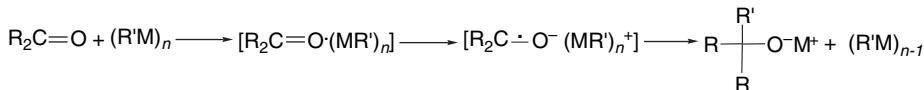
⁸² E. Kaufmann, P. v. R. Schleyer, K. N. Houk, and Y.-D. Wu, *J. Am. Chem. Soc.*, **107**, 5560 (1985).

⁸³ M. A. Al-Aseer, B. D. Allison, and S. G. Smith, *J. Org. Chem.*, **50**, 2715 (1985).

The kinetics of reaction of Grignard reagents with ketones is also subject to a number of complications. The purity of the magnesium metal used in the preparation of the Grignard reagent is crucial since trace transition metal impurities have a major effect on the observed reaction rates. One of the most thorough studies available involves the reaction of methylmagnesium bromide with 2-methylbenzophenone in diethyl ether.⁸⁴ The results suggest a mechanism similar to that discussed for alkylolithium reactions. There is initial complexation between the ketone and Grignard reagent. The main Grignard species, CH_3MgBr , is in equilibrium with $(\text{CH}_3)_2\text{Mg}$, which can contribute to the overall rate. The product alkoxide forms a complex with the Grignard reagent to give yet another reactive species. The general mechanistic scheme is outlined below.



There is another possible mechanism for addition of organometallic reagents to carbonyl compounds, which involves a discrete electron transfer step.⁸⁵



The distinguishing feature of this mechanism is the second step, in which an electron is transferred from the organometallic reagent to the carbonyl compound to give the radical anion of the carbonyl compound. Subsequent collapse of the radical ion pair with transfer of an alkyl group to carbon gives the same product that is formed by the direct nucleophilic addition mechanism. The electron transfer mechanism would be expected to be favored by structural features that stabilize the radical anion intermediate. Aryl ketones and diones fulfill this requirement and evidence for the electron transfer mechanism has been accumulated for such ketones. In several cases it is possible to observe a radical anion intermediate by ESR spectroscopy.⁸⁶ (See Section 11.1.3 for a discussion of some of the limits of this methodology.) The relative importance of the electron transfer mechanisms also depends on the ease of oxidation of the organometallic reagent. Allyllithium is particularly likely to react by the electron transfer mechanism because of its ease of oxidation.⁸⁷

⁸⁴. E. C. Ashby, J. Laemmle, and H. M. Neumann, *J. Am. Chem. Soc.*, **94**, 5421 (1972).

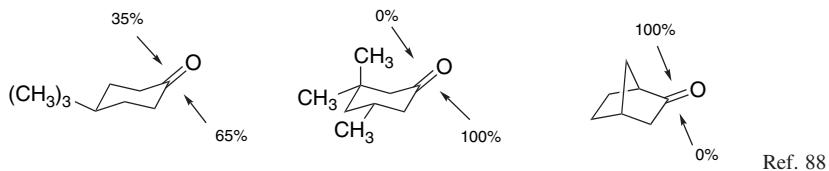
⁸⁵. E. C. Ashby, *Pure Appl. Chem.*, **52**, 545 (1980); E. C. Ashby, J. Laemmle, and H. M. Neuman, *Acc. Chem. Res.*, **7**, 272 (1974).

⁸⁶. K. Maruyama and T. Katagiri, *J. Am. Chem. Soc.*, **108**, 6263 (1986); E. C. Ashby and A. B. Goel, *J. Am. Chem. Soc.*, **103**, 4983 (1981); T. Lund, M. L. Pedersen, and L. A. Frandsen, *Tetrahedron Lett.*, **35**, 9225 (1994).

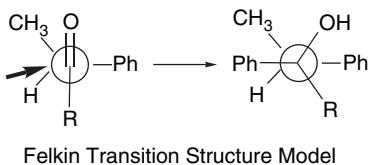
⁸⁷. J. J. Gajewski, W. Bocian, N. J. Harris, L. P. Olson, and J. P. Gajewski, *J. Am. Chem. Soc.*, **121**, 326 (1999).

7.6.2. Stereoselectivity of Organometallic Addition Reactions

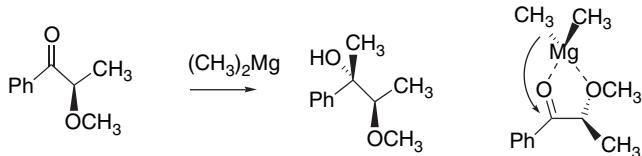
The stereochemistry of organometallic additions with carbonyl compounds fits into the general pattern for nucleophilic attack discussed in Chapter 2. With 4-*t*-butylcyclohexanone there is a preference for equatorial approach, but the selectivity is low. Enhanced steric factors promote stereoselective addition.



The stereochemistry of organometallic additions in acyclic carbonyl compounds has also been examined. Additions of Grignard reagents to ketones and aldehydes was one of the reactions that led to the formulation of Cram's rule (see p. 179).⁸⁹ Many ketones and aldehydes have subsequently been subjected to studies to determine the degree of stereoselectivity. Cram's rule is obeyed when no special complexing functional groups are present near the reaction site. One series of studies is summarized in Table 7.5. These data show consistent agreement with Cram's rule and the Felkin TS, as discussed in Section 2.4.1.2.



The role of chelation has been investigated both experimentally and computationally. In experimental studies, it was found that an α -methoxy group increases the rate of addition of dimethylmagnesium to propiophenone approximately 2000-fold.⁹⁰ The rate acceleration indicates that chelation not only controls stereochemistry but also facilitates the addition step. The methyl group adds from the less hindered face of the chelate. The reaction gives a greater than 99:1 preference for chelation-controlled addition.



⁸⁸ E. C. Ashby and S. A. Noding, *J. Org. Chem.*, **44**, 4371 (1979).

⁸⁹ D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952); D. J. Cram and J. D. Knight, *J. Am. Chem. Soc.*, **74**, 5835 (1952); F. A. Abd Elhafez and D. J. Cram, *J. Am. Chem. Soc.*, **74**, 5846 (1952).

⁹⁰ S. V. Frye, E. L. Eliel, and R. Cloux, *J. Am. Chem. Soc.*, **109**, 1862 (1987); X. Chen, E. R. Hortelano, E. L. Eliel, and S. V. Frye, *J. Am. Chem. Soc.*, **112**, 6130 (1990).

Table 7.5. Stereoselectivity in Addition of Organometallic Reagents to Some Chiral Aldehydes and Ketones^a

R	L	M	S	R'M	Percent of major product
H	Ph	CH ₃	H	CH ₃ MgBr	71
H	Ph	CH ₃	H	PhMgBr	78
H	t-C ₄ H ₉	CH ₃	H	PhMgBr	98
CH ₃	Ph	CH ₃	H	C ₂ H ₅ Li	93
CH ₃	Ph	CH ₃	H	C ₂ H ₅ MgBr	88
CH ₃	Ph	CH ₃	H	t-C ₄ H ₉ MgBr	96
C ₂ H ₅	Ph	CH ₃	H	CH ₃ MgBr	86
C ₂ H ₅	Ph	CH ₃	H	CH ₃ Li	94
C ₂ H ₅	Ph	CH ₃	H	PhLi	85
i-C ₃ H ₇	Ph	CH ₃	H	CH ₃ MgBr	90
i-C ₃ H ₇	Ph	CH ₃	H	CH ₃ Li	96
i-C ₃ H ₇	Ph	CH ₃	H	PhLi	96
t-C ₄ H ₉	Ph	CH ₃	H	CH ₃ MgBr	96
t-C ₄ H ₉	Ph	CH ₃	H	CH ₃ Li	97
t-C ₄ H ₉	Ph	CH ₃	H	PhLi	98
Ph	Ph	CH ₃	H	CH ₃ MgBr	87
Ph	Ph	CH ₃	H	CH ₃ Li	97
Ph	Ph	CH ₃	H	t-C ₄ H ₉ MgBr	96

a. Data from O. Arjona, R. Perez-Ossorio, A. Perez-Rubalcaba, and M. L. Quiroga, *J. Chem. Soc., Perkin Trans. 2*, 587 (1981); C. Alvarez-Ibarra, P. Perez-Ossorio, A. Perez-Rubalcaba, M. L. Quiroga, and M. J. Santesmases, *J. Chem. Soc., Perkin Trans. 2*, 1645 (1983).

An α -benzyloxy group was found to cause rate acceleration of more than 100, relative to a nonchelating α -trimethylsiloxy group. On the other hand, a 4-benzyloxy group in 2-butanone (β -substitution) caused only a 20% rate increase.

Computational studies were carried out on the addition reaction of dimethylmagnesium to several α - and β -substituted carbonyl compounds, including methoxyacet-aldehyde, methoxyacetone, and 3-methoxypropanal. MP2/6-31+G* energies were computed for structures minimized with HF/3-31G calculations.⁹¹ Some of the salient features of this study are summarized in Figure 7.14, which compares relative energy of reactants, prereaction complexes, TS, and products. In Panel A, the energies of acetone (A), methoxyacetone (B), and methoxyacetaldehyde (C) are shown. Both of the chelated TSs have lower ΔH than for acetone, in agreement with the experimental finding of rate acceleration by an α -methoxy substituent. The structures of the TS for the chelated reactants also indicate an earlier TS than for acetone. Furthermore, IRC analysis indicates that chelation is maintained throughout the course of the reaction. Use of a continuum solvent model ($\epsilon = 7.58$) resulted in only small changes in the computed ΔH^\ddagger . These results are all consistent with chelation control of reagent approach for α -methoxy substituents.

The results for the β -methoxy substituents in 3-methoxypropanal (D) and 4-methoxy-2-butanone (E) are less clear. There are two chelated TSs of comparable energy, and only the chairlike TS suggests strong diastereoselectivity. There is also a qualitative difference in regard to the experimental kinetic studies. The

SECTION 7.6

Addition of
Organometallic Reagents
to Carbonyl Groups

⁹¹ S. Mori, M. Nakamura, E. Nakamura, N. Koga, and K. Morokuma, *J. Am. Chem. Soc.*, **117**, 5055 (1995).

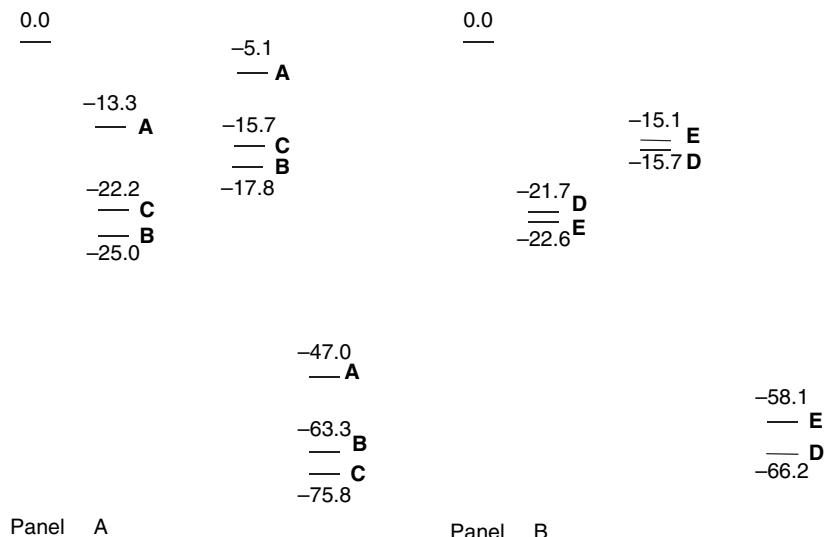
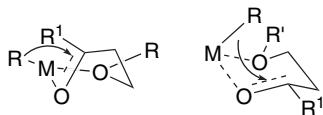


Fig. 7.14. Panel A: Relative ΔH of reactant complex, transition structure, and products at 0°C (including ZPE correction) for acetone (**A**), methoxyacetone (**B**), and methoxyacetaldehyde (**C**). Panel B: Relative ΔH at 0°C (including ZPE correction) for 3-methoxypropanal (**D**) and 4-methoxy-2-butanone (**E**). Data from *J. Am. Chem. Soc.*, **117**, 5055 (1995).

calculated activation barriers for β -methoxy groups are similar to those for α -methoxy substituents, whereas the experimental kinetic studies indicate that β -substituents are much less activating.

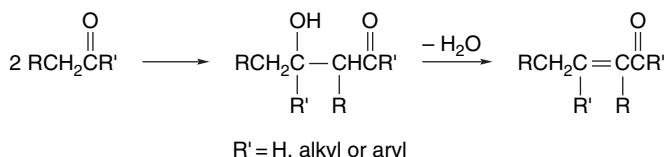


7.7. Addition of Enolates and Enols to Carbonyl Compounds: The Aldol Addition and Condensation Reactions

7.7.1. The General Mechanisms

The prototypical *aldol addition reaction* is the acid- or base-catalyzed dimerization of a ketone or aldehyde.⁹² Under certain conditions, the reaction product may undergo dehydration leading to an α,β -unsaturated aldehyde or ketone. This variant can be called the *aldol condensation*.

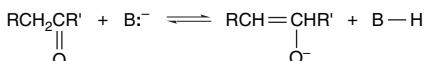
⁹². A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 1 (1968); R. L. Reeves, in *Chemistry of the Carbonyl Group*, S. Patai, ed., Interscience, New York, 1966, pp. 580–593; H. O. House, *Modern Synthetic Reactions*, 2nd Edition, W. A. Benjamin, Menlo Park, CA, 1972, pp. 629–682; C. H. Heathcock, in *Asymmetric Synthesis*, Vol 2, J. D. Morrison, ed., 1984; C. H. Heathcock, in *Comprehensive Carbanion Chemistry*, E. Bunzel and T. Durst, eds., Elsevier, Amsterdam, 1984, Chap. 6.



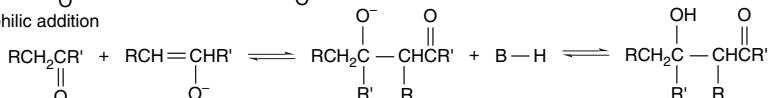
The mechanism of the base-catalyzed reaction involves equilibrium formation of the enolate ion, followed by addition of the enolate to the carbonyl group of the aldehyde or ketone. These reactions of aldehydes occur in dilute basic solution at or below room temperature. Under somewhat more vigorous conditions, such as higher temperature or increased base concentration, the elimination step occurs.

1. Addition phase

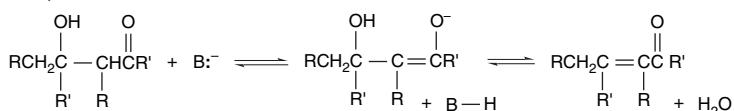
a. Enolate formation



b. Nucleophilic addition



2. Dehydration phase

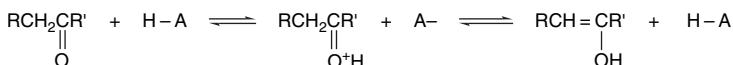


It is also possible to carry out the aldol condensation under acidic conditions. The mechanism was established in detail for acetaldehyde.⁹³ Under conditions of acid catalysis, it is the enol form of the aldehyde or ketone that functions as the nucleophile. The carbonyl group is activated toward nucleophilic attack by O-protonation.

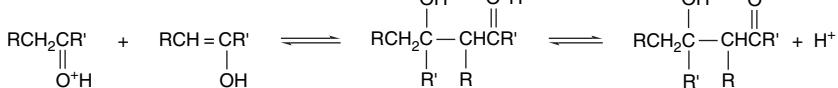
Acid-Catalyzed Mechanism

1. Addition phase

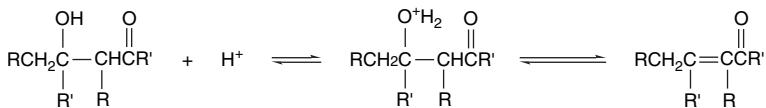
a. Enolization



b. Addition



2. Dehydration phase

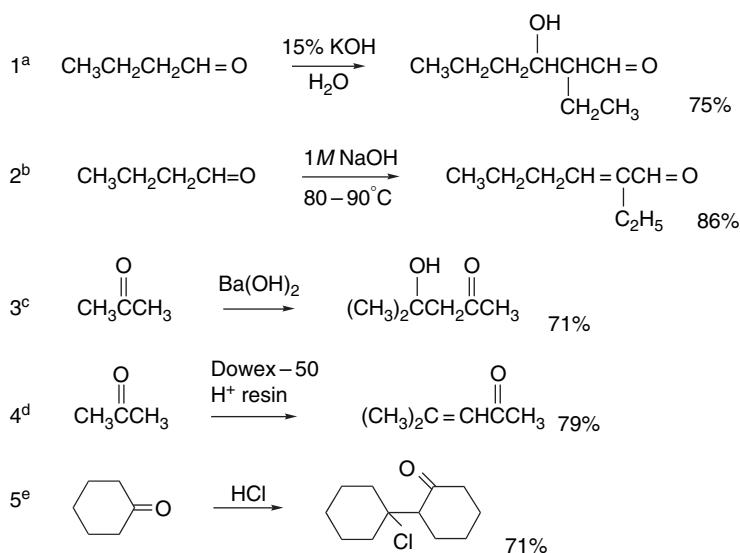


⁹³ L. M. Baigrie, R. A. Cox, H. Slebocka-Tilk, M. Tencer, and T. T. Tidwell, *J. Am. Chem. Soc.*, **107**, 3640 (1985).

In general, the reactions in the addition phase of both the base- and acid-catalyzed mechanisms are reversible. The equilibrium constant for addition is usually unfavorable for ketones. The equilibrium constant for the dehydration phase is usually favorable because of the conjugated α,β -unsaturated carbonyl system that is formed. When the reaction conditions are sufficiently vigorous to cause dehydration, the overall reaction can go to completion, even if the equilibrium constant for the addition step is unfavorable.

Several examples of aldol addition and condensation are given in Scheme 7.3. Entries 1 and 2 are typical aldol reactions of aldehydes, with and without dehydration. The reaction in Entry 1 was done with 15% KOH in aqueous solution at room temperature. The condensation reaction in Entry 2 was carried out at 80°–90°C with 1 M NaOH. Entries 3 and 4 show addition and condensation reactions of acetone. Entry 3 features a clever way of overcoming the unfavorable equilibrium of the addition step. The basic catalyst is contained in a separate compartment of a Soxhlet extractor. Acetone is repeatedly passed over the basic catalyst by distillation and the condensate returns to the flask. Since there is no catalyst present in the flask, the adduct remains stable. The concentration of the addition product builds up as the more volatile acetone distills preferentially. The acid-catalyzed condensation in Entry 4 is carried out similarly. The acetone is continuously passed over the acidic resin, and the reaction is driven forward by the stability of the conjugated condensation product. In Entry 5, the final product is a β -chloroketone, presumably formed by addition of HCl to a dehydrated intermediate.

Scheme 7.3. Examples of Aldol Addition and Condensation Reactions



a. V. Grignard and A. Vesterman, *Bull. Chim. Soc. Fr.*, **37**, 425 (1925); *Chem. Abstr.*, **19**, 1852 (1925).

b. M. Hausemann, *Helv. Chim. Acta*, **34**, 1482 (1951).

c. J. B. Conant and N. Tuttle, *Org. Synth.*, **I**, 199 (1941).

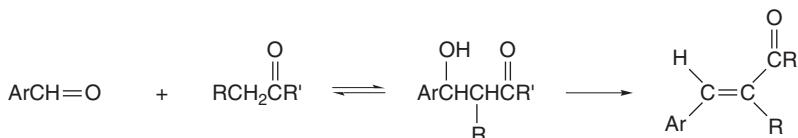
d. N. B. Lorette, *J. Org. Chem.*, **22**, 346 (1957).

e. O. Wallach, *Berichte*, **40**, 70 (1907); E. Wenkert, S. K. Bhattacharya, and E. M. Wilson, *J. Chem. Soc.*, 5617 (1964).

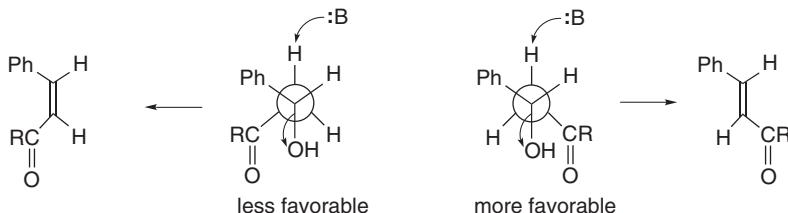
SECTION 7.7

Addition of Enolates and Enols to Carbonyl Compounds: The Aldol Addition and Condensation Reactions

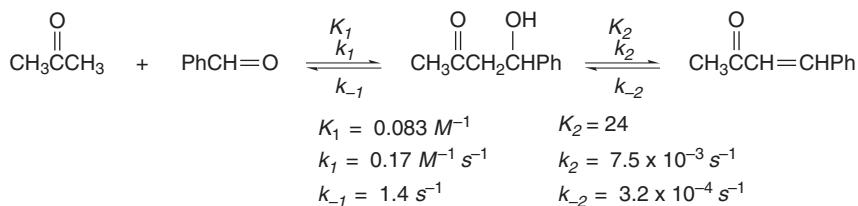
Aldol addition and condensation reactions involving two different carbonyl compounds are called *mixed aldol reactions*. To be useful as a method for synthesis there must be some basis for controlling which carbonyl component serves as the electrophile and which acts as the enolate precursor. One of the most general mixed aldol condensations involves the use of aromatic aldehydes with alkyl ketones or aldehydes. There are numerous examples of both acid- and base-catalyzed mixed aldol condensations involving aromatic aldehydes. The reaction is sometimes referred to as the *Claisen-Schmidt condensation*. Aromatic aldehydes are incapable of enolization and cannot function as the nucleophilic component. Furthermore, dehydration is especially favorable because the resulting enone is conjugated with the aromatic ring.



There is a pronounced preference for the formation of a *trans* double bond in the Claisen-Schmidt condensation of methyl ketones. This stereoselectivity arises in the dehydration step. In the TS for elimination to a *cis* double bond, an unfavorable steric interaction develops between the substituent (R) and the phenyl group. This interaction is absent in the TS for elimination to the *trans* double bond.



The dehydration reactions require somewhat higher activation energies than the addition step. Detailed studies have provided rate and equilibrium constants for the individual steps in a few cases. The results for the acetone-benzaldehyde system in the presence of hydroxide ion are given below. Note that K_2 is sufficiently large to drive the first equilibrium forward.



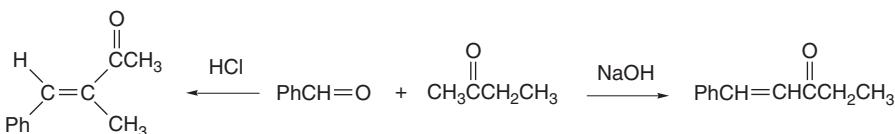
Ref. 94

Additional insight into the factors affecting product structure was obtained by study of the condensation of 2-butanone with benzaldehyde.⁹⁵ When catalyzed by base,

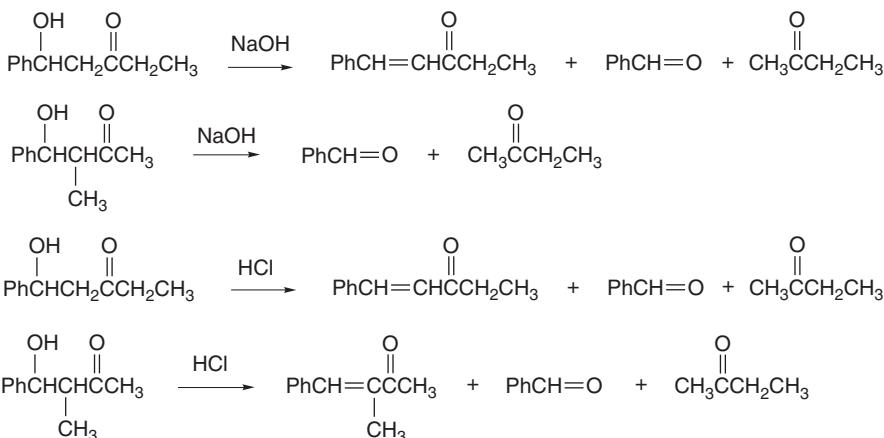
⁹⁴ J. P. Guthrie, J. Cossar, and K. F. Taylor, *Can. J. Chem.*, **62**, 1958 (1984).

⁹⁵ M. Stiles, D. Wolf, and G. V. Hudson, *J. Am. Chem. Soc.*, **81**, 628 (1959); D. S. Noyce and W. A. Pryor, **81**, 618 (1959); D. S. Noyce and L. R. Snyder, **81**, 620 (1959); D. S. Noyce and W. L. Reed, *J. Am. Chem. Soc.*, **81**, 624 (1959).

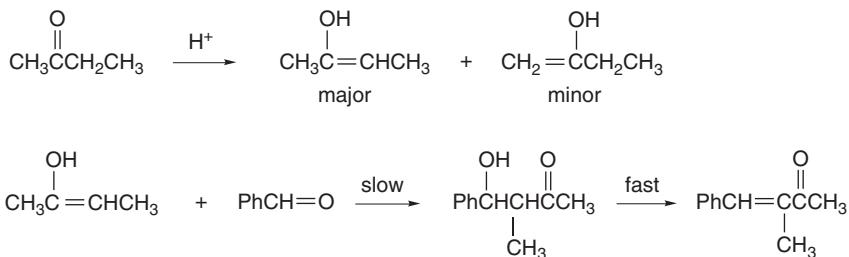
2-butanone reacts with benzaldehyde at the methyl group to give 1-phenylpent-1-en-3-one. Under acid-catalyzed conditions the product is the result of condensation at the methylene group, namely 3-methyl-4-phenylbut-3-en-2-one.



The results indicate that the product ratio is determined by the competition among the various reaction steps. Under the reaction conditions used, it is not possible to isolate the intermediate ketols because the addition step is rate limiting. These intermediates can be prepared by alternative methods and they behave as shown in the following equations.



These results establish that the base-catalyzed dehydration is slow relative to the reverse of the addition step for the branched-chain isomer. The reason for selective formation of the straight-chain product under conditions of base catalysis is then apparent. In base, the straight-chain ketol is the only intermediate that is dehydrated. The branched-chain ketol reverts to starting material. Under acid conditions, both intermediates are dehydrated. However, under acid-catalyzed conditions the branched-chain ketol is formed most rapidly because of the preference for acid-catalyzed enolization to give the more-substituted enol (see Section 6.3).



In general, the product ratio of a mixed aldol condensation depends upon the individual reaction rates in the equilibrium process. Most methyl ketones show a pattern similar

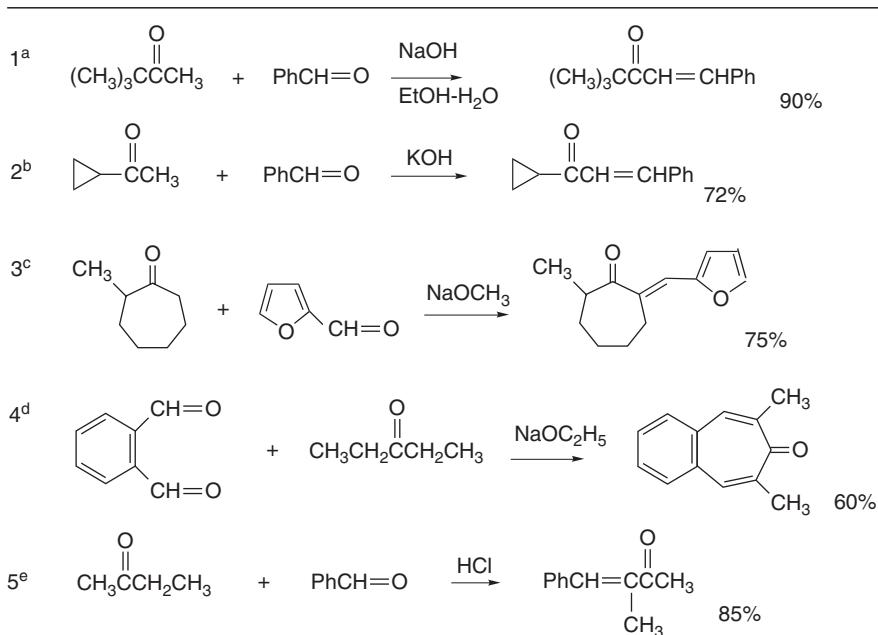
to 2-butanone in reactions with aromatic aldehydes. Base catalysis favors reaction at a methyl position over a methylene group, whereas acid catalysis gives the opposite preference.

Scheme 7.4 presents some representative examples of Claisen-Schmidt reactions. Entries 1 and 2 are typical base-catalyzed condensations at methyl groups. Entry 3 illustrates the use of a cyclic ketone, and reaction occurs at the methylene group, where dehydration is possible. The stereochemistry presumably places the furan ring *trans* to the carbonyl group for maximum conjugation. Entry 4 shows the use of phthalaldehyde to effect a cyclization. Entry 5 illustrates the preference for condensation at the more-substituted position under acidic conditions.

7.7.3. Control of Regiochemistry and Stereochemistry of Aldol Reactions of Ketones

The wide synthetic applicability of the aldol reaction depends on the ability to achieve both versatility in reactants and control of regiochemistry and stereochemistry. The term *directed aldol addition*⁹⁶ is applied to reaction conditions that are designed to achieve specific regio- and stereochemical outcomes. Control of product structure requires that one reactant act exclusively as the electrophile and the other exclusively

Scheme 7.4. Mixed Aldol Condensation Reactions of Ketones and Aromatic Aldehydes



a. G. A. Hill and G. Bramann, *Org. Synth.*, **I**, 81 (1941).

b. S. C. Bunce, H. J. Dorsman, and F. D. Popp, *J. Chem. Soc.*, 303 (1963).

c. A. M. Islam and M. T. Zenality, *J. Am. Chem. Soc.*, **79**, 6023 (1957).

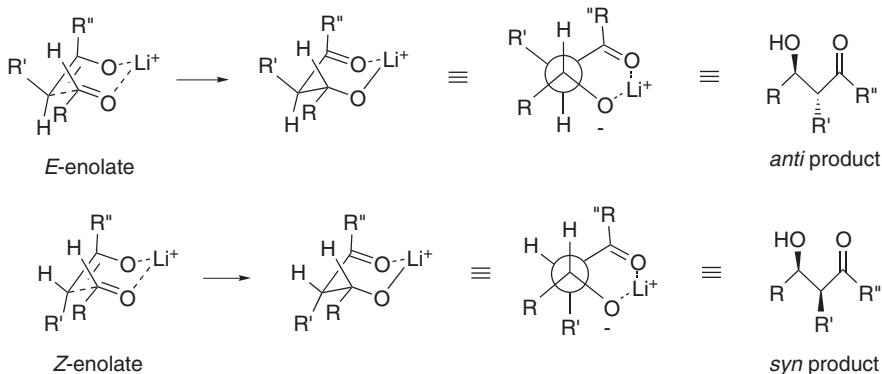
d. D. Meuche, H. Strauss, and E. Heilbronner, *Helv. Chim. Acta*, **41**, 2220 (1958).

e. M. E. Kronenberg and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **84**, 17 (1965).

⁹⁶. T. Mukaiyama, *Org. React.*, **28**, 203 (1982).

as the nucleophile. This can be achieved by preforming the reactive nucleophilic enolate and ensuring that the addition step is fast relative to proton exchange between the nucleophilic and electrophilic reactants. These reactions are under *kinetic control*, both at the stage of forming the enolate and at the addition step. The enolate that is to serve as the nucleophile is generated stoichiometrically, usually with lithium as the counterion in an aprotic solvent. Under these conditions enolates do not equilibrate with the other regio- or stereoisomeric enolates that can be formed from the ketone (see Section 6.3). The electrophilic carbonyl compound is then added. The structure of the reaction product is determined primarily by two factors: (1) the *E*- or *Z*-configuration of the initial enolate and (2) the structure of the TS for addition to the electrophilic carbonyl group.

The fundamental mechanistic concept for stereochemical control of an aldol reaction under conditions of kinetic control is based on a cyclic TS in which both the carbonyl and enolate oxygen are coordinated to a Lewis acid.⁹⁷ This Lewis acid promotes reaction by enhancing the carbonyl group electrophilicity and by bringing the reactants together in the TS. It is further assumed that the structure of this TS is sufficiently similar to that of chair cyclohexane that the conformational concepts for cyclohexane derivatives can be applied. We use the Li⁺ cation in our initial discussion, but other metal cations and electrophilic atoms can play the same role. We discuss reactions of boron, titanium, and tin enolates shortly. In the structures below, the reacting aldehyde is shown with R rather than H in the equatorial-like position. The orientation of the aldehyde substituent establishes the degree of facial selectivity. A consequence of the cyclic TS is that the reaction is *stereospecific* with respect to the *E*- or *Z*-configuration of the enolate. The *E*-enolate will give the *anti*-aldol product whereas the *Z*-enolate will give the *syn*-aldol.

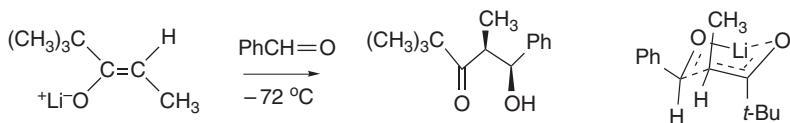


Owing to the dependence of the product stereochemistry on enolate configuration, control of the stereochemistry of enolate formation is important. For ketones with one relatively bulky group, the *Z*-enolate is favored, resulting in formation of the *syn*-aldol product. This is the case, for example, in the reaction of 2,2-dimethyl-3-pentanone and

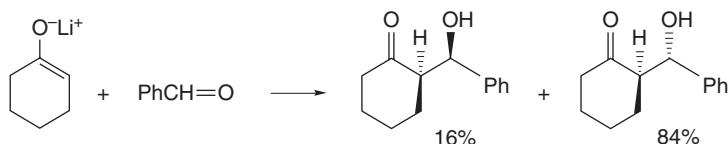
⁹⁷. H. E. Zimmerman and M. D. Traxler, *J. Am. Chem. Soc.*, **79**, 1920 (1957); C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).

Addition of Enolates and Enols to Carbonyl Compounds: The Aldol Addition and Condensation Reactions

benzaldehyde.⁹⁷ The product stereochemistry is correctly predicted if the aldehyde is in a conformation with the phenyl substituent in an equatorial position in the cyclic TS.



The enolates derived from cyclic ketones are necessarily *E*-isomers. The enolate of cyclohexanone reacts with benzaldehyde to give both possible stereoisomeric products under kinetically controlled conditions. The stereoselectivity is about 6:1 in favor of the *anti* isomer under optimum conditions.⁹⁸



While ketones with one tertiary alkyl substituent give mainly the *Z*-enolate, less highly substituted ketones usually give mixtures of *E*- and *Z*-enolates.⁹⁹ Therefore efforts aimed at expanding the scope of stereoselective aldol condensations have been directed at two facets of the problem: (1) control of enolate stereochemistry, and (2) enhancement of the degree of stereoselectivity in the addition step. The *E*:*Z* ratio can be modified by the precise conditions for formation of the enolate. For example, the *E*:*Z* ratio for 3-pentanone and 2-methyl-3-pentanone can be increased by use of a 1:1 lithium tetramethylpiperidide-LiBr mixture for kinetic enolization.¹⁰⁰ The precise mechanism of this effect is not clear, but it is probably due to an aggregate species containing bromide acting as the base.¹⁰¹ Relatively weakly basic lithium anilides, specifically lithium 2,4,5-trichloroanilide and lithium diphenylamide, give high *Z*:*E* ratios.¹⁰² On the other hand, lithium *N*-trimethylsilyl-*iso*-propylamide and lithium *N*-trimethylsilyl-*tert*-butylamide give selectivity for the *E*-enolate.¹⁰³

E : Z Stereoselectivity						
R	LDA	LiHMDS	LiTMP	LiTMP-LiBr	LiTMSN <i>t</i> Bu	LiNAr
Ethyl	77:33	34:66	83:17	98:2	92:8	11:89
Isopropyl	63:37	2:98	66:34	95:5	94:6	2:98
<i>t</i> -Butyl	1:99	>2:98	<5:>95	<5:95	11:89	0:100

^{98.} M. Majewski and D. M. Gleave, *Tetrahedron Lett.*, **30**, 5681 (1989).

^{99.} R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976); W. A. Kleschick, C. T. Buse, and C. H. Heathcock, *J. Am. Chem. Soc.*, **99**, 247 (1977); Z. A. Fataftah, I. E. Kopka, and M. W. Rathke, *J. Am. Chem. Soc.*, **102**, 3959 (1980).

^{100.} P. L. Hall, J. H. Gilchrist, and D. B. Collum, *J. Am. Chem. Soc.*, **113**, 9571 (1991).

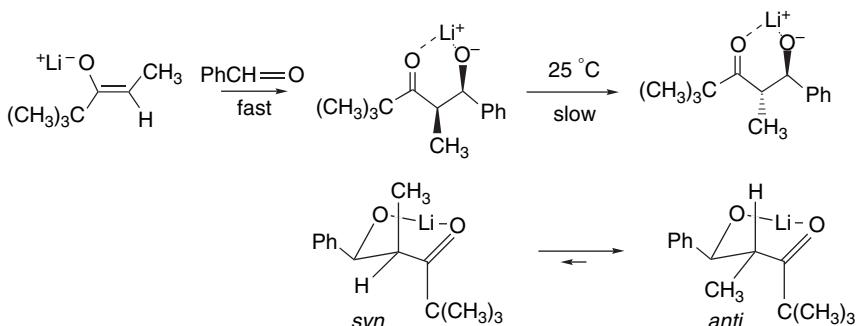
^{101.} F. S. Mair, W. Clegg, and P. A. O'Neil, *J. Am. Chem. Soc.*, **115**, 3388 (1993).

^{102.} L. Xie, K. Vanlandeghem, K. M. Isenberger, and C. Bernier, *J. Org. Chem.*, **68**, 641 (2003).

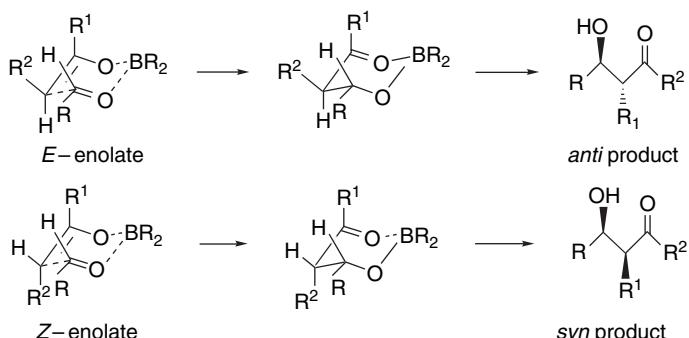
^{103.} L. Xie, K. M. Isenberger, G. Held, and L. M. Dahl, *J. Org. Chem.*, **62**, 7516 (1997).

Under other reaction conditions, the product can result from *thermodynamic control*. Aldol reactions can be effected for many compounds using less than a stoichiometric amount of base. In these circumstances, the aldol reaction is reversible and the product ratio is determined by the relative stability of the various possible products. Thermodynamic conditions also permit equilibration among all the enolates of the nucleophile. The conditions that lead to equilibration include higher reaction temperatures, the presence of protic or dissociating polar solvents, and the use of less tightly coordinating cations.

When the aldol addition reaction is carried out under thermodynamic conditions, the difference in stability of the stereoisomeric *anti* and *syn* products determines the product composition. In the case of lithium enolates, the adducts can be equilibrated by keeping the reaction mixture at room temperature. This has been done, for example, for the product from the reaction of the enolate of ethyl *t*-butyl ketone and benzaldehyde. The greater stability of the *anti* isomer is attributed to the pseudoequatorial position of the methyl group in the chairlike product chelate. With larger substituent groups, the thermodynamic preference for the *anti* isomer is still greater.¹⁰⁴



Another important version of the aldol reaction involves the use of boron enolates.¹⁰⁵ A cyclic TS similar to that for lithium enolates is involved and the same relationship exists between enolate geometry and product stereochemistry. In general, the stereoselectivity is higher than for lithium enolates. The O–B bond distances are shorter than those in lithium enolates, and this leads to a more compact TS and magnifies the steric interactions that control facial stereoselectivity. As with lithium enolates, the enolate stereochemistry controls diastereoselectivity.

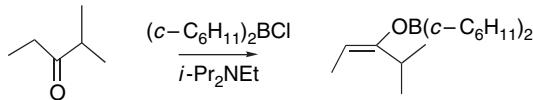


¹⁰⁴ C. H. Heathcock and J. Lampe, *J. Org. Chem.*, **48**, 4330 (1983).

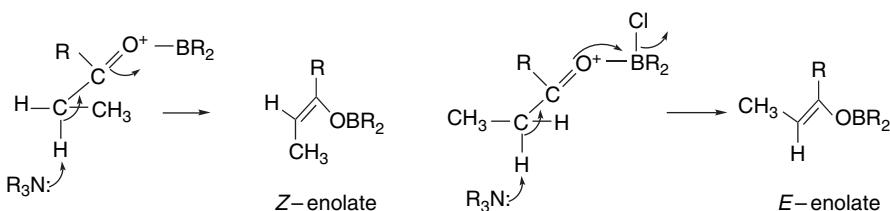
¹⁰⁵ C. J. Cowden and I. A. Paterson, *Org. React.*, **51**, 1 (1997); E. Tagliavini, C. Trombini, and A. Umani-Ronchi, *Adv. Carbanion Chem.*, **2**, 111 (1996).

SECTION 7.7

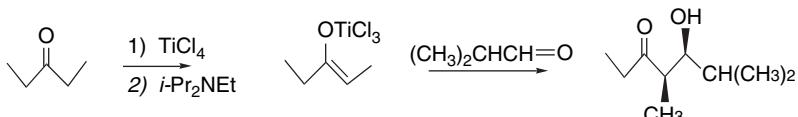
Addition of Enolates and Enols to Carbonyl Compounds: The Aldol Addition and Condensation Reactions



The contrasting stereoselectivity of the boron triflates and chlorides has been discussed in terms of reactant conformation and the stereoelectronic requirement for perpendicular alignment of the hydrogen with the carbonyl group π orbital.¹⁰⁸ The distinction between the two types of borylation reagents seems to lie in the extent of dissociation of the leaving group. The triflate is likely present as an ion pair, whereas with the less reactive chloride, the deprotonation may be a concerted (E2-like) process. The difference between trigonal and tetrahedral coordination of boron affects the steric interactions and reactant conformation. The two proposed TSs are shown below.



Titanium enolates can be prepared from lithium enolates by reaction with a trialkoxytitanium(IV) chloride, such as tri-(isopropoxy)titanium chloride.¹⁰⁹ Titanium enolates can also be prepared directly from ketones by reaction with $TiCl_4$ and a tertiary amine.¹¹⁰



¹⁰⁶ D. A. Evans, E. Vogel, and J. V. Nelson, *J. Am. Chem. Soc.*, **101**, 6120 (1979); D. A. Evans, J. V. Nelson, E. Vogel, and T. R. Taber, *J. Am. Chem. Soc.*, **103**, 3099 (1981).

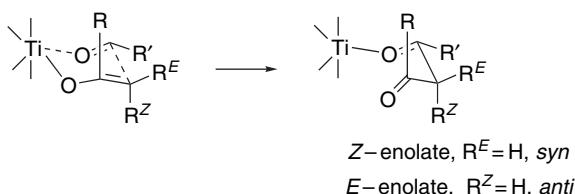
¹⁰⁷ H. C. Brown, R. K. Dhar, R. K. Bakshi, P. K. Pandiarajan, and B. Singaram, *J. Am. Chem. Soc.*, **111**, 3441 (1989); H. C. Brown, R. K. Dhar, K. Ganeshan, and B. Singaram, *J. Org. Chem.*, **57**, 499 (1992); H. C. Brown, R. K. Dhar, K. Ganeshan, and B. Singaram, *J. Org. Chem.*, **57**, 2716 (1992); H. C. Brown, K. Ganeshan, and R. K. Dhar, *J. Org. Chem.*, **58**, 147 (1993); K. Ganeshan and H. C. Brown, *J. Org. Chem.*, **58**, 7162 (1993).

¹⁰⁸ J. M. Goodman and I. Paterson, *Tetrahedron Lett.*, **33**, 7223 (1992); E. J. Corey and S. S. Kim, *J. Am. Chem. Soc.*, **112**, 4976 (1990).

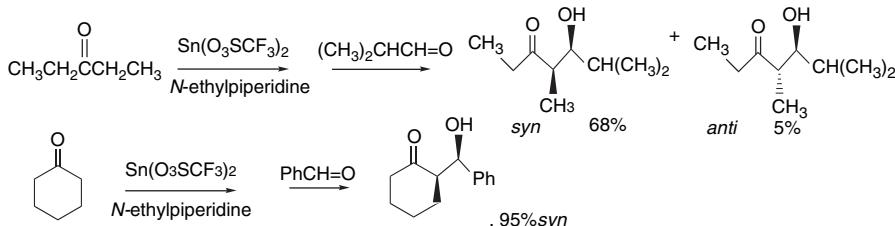
¹⁰⁹ C. Siegel and E. R. Thornton, *J. Am. Chem. Soc.*, **111**, 5722 (1989).

¹¹⁰ D. A. Evans, D. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, **113**, 1047 (1991).

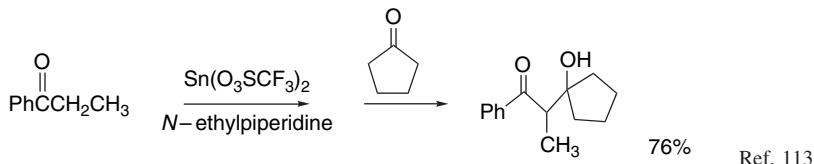
Under these conditions, the *Z*-enolate is formed and the aldol adducts have *syn* stereoselectivity. The addition proceeds through a cyclic TS assembled around titanium.



Tin enolates can be generated from ketones and $\text{Sn}(\text{II})(\text{O}_3\text{SCF}_3)_2$ in the presence of tertiary amines.¹¹¹ The subsequent aldol addition is *syn* selective.¹¹²



Tin(II) enolates prepared in this way also show good reactivity toward ketones as the carbonyl component.



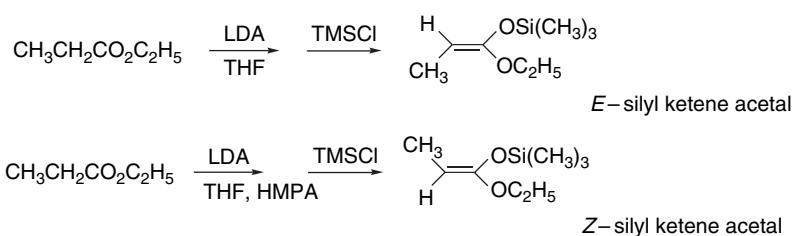
7.7.4. Aldol Reactions of Other Carbonyl Compounds

The enolates of other carbonyl compounds can be used in mixed aldol condensations. Extensive use has been made of the enolates of esters, thioesters, and amides. Of particular importance are several modified amides, such as those derived from oxazolidinones, that can be used as chiral auxiliaries. The methods for formation of these enolates are similar to those for ketones. Lithium, boron, tin, and titanium derivatives have all been used. Because of their usefulness in aldol additions and other synthetic methods (see especially Section 6.4.2.3, Part B), there has been a good deal of interest in the factors that control the stereoselectivity of enolate formation from esters. For simple esters such as ethyl propanoate, the *E*-enolate is preferred under kinetic conditions using a strong base such as LDA in THF solution. Inclusion of a

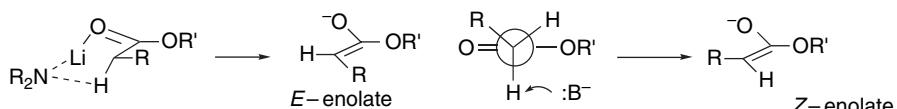
¹¹¹. T. Mukaiyama, N. Isawa, R. W. Stevens, and T. Haga, *Tetrahedron*, **40**, 1381 (1984); T. Mukaiyama and S. Kobayashi, *Org. React.*, **46**, 1 (1994); I. Shibata and A. Babu, *Org. Prep. Proc. Int.*, **26**, 85 (1994).

¹¹². T. Mukaiyama, R. W. Stevens, and N. Iwasawa, *Chem. Lett.*, 353 (1982).

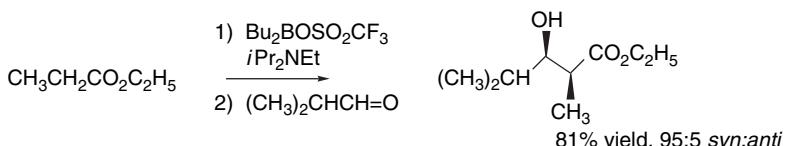
¹¹³. R. W. Stevens, N. Iwasawa, and T. Mukaiyama, *Chem. Lett.*, 1459 (1982).



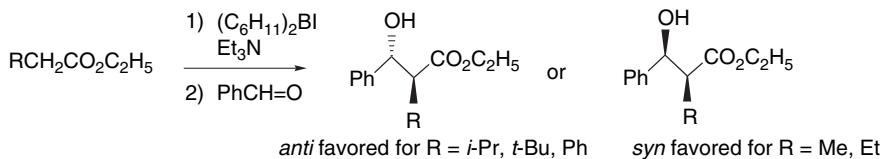
These observations are explained in terms of a cyclic TS for the LDA/THF conditions and a more open TS in the presence of an aprotic dipolar solvent.



Boron enolates can also be obtained from esters¹¹⁵ and amides¹¹⁶ and undergo aldol addition reactions. Various combinations of borylating reagents and amines have been used and the *E*:*Z* ratios are dependent on the reagents and conditions. In most cases esters give *Z*-enolates, which lead to *syn* adducts, but there are exceptions. For example, branched-chained esters give mainly *anti* adducts when the enolates are formed using dicyclohexyliodoborane.



Ref. 117



Ref. 115

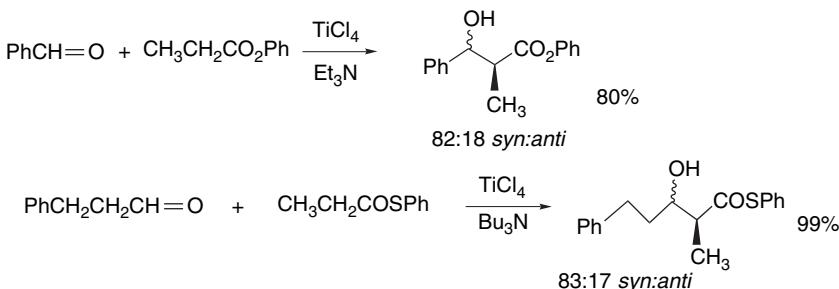
¹¹⁴ R. E. Ireland, P. Wipf, and J. D. Armstrong, III, *J. Org. Chem.*, **56**, 650 (1991).

¹¹⁵ K. Ganesan and H. C. Brown, *J. Org. Chem.*, **59**, 2336 (1994).

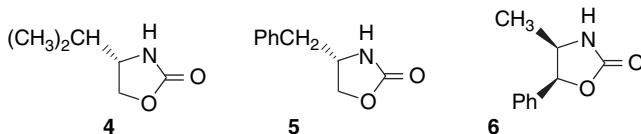
¹¹⁶ K. Ganesan and H. C. Brown, *J. Org. Chem.*, **59**, 7346 (1994).

¹¹⁷ A. Abiko, J.-F. Liu, and S. Masamune, *J. Org. Chem.*, **61**, 2590 (1996).

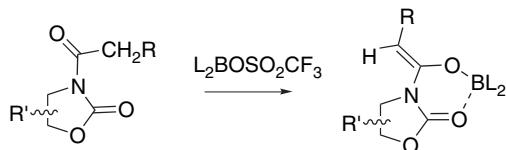
Phenyl and phenylthio esters have proven to be advantageous in TiCl_4 -mediated additions, perhaps because they are slightly more acidic than the alkyl analogs. The reactions show *syn* diastereoselectivity.¹¹⁸



The methods that we have just discussed can be used to control the ratio of *syn* and *anti* diastereomeric products. It is often desired to also control the reaction to provide a specific enantiomer. Nearby stereocenters in either the carbonyl compound or the enolate can impose facial selectivity. Chiral auxiliaries can achieve the same effect. Finally, use of chiral Lewis acids as catalysts can also achieve enantioselectivity. Much effort has also been devoted to the use of chiral auxiliaries and chiral catalysts to effect enantioselective aldol reactions.¹¹⁹ A very useful approach for enantioselective aldol additions is based on the oxazolidinones **4**, **5**, and **6**.



These compounds are readily available in enantiomerically pure form. They can be acylated and converted to the lithium or boron enolates by the same methods applicable to ketones and esters. When they are converted to boron enolates using di-*n*-butylboron triflate and triethylamine, the enolates are the *Z*-stereoisomers.¹²⁰ The carbonyl oxygen of the oxazolidinone ring is bonded to the boron.



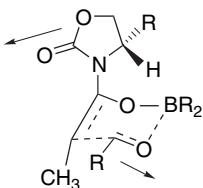
Reaction occurs through a cyclic TS in which the aldehyde displaces the oxazolidinone oxygen as a boron ligand. The oxazolinone substituents direct the approach of the aldehyde. The conformation of the addition TS for boron enolates is believed to have

¹¹⁸. Y. Tanabe, N. Matsumoto, S. Funakoshi, and N. Mantra, *Synlett*, 1959 (2001).

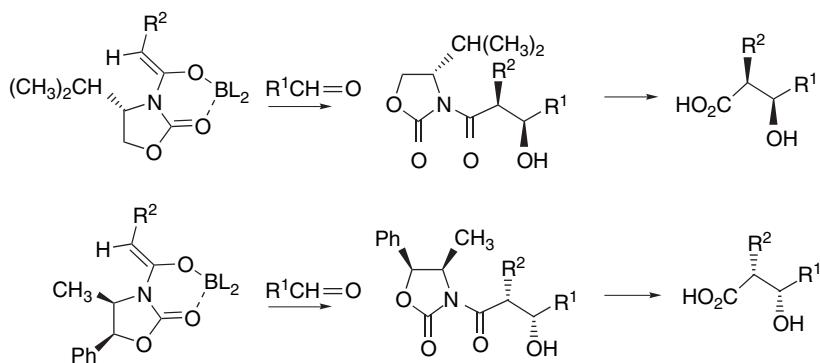
¹¹⁹. M. Braun and H. Sacha, *J. prakt. Chem.*, **335**, 653 (1993); S. G. Nelson, *Tetrahedron: Asymmetry*, **9**, 357 (1998); E. Carreira, in *Catalytic Asymmetric Synthesis*, 2nd Edition, I. Ojima, ed., Wiley-VCH, 2000, pp. 513–541.

¹²⁰. D. A. Evans, J. Bartroli, and T. L. Shih, *J. Am. Chem. Soc.*, **103**, 2127 (1981).

the oxazolidinone ring oriented with opposed dipoles of the ring and the aldehyde carbonyl groups.

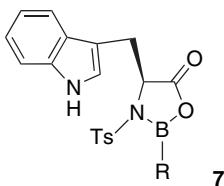


Because of the opposite steric encumbrance provided by **4** and **6**, the products, both of which are *syn*, result from opposite facial selectivity and have opposite absolute configuration. The acyl oxazolidinones are solvolyzed in water or alcohols to give the enantiomeric β-hydroxy acid or ester. Alternatively, they can be reduced to aldehydes or alcohols.



We discuss other chiral auxiliaries and other strategies for controlling facial selectivity in Section 2.1.3 of Part B.

There are also several catalysts that can effect enantioselective aldol addition. The reactions generally involve enolate equivalents, such as silyl enol ethers, that are unreactive toward the carbonyl component alone, but can react when activated by a Lewis acid. The tryptophan-based oxaborazolidinone **7** has proven to be a useful catalyst¹²¹ that induces preferential *re* facial attack on simple aldehydes.



The enantioselectivity appears to involve the shielding of the *si* face by the indole ring, through a π-stacking interaction, as indicated in Fig. 7.15.¹²²

¹²¹ E. J. Corey, C. L. Cywin, and T. D. Roper, *Tetrahedron Lett.*, **33**, 6907 (1992); E. J. Corey, T.-P. Loh, T. D. Roper, M. D. Azimioara, and M. C. Noe, *J. Am. Chem. Soc.*, **114**, 8290 (1992).

¹²² The model is from S. G. Nelson, *Tetrahedron: Asymmetry*, **9**, 357 (1998).

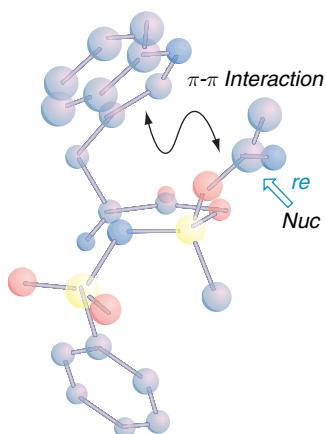
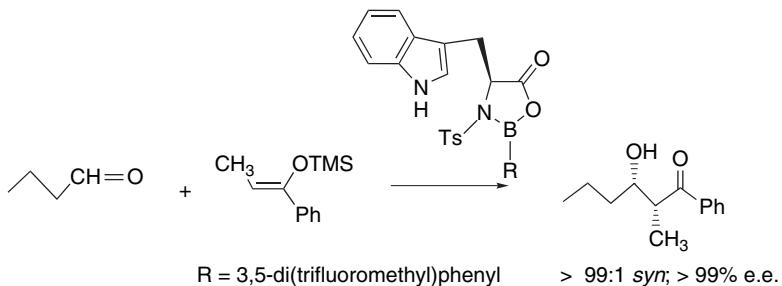
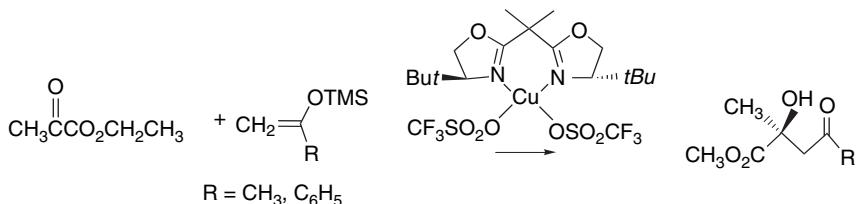


Fig. 7.15. Facial selectivity of 3-indolylmethyloxaborazolidinone catalyst. Reproduced from *Tetrahedron Asymmetry*, **9**, 357 (1998), by permission of Elsevier. (See also color insert.)

The *B*-3,5-di(trifluoromethyl)phenyl derivative was found to be a very effective catalyst.¹²³



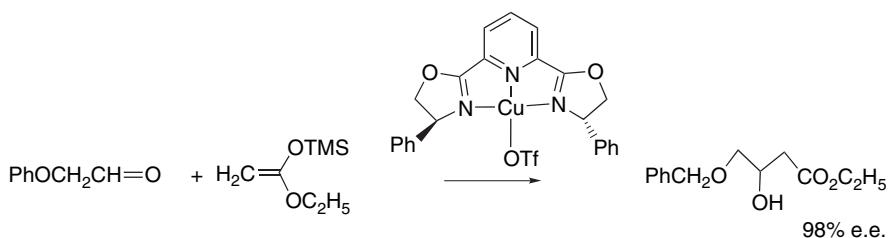
Another effective group of catalysts is made up of the copper bis-oxazolines.¹²⁴



¹²³. K. Ishihara, S. Kondo, and H. Yamamoto, *J. Org. Chem.*, **65**, 9125 (2000).

¹²⁴. D. A. Evans, J. A. Murry, and M. C. Kozlowski, *J. Am. Chem. Soc.*, **118**, 5814 (1996).

These and similar catalysts are effective with silyl ketene acetals and silyl ketene thioacetals.¹²⁵



These catalysts function as Lewis acids at the carbonyl oxygen. The chiral ligands promote facial selectivity.¹²⁶ Figure 7.16 shows a representation of the reactant complex.

In summary, several factors determine the stereochemical outcome of aldol addition reactions. The diastereoechemical preference of the *syn* or *anti* isomer is determined by the configuration of the enolate and the orientation of the aldehyde within the TS. Chirality in either reactant introduces another stereochemical influence. The use of chiral auxiliaries can promote high facial selectivity in the approach of the aldehyde and thus permit the preparation of enantiomerically enriched products. The same outcome can be achieved using chiral Lewis acids as reaction catalysts.

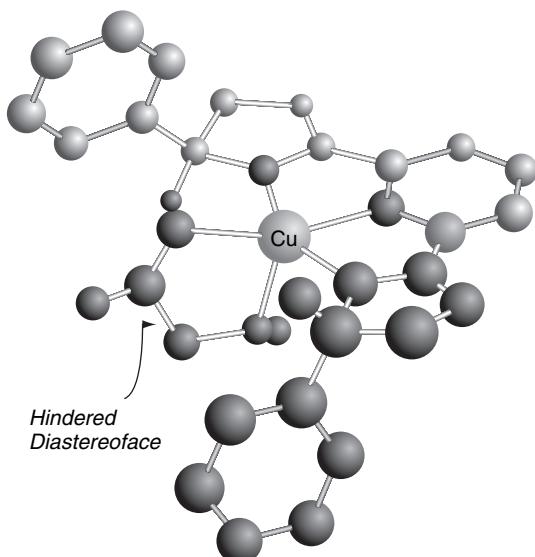


Fig. 7.16. Facial selectivity of diphenyl pyridine-*bis*-oxazoline catalysts. Reproduced from *Tetrahedron Asymmetry*, **9**, 357 (1998), by permission of Elsevier.

¹²⁵ D. A. Evans, D. W. C. MacMillan, and K. R. Campos, *J. Am. Chem. Soc.*, **119**, 10859 (1997); D. A. Evans, M. C. Kozlowski, C. S. Burgey, and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **119**, 7893 (1997).

¹²⁶ The model is from S. G. Nelson, *Tetrahedron: Asymmetry*, **9**, 357 (1998).

General References

CHAPTER 7

Addition, Condensation
and Substitution
Reactions of Carbonyl
Compounds

- M. L. Bender, *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley-Interscience, New York, 1971.
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Problems

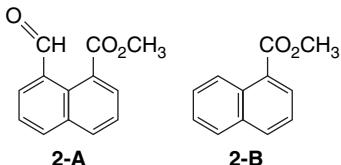
(References for these problems will be found on page 1162.)

- 7.1. The hydrates of aldehydes and ketones are considerably more acidic than alcohols (pK 16–19). Some values are shown below. How do you account for this enhanced acidity? Explain the relative order of acidity for the compounds in the list.

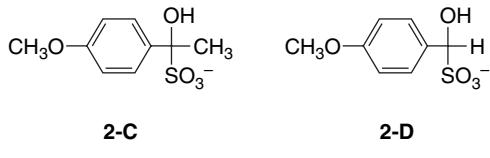
Hydrate	pK
$\text{CH}_2(\text{OH})_2$	13.3
$\text{CH}_3\text{CH}(\text{OH})_2$	13.6
$\text{Cl}_3\text{CCH}(\text{OH})_2$	10.0
$\text{PhC}(\text{CF}_3)(\text{OH})_2$	10.0
$3\text{-NO}_2\text{PhC}(\text{CF}_3)(\text{OH})_2$	9.2

- 7.2. Suggest explanations for each of the following observations:

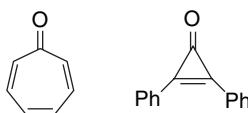
- The equilibrium constant for cyanohydrin formation for 3,3-dimethyl-2-butanone (pinacolone) is 40 times larger than for acetophenone.
- The ester **2-A** undergoes alkaline hydrolysis 8300 faster than the unsubstituted analog **2-B**.



- Under comparable conditions, the general base-catalyzed elimination of bisulfite ion from **2-C** is about 10 times faster than for **2-D**.



- d. The rates of isotopic exchange of the carbonyl oxygen in tropone (**2-E**) and 2,3-diphenyl-cyclopropenone (**2-F**) are much less than for acetophenone.



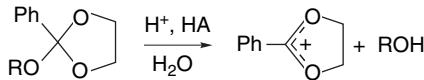
2-E **2-F**

- 7.3. Arrange each series of compounds in order of decreasing rate of acid-catalyzed hydrolysis of the corresponding diethyl acetals. Explain your reasoning.

- acetaldehyde, chloroacetaldehyde, buten-2-al
- acetaldehyde, formaldehyde, acetone
- cyclopentanone, cyclohexanone, camphor
- acetone, 3,3-dimethyl-2-butanone, 4,4-dimethyl-2-butanone
- benzaldehyde, 4-methoxybenzaldehyde, butanal

- 7.4 The acid-catalyzed hydrolysis of 2-alkoxy-2-phenyl-1,3-dioxolane exhibits general acid catalysis of the initial rate-determining cleavage under some circumstances, as is indicated by the rate law:

$$k_{\text{obs}} = k_{\text{H}^+}[\text{H}^+] + k_{\text{H}_2\text{O}}[\text{H}_2\text{O}] + k_{\text{HA}}[\text{HA}]$$

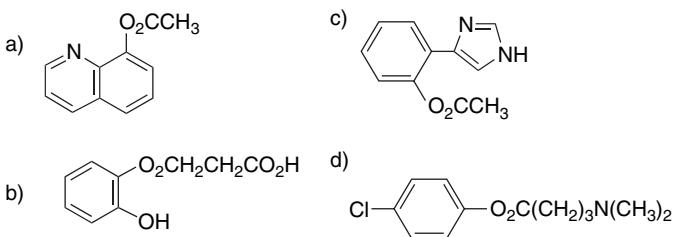


The Brønsted relationship (see Section 3.7.1.2 to review the Brønsted catalysis law) shows a correlation with the identity of the alkoxy group. The alkoxy groups derived from more acidic alcohols have lower Brønsted coefficients α .

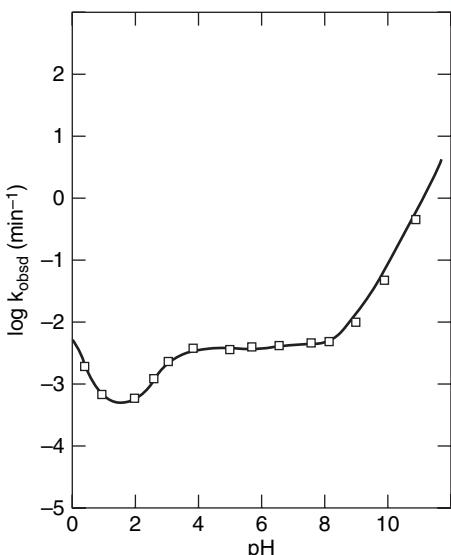
Alcohol	pK	α
Cl ₂ CHCH ₂ OH	12.9	0.69
ClCH ₂ CH ₂ OH	14.3	0.80
CH ₃ OCH ₂ CH ₂ OH	14.8	0.85
CH ₃ OH	15.7	0.90

What information about the reaction mechanism does this correlation provide? Interpret the results in terms of a More O’Ferrall-Jencks two-dimensional potential energy diagram.

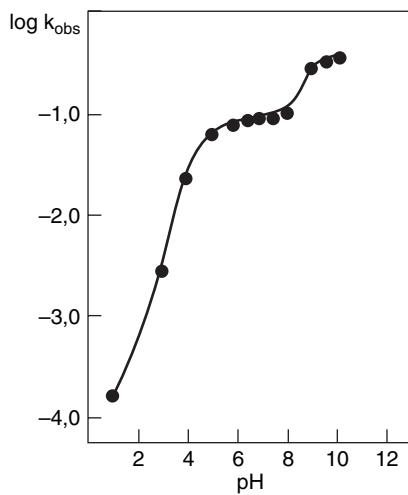
- 7.5 Each of the following molecules is capable of some form of intramolecular catalysis of ester hydrolysis. For each reactant, indicate one or more possible mechanisms for intramolecular catalysis. Indicate the relationship that you would expect to exist between the catalytic mechanism and the pH. Determine if that relationship is consistent with the experimental pH-rate profile shown in Fig. 7.P5. Depict a mechanism showing the proposed catalysis.



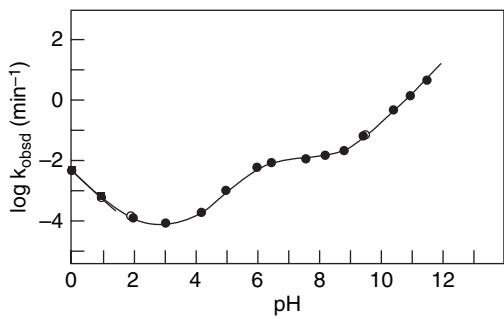
(a)



(b)



(c)



(d)

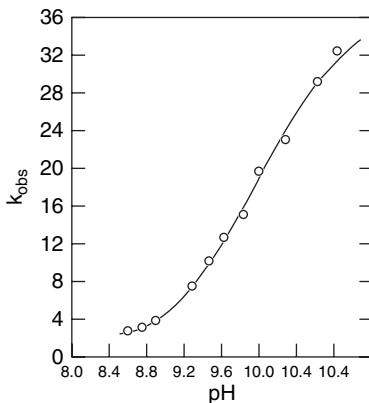
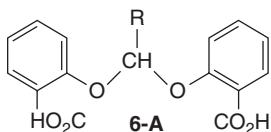


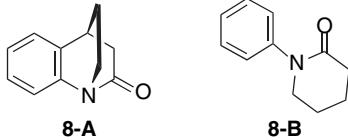
Fig. 7.P5. Reproduced from problem references 5 a-d by permission of the American Chemical Society.

7.6 Derive the general expression for the observed rate of hydrolysis of compound **6-A** as a function of pH. Assume that intramolecular general acid catalysis outweighs specific acid catalysis in the region between pH 3 and pH 9.

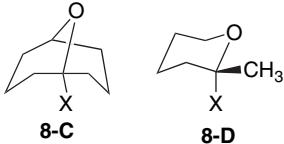


- 7.7. Enantiomerically pure dipeptide is obtained when the 4-nitrophenyl ester of *N*-benzoyl-L-leucine is coupled with ethyl glycinate in ethyl acetate. If, however, the leucine ester is treated with 1-methylpiperidine in chloroform for 30 min prior to coupling, the dipeptide is nearly completely racemized. Treatment of the leucine ester with 1-methylpiperidine leads to formation of a crystalline material of composition $C_{13}H_{15}NO_2$, which has strong IR bands at 1832 and 1664 cm^{-1} . Explain how racemization occurs and suggest a reasonable structure for the crystalline material.
- 7.8 Provide an explanation in terms of structure and mechanism for the following observations:

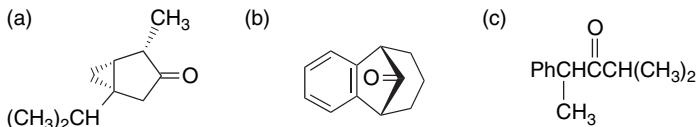
- a. The bicyclic lactam **8-A** hydrolyzes 10^7 times faster than the related monocyclic compound **8-B**



- b. Leaving groups X solvolyze from the bicyclic structure **8-C** at a rate that is 10^{-13} less than for the monocyclic analog **8-D**.



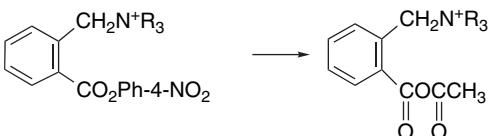
- 7.9. Analyze the factors that determine the stereoselectivity of the addition of organometallic compounds to the following ketones. Predict the stereochemistry of the major product.



- 7.10. Indicate which of the compounds of each of the following pairs will have the more negative free-energy change for hydrolysis at pH 7. Explain your reasoning.

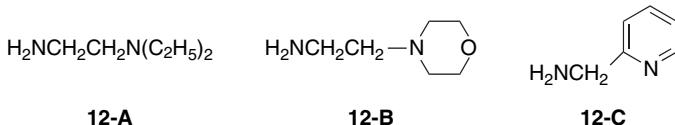
- (a) $\text{CH}_3\text{CO}_2\text{CH}_3$ or $\text{CH}_3\overset{\text{O}}{\parallel}\text{CSCH}_3$ (d) $\text{CH}_3\text{CO}_2\text{CH}_3$ or $\text{CH}_3\overset{\text{O}}{\parallel}\text{CCH}_2\text{CO}_2\text{CH}_3$
- (b) $\text{CH}_3\text{CO}_2\text{CH}_3$ or $\text{CH}_3\overset{\text{O}}{\parallel}\text{COP(OH)}_2$ (e) $\text{CH}_3\text{CO}_2\text{CH}_3$ or $\text{CH}_3\overset{\text{O}}{\parallel}\text{C}-\text{N}(\text{C}_6\text{H}_5)_2$
- (c) $\text{CH}_3\text{CO}_2\text{CH}_3$ or $\text{H}_2\text{NCH}_2\text{CO}_2\text{CH}_3$ (f) $\text{CH}_3\text{CO}_2\text{CH}_3$ or $\text{CH}_3\text{CON}(\text{CH}_3)_2$

7.11. Sodium acetate reacts with 4-nitrophenyl benzoates to give mixed anhydrides when the reaction is conducted in a polar aprotic solvent in the presence of a crown ether. The reaction is strongly accelerated by a quaternary nitrogen substituent in the *ortho* position. Suggest an explanation for this substituent effect.



introduction of $^+\text{NR}_3$ substituent
accelerates the reaction by $> 10^3$.

7.12. The kinetics of the hydrolysis of a series of imines derived from benzophenone and primary amines reveals a normal dependence of mechanism on pH with rate-determining nucleophilic attack at high pH and rate-determining decomposition of the tetrahedral intermediate at low pH. The primary amines show a linear correlation between the rate of nucleophilic addition and the basicity of the amine. Several diamines, in particular **12-A**, **12-B**, and **12-C**, all showed positive (more reactive) deviation from the correlation line for other primary amines. Why might these amines be more reactive than predicted on the basis of their basicity?

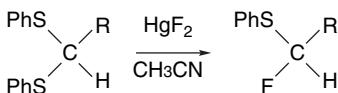


7.13. The following data give the dissociation constants and rate of acetaldehyde hydration catalysis by each acid. Treat the data according to the Brønsted equation and discuss the mechanistic significance of the results.

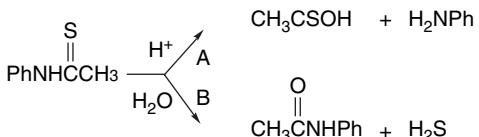
Acid	K_a	k_{hydr} $\text{mol}^{-1}\text{s}^{-1}$
Formic	1.77×10^{-4}	1.74
Phenylacetic	4.9×10^{-5}	0.91
Acetic	1.75×10^{-5}	0.47
Pivalic	9.4×10^{-6}	0.33

7.14. 1,1-(Diphenylthio)alkanes react with mercuric fluoride to give 1-fluoro-1-(phenylthio)alkanes. Provide a likely mechanism for this reaction. Consider

such questions as: (1) is the reaction an S_N1 or S_N2 process? Would NaF cause the same reaction? Why is only one of the phenylthio groups replaced?



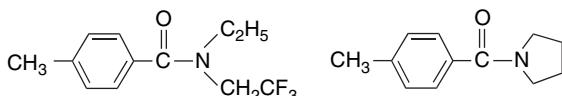
- 7.15. The acid-catalyzed hydrolysis of thioacetanilide can follow two different courses.



The product composition is a function of acid concentration, as shown below. Provide a mechanism that accounts for the change in product composition as a function of acid concentration.

H_2SO_4 (% by weight)	1.1	3.2	6.1	12	18	36	48
% formed by path A	20	50	55	65	75	96	100

- 7.16. A comparison of the kinetics of hydrolysis and isotopic exchange of amides **16-A** and **16-B** gave the data below for reactions conducted in 0.1–1.0 M $[-\text{OH}]$. An interesting observation is that there is more C=O exchange for **16-A** than for **16-B**. From this information and the other data given, propose a stepwise mechanism for hydrolysis of each amide. Make a qualitative comparison of the behavior of the substituent effects on the various steps in the mechanisms.



$k_{\text{ex/hydrol}}$	(1.0 M $^-$ OD in D_2O)	35.6	0.04
k_{ex}	(100 °C; 1.0 M $^-$ OD in D_2O)	$1.09 \times 10^{-3} \text{ s}^{-1}$	$1.53 \times 10^{-5} \text{ s}^{-1}$
k_{hydrol}	(100 °C; 1.0 M $^-$ OD in D_2O)	$3.06 \times 10^{-5} \text{ s}^{-1}$	$3.85 \times 10^{-4} \text{ s}^{-1}$
ΔG^*_{ex}	(100 °C)	26.5 kcal/mol	27.1 kcal/mol
$\Delta G^*_{\text{hydrol}}$	(100 °C)	29.6 kcal/mol	24.4 kcal/mol

- 7.17. Data pertaining to substituent effects on the acid-catalyzed hydrolysis of mixed aryl-methyl acetals of benzaldehyde are given below. The reactions exhibited general acid catalysis, and the Brønsted α values are tabulated for a series of substituents in both the benzaldehyde ring and the phenoxy group. Discuss the information that these data provide about the nature of the TS for the first hydrolysis step, making reference to a three-dimensional energy diagram.

X	Series I, substituent in Ar		Series II, substituent in Ar'		α
	$k_{\text{cat}}^{\text{a}}$	α	X	$k_{\text{cat}}^{\text{a}}$	
<i>m</i> -NO ₂	2.7×10^{-4}	1.05	<i>m</i> -NO ₂	8.85×10^{-2}	0.49
<i>m</i> -F	2.2×10^{-3}	0.92	<i>m</i> -Br	4.7×10^{-2}	0.65
<i>m</i> -CH ₃ O	9.6×10^{-3}	0.78	<i>m</i> -F	2.45×10^{-2}	0.67
H	1.3×10^{-2}	0.77	<i>m</i> -CH ₃ O	2.55×10^{-2}	0.71
<i>p</i> -CH ₃	1.1×10^{-1}	0.72	H	1.3×10^{-2}	0.77
<i>p</i> -CH ₃ O	2.8×10^{-1}	0.68	<i>p</i> -CH ₃	1.3×10^{-2}	0.88
			<i>p</i> -CH ₃ O	1.65×10^{-2}	0.96

a. Rate constant in s^{-1} for catalysis by acetic acid.

- 7.18. The introduction of an additional carboxy function into the structure of aspirin results in a significant rate enhancement of hydrolysis. The hydrolysis is 6300 times faster than for the monoanion of aspirin. 3-Hydroxyphthalic anhydride is an observable intermediate. The pH-rate profile is shown in Figure 7.P18. Suggest a mechanism to account for the accelerated hydrolysis involving both of the carboxy derivatives.

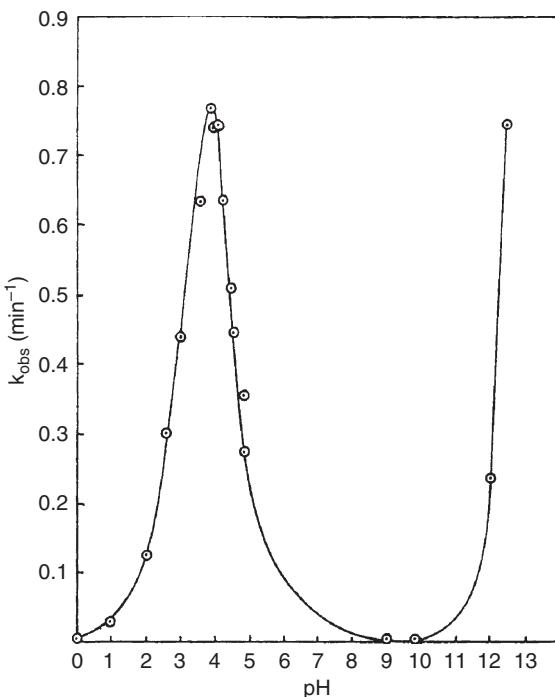
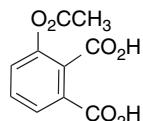


Fig. 7.P18. pH-Rate profile for hydrolysis of 3-acetoxyphthalic acid. Reproduced from *J. Am. Chem. Soc.*, **90**, 5833 (1968), by permission of the American Chemical Society.

- 7.19. The hydrolysis of the lactone **19-A** shows catalysis by acetate ion, with the rate expression being

$$k_{\text{obs}} = 1.6 \times 10^{-6} + 6.4 \times 10^{-4}[\text{H}^+] + 2.08 \times 10^{-5}[\text{OAc}^-] + 49[\text{OH}^-]\text{s}^{-1}$$

This expression results in a pH-rate profile shown in Figure 7.P19, with acetate catalysis being significant in the pH range 3–6. The reaction shows a solvent isotope effect of 2.65. Discuss how the catalysis by acetate might occur. What are the likely mechanisms for hydrolysis at pH < 1 and pH > 7, where the rates are linearly dependent on $[\text{H}^+]$ and $[\text{OH}^-]$, respectively?

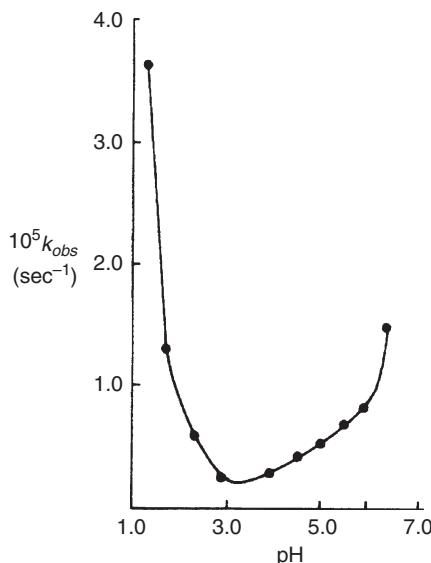
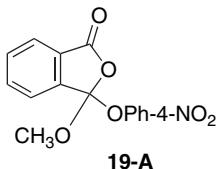
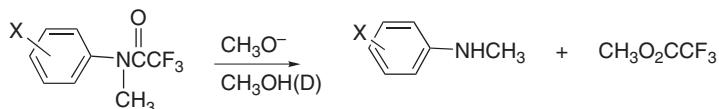


Fig. 7.P19. pH-Rate profile for hydrolysis of **19-A** in acetate buffer solution. Reproduced from *J. Am. Chem. Soc.*, **103**, 3555 (1981), by permission of the American Chemical Society.

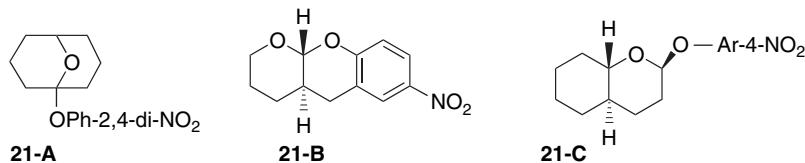
- 7.20. Some data on substituent effects for the reaction of trifluoroacetanilides with methoxide ion in methanol and methanol-OD are given below. Calculate the isotope effect for each reactant. Plot the rate data against appropriate Hammett substituent constants. What facets of the data are in specific agreement with the normal addition-intermediate mechanism proceeding through a tetrahedral intermediate? What facets of the data suggest other complications? Propose a mechanism that is consistent with the data given.



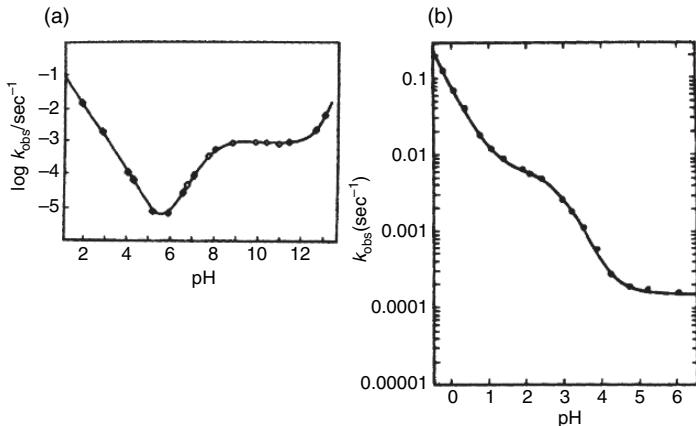
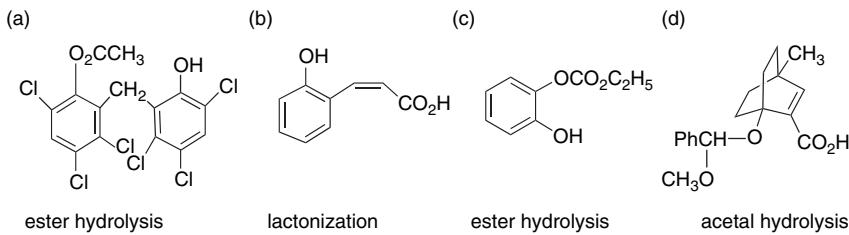
X	$k_{\text{CH}_3\text{OH}}$	$k_{\text{CH}_3\text{OD}}$
<i>m</i> -NO ₂	5.75	8.13
<i>m</i> -Br	0.524	0.464
<i>p</i> -Cl	0.265	0.274
<i>p</i> -Br	0.349	0.346
<i>m</i> -Cl	0.513	0.430
<i>m</i> -OCH ₃	0.110	0.101
H	0.104	0.0899
<i>m</i> -CH ₃	0.0833	0.0595
<i>p</i> -CH ₃	0.0729	0.0451
<i>p</i> -OCH ₃	0.0564	0.0321

a. Second-order rate constants in $M^{-1} \text{ s}^{-1}$.

- 7.21. The order of the reactivity of the cyclic acetals toward hydrolysis is **21-A** << **21-B** << **21-C**. Offer an explanation for the large differences in reactivity of these acetals.



- 7.22. Examine the structure of the following reactants and the corresponding pH-rate profiles. Offer mechanisms for each reaction that is consistent with the pH-rate profile. Indicate the most likely mechanism corresponding to each feature of the profile.



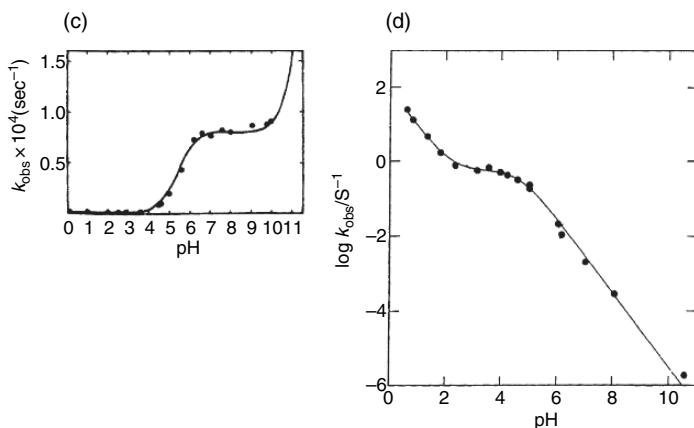
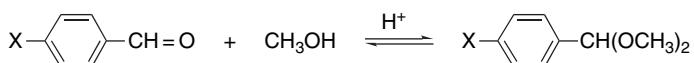
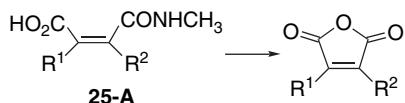


Fig. 7.P22. Reproduced from problem references 22a–c, by permission of the American Chemical Society and reference 22d by permission of the Royal Society of Chemistry.

- 7.23. The pH-rate profiles for 2-carboxy- and 4-carboxy benzylidene acetals of the *trans*-1,2-cyclohexanediol are shown in Figure 7.P23a (page 708). Figure 7.P23b is the pH-rate profile of 3-(*trans*-2-hydroxycyclohexyloxy) phthalide, an intermediate isolated from the 2-carboxy derivative. Interpret both the relative rates and the form of the pH-rate profiles.
- 7.24. The rates of both formation and hydrolysis of dimethyl acetals of *p*-substituted benzaldehydes are substituent dependent. Do you expect the rate of formation to increase or decrease with the increasing EWG strength of the substituent? How do you expect the rate of hydrolysis to respond to the nature of the substituent? The equilibrium constant for acetal formation is determined by these two rates. How do you expect K to vary with substitution?



- 7.25. Figure 7.P25 (page 709) gives the pH-rate profile for conversion of the acid **25-A** to the anhydride in aqueous solution. Note that the rate of the reaction increases with the size of the alkyl substituent, and, although not shown, the compound with both R^1 and $\text{R}^2 = \text{CH}_3$ is still more reactive. Suggest a mechanism for the reaction, including the structure of any intermediate. How do you account for the effect of the alkyl substituents on the reaction rate?



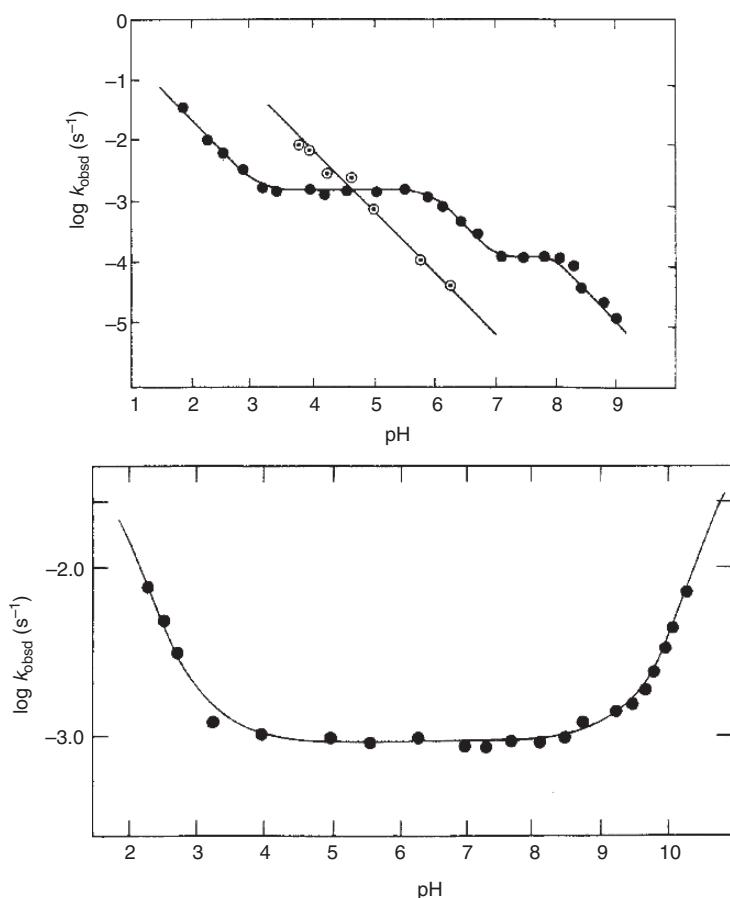


Fig. 7.P23. (a) pH-Rate profile for hydrolysis of 2-carboxy (solid circles) and 4-carboxy (open circles) benzylidene acetals of *trans*-1,2-cyclohexanediol. (b) pH-Rate profile for 3-(*trans*-2-hydroxycyclohexyloxy)phthalide, an intermediate isolated from the 2-carboxy derivative. Reproduced from *J. Am. Chem. Soc.*, **118**, 12956 (1996), by permission of the American Chemical Society.

- 7.26. Assume that the general mechanism for imine hydrolysis described on p. 647–648 is operative. Assume that a steady state approximation can be applied to the tetrahedral intermediate. Derive the kinetic expression for the observed rate of imine hydrolysis. What variables have to be determined to construct the pH-rate profile? What simplifying assumptions can be justified at very high and very low pH values? What are the kinetic expressions that result from these assumptions?
- 7.27. Give the expected structure, including stereochemistry if appropriate, for the products of the following reactions:

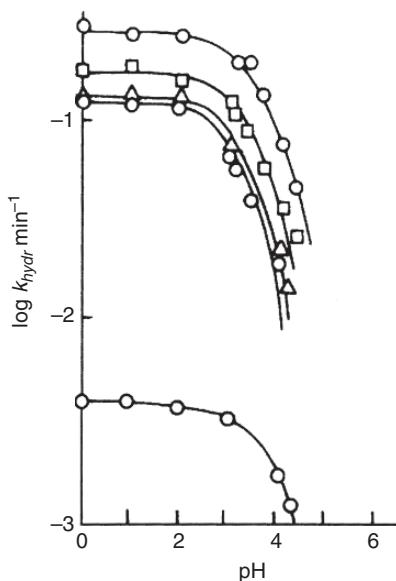
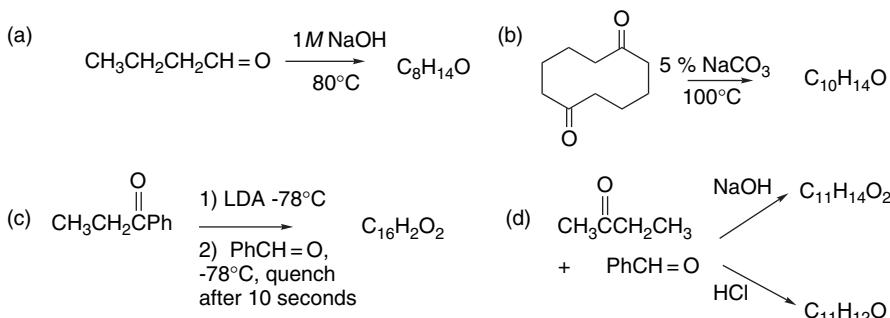
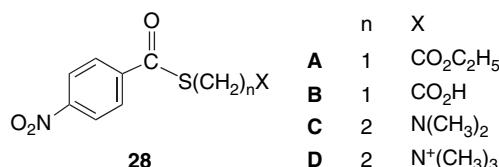


Fig. 7.P25. pH-Rate profile for the hydrolysis of alkyl *N*-methylmaleamic acids at 39°C. The order of increasing reactivity is R¹ = H < Me < Et < i-Pr << t-Bu. Reproduced from *J. Chem. Soc., Perkin Trans. 2*, 1206 (1972), by permission of the Royal Society of Chemistry.



7.28. Figure 7.P28 (page 710) gives the pH-rate profile for the hydrolysis of thioesters **28-A–D** and indicates differing dependence on pH, depending on the thiol substituents. Propose a mechanism that would account for the observed pH dependence in each case.



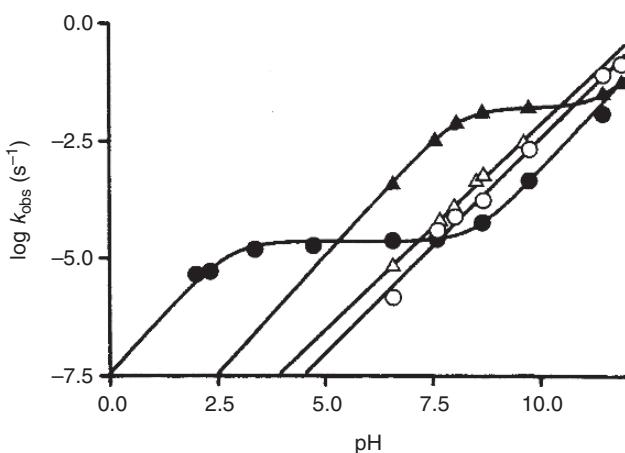


Fig. 7.P28. pH-Rate plots for thioesters **28-A** (○), **28-B** (●), **28-C** (▲) and **28-D** (△). Reproduced from *J. Org. Chem.*, **62**, 4816 (1997), by permission of the American Chemical Society.

- 7.29. Figure 7.P29 gives the pH-rate profile for alkaline hydrolysis of two substituted salicylate amides, as compared with benzamide. Consider whether the pH-rate profiles for the salicylamides are more consistent with mechanism (A), intramolecular basic catalysis of water attack, or (B), intramolecular acid catalysis of hydroxide ion attack.

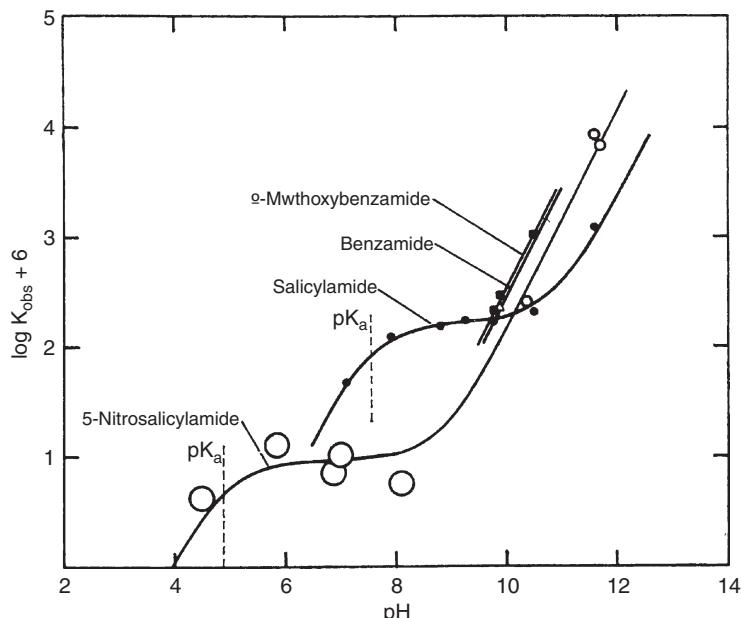
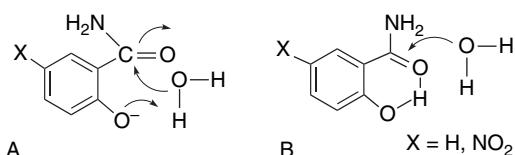


Fig. 7.P29. pH-Rate profiles for substituted salicylamides compared to benzamide in water at 100°C. The rate constants are in min^{-1} . Reproduced from *J. Org. Chem.*, **30**, 1668 (1965), by permission of the American Chemical Society.



- 7.30. The hydrolysis of the ester group in 2-acetoxybenzaldehyde is accelerated by about 10^4 , relative to the 4-isomer. The rate of hydrolysis in the pH range 6.0–8.5 follows the rate expression

$$\text{Rate} = k_0 + k[-\text{OH}]$$

Both the k_0 and $k[-\text{OH}]$ terms are larger than for the 4-isomer. When the hydrolysis is carried out in ^{18}O -labeled water, the acetic acid contains 50% ^{18}O . Suggest a mechanism that is consistent with these observations.

- 7.31. The pH-rate profile for the hydrolysis of 4-nitrophenyl 2-aminobenzoate is given in Figure 7.13 (p. 674). The reaction exhibits a solvent isotope effect of ~ 0.5 in D_2O . Suggest possible mechanisms for the reaction, based on the shape of the pH-rate profile and chemical structure considerations. Derive the kinetic expression for the most likely mechanism.

Aromaticity

Introduction

The meaning of the word *aromaticity* has evolved as understanding of the special properties of benzene and other aromatic molecules has deepened.¹ Originally, aromaticity was associated with a specific chemical reactivity. The aromatic hydrocarbons undergo substitution reactions in preference to addition. Later, the idea of special stability became more important. Benzene can be shown to be much lower in enthalpy than predicted by summation of the normal bond energies for the C=C, C–C, and C–H bonds in the Kekulé representation of benzene (see p. 265). Aromaticity is now generally associated with this property of special stability of certain completely conjugated cyclic molecules. A major contribution to the stability of aromatic systems comes from the delocalization of π electrons in these molecules, which also imparts other properties that are characteristic of aromaticity, especially a diamagnetic ring current.

Aromaticity is usually described in MO terminology. Cyclic structures that have a particularly stable arrangement of occupied π molecular orbitals are called aromatic. *Hückel's rule*, a familiar expression of the relationship between an MO description of structure and aromaticity, is derived from Hückel molecular orbital (HMO) theory and states that *planar monocyclic completely conjugated hydrocarbons will be aromatic when the ring contains $(4n + 2)\pi$ electrons*. HMO calculations assign the π -orbital energies of the cyclic unsaturated systems of ring size three to nine as shown in Figure 8.1. (See Section 1.5, p. 27 to review HMO theory.)

Orbitals below the dotted reference line in the figure are bonding orbitals; when they are filled, the molecule is stabilized. The orbitals that fall on the reference line are nonbonding; electrons in these orbitals are neither stabilizing nor destabilizing. The orbitals above the reference line are antibonding; electrons in these orbitals

¹. M. Glukhovtsev, *J. Chem. Ed.*, **74**, 132 (1997); D. Lloyd, *J. Chem. Inf. Comput. Sci.*, **36**, 442 (1996), Z. Zhou, *Int. Rev. Phys. Chem.*, **11**, 243 (1992); J. P. Snyder, *Nonbenzenoid Aromatics*, Vol. 1, Academic Press, New York, 1969, Chap. 1. A series of reviews on many aspects of aromaticity is published in *Chem. Rev.*, **101**, 1115–1566 (2001).

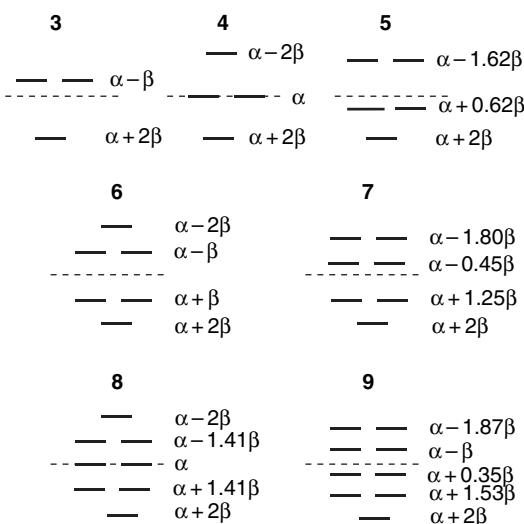
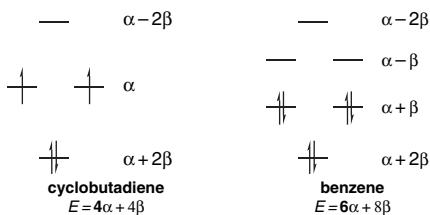


Fig. 8.1. HMO energies for conjugated planar ring systems of three to nine carbon atoms.

destabilize the molecule. The dramatic difference in properties of cyclobutadiene (extremely unstable) and benzene (very stable) are explicable in terms of these HMO diagrams.



Cyclobutadiene has two bonding electrons, but the other two electrons are unpaired because of the degeneracy of the two nonbonding orbitals. The two electrons in the nonbonding levels do not contribute to the stabilization of the molecule. The total HMO energy is $4\alpha + 4\beta$, which is the same as for two isolated double bonds. Furthermore, as these electrons occupy a high-energy orbital, they are particularly available for chemical reactions. As we shall see shortly, experimental evidence indicates that cyclobutadiene is rectangular rather than square. This modifies somewhat the orbital picture from the simple HMO pattern, which applies to a square geometry. The two nonbonding levels are no longer degenerate, so cyclobutadiene is not predicted to have unpaired electrons. Nevertheless, higher-level calculations agree with the Hückel concept in predicting cyclobutadiene to be an extremely unstable molecule with a high-lying HOMO. We will see that several methods of analysis indicate that cyclobutadiene is not only highly reactive, but is also *less stable* than an isolated diene. Cyclobutadiene is called *antiaromatic*.²

Simple Hückel calculations on benzene, in contrast, place all the π electrons in bonding MOs. The π -electron energy of the benzene molecule is calculated by

². R. Breslow, *Acc. Chem. Res.*, **6**, 393 (1973).

summing the energies of the six π -electrons, which is $6\alpha + 8\beta$, lower by 2β than the value of $6\alpha + 6\beta$ for three isolated double bonds. Thus the HMO method predicts a special stabilization for benzene.

The eight-electron cyclic conjugated polyene is 1,3,5,7-cyclooctatetraene, which was first synthesized in 1911.³ Cyclooctatetraene is not much different in reactivity and stability from noncyclic conjugated polyenes. It has no aromatic characteristics. Structural studies determined that cyclooctatetraene is nonplanar, and its most stable structure is tub-shaped. This reduces the overlap between the π bonds, and since the molecule is not planar, the HMO orbital pattern does not apply. Cyclooctatetraene is neither aromatic nor antiaromatic.

The pattern for planar conjugated systems established for cyclobutadiene, benzene, and cyclooctatetraene persists for larger rings. All $4n + 2$ systems are predicted to have all electrons paired in bonding MOs with net stabilization relative to isolated double bonds. In contrast, planar systems containing $4n$ π electrons are predicted to have two degenerate orbitals, each with one unpaired electron. This pattern is the theoretical basis of the Hückel rule.

8.1. Criteria of Aromaticity

HMO theory and Hückel's rule make a good starting point for considering the two molecules, benzene and cyclobutadiene, that are at opposite extremes of aromaticity. There are many other structures that can be described as aromatic or antiaromatic. In this section, we discuss various criteria of aromaticity and its effect on the properties of a few prototypical compounds. In the sections that follow, we look at various specific compounds, including charged rings and homoaromatic systems, as well as polycyclic and heterocyclic rings. We apply these criteria to evaluating aromaticity. We consider three types of criteria: (1) *energy data* indicating thermodynamic stabilization or destabilization; (2) *structural information*, particularly as it relates to bond lengths indicating delocalized structures; and (3) *electronic properties*, including energy levels, electron distribution, and polarizability. The third group of properties includes the response of the electrons to a magnetic field, which can be observed through NMR and magnetic susceptibility measurements. For the most part we use benzene, naphthalene, anthracene, and phenanthrene as examples of aromatic molecules, cyclobutadiene as an example of an antiaromatic molecule, and 1,3,5,7-cyclooctatetraene as a nonaromatic molecule.

8.1.1. The Energy Criterion for Aromaticity

One approach to evaluation of the aromaticity of a molecule is to determine the extent of thermodynamic stabilization. Attempts to describe stabilization of a given aromatic molecule in terms of simple HMO calculations have centered on the *delocalization energy*. The total π -electron energy of a molecule is expressed in terms of the energy parameters α and β that are used in HMO calculations. This energy value can be compared to that for a hypothetical localized version of the same molecule. The HMO energy for the π electrons of benzene is $6\alpha + 8\beta$. The same quantity for

³ R. Willstätter and E. Waser, *Ber.*, **44**, 3423 (1911); R. Willstätter and M. Heidelberger, *Ber.*, **46**, 517 (1913); A. C. Cope and C. G. Overberger, *J. Am. Chem. Soc.*, **70**, 1433 (1948).

the hypothetical localized model cyclohexatriene is $6\alpha + 6\beta$, the sum of three isolated C=C bonds. The difference of 2β is called the *delocalization energy* or *resonance energy*. Although this quantity can be used for comparing related systems, it is not a measurable physical quantity; rather, it is a comparison between a real molecule and a hypothetical one and depends on the definition of the reference point.

There have been two general approaches to determining the amount of stabilization that results from aromatic delocalization. One is to use experimental thermodynamic measurements. Bond energies, as we discussed in Chapter 3, are nearly additive when there are no special interactions among the various bond types. Thus it is possible to assign such quantities as the heat of combustion or heat of hydrogenation of “cyclohexatriene” by assuming that it is a compound with no interaction between the conjugated double bonds. For example, a very simple calculation of the heat of hydrogenation for cyclohexatriene would be to multiply the heat of hydrogenation of cyclohexene by 3, i.e., $3 \times 28.6 = 85.8$ kcal/mol. The actual heat of hydrogenation of benzene is 49.8 kcal/mol, suggesting a total stabilization or delocalization energy of 36 kcal/mol. The difference between the calculated and corresponding measured thermodynamic property of benzene is taken to be the aromatic stabilization. There are other, more elaborate, ways of approximating the thermodynamic properties of the hypothetical cyclohexatriene. There are also other possible reference points. Most estimates of the thermodynamic stabilization of benzene are in the range 20–40 kcal/mol, but the stabilization cannot be determined in an absolute sense since it depends on the choice of the reference molecules and the properties ascribed to them.

The second general approach to estimating aromatic stabilization is to use computational methods. This has already been illustrated by the discussion of benzene according to HMO theory, which assigns the stabilization energy as 2β units. More advanced MO and DFT methods can assign the stabilization energy in a more quantitative way. The most successful method is to perform calculations on the aromatic compound and on a linear, conjugated polyene containing the same number of double bonds.⁴ This method assigns a resonance stabilization of zero to the polyene, even though it is known by thermodynamic criteria that conjugated polyenes do have some stabilization relative to isomeric compounds with isolated double bonds. In effect, this method defines the stabilization *over and above that present in the conjugated polyene*. With this definition, semiempirical MO calculations assign a value of about 20 kcal/mol to the resonance energy of benzene, relative to 1,3,5-hexatriene. The use of polyenes as reference compounds gives better agreement with experimental trends in stability than comparison with the sums of isolated double bonds. It is very significant that MO calculations indicate a *destabilization* of certain conjugated cyclic polyenes, cyclobutadiene in particular. This conclusion has recently been supported experimentally. The technique of photoacoustic calorimetry provided the first experimental thermodynamic data on cyclobutadiene. The ΔH_f value of 114 ± 11 kcal/mol leads to a total destabilization of 87 kcal/mol, of which 32 kcal/mol is attributed to ring strain and 55 kcal/mol to antiaromaticity.⁵

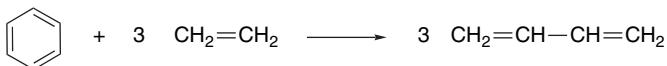
The isodesmic reaction method (see Section 1.2.6) has also been applied to the calculation of the resonance stabilization of benzene. *Homodesmotic reactions*, a special version of isodesmic reactions, can also be used.⁶ Homodesmotic reactions

⁴ M. J. S. Dewar and C. de Llano, *J. Am. Chem. Soc.*, **91**, 789 (1969).

⁵ A. A. Deniz, K. S. Peters, and G. J. Snyder, *Science*, **286**, 1119 (1999).

⁶ P. George, M. Trachtman, C. W. Bock, and A. M. Brett, *J. Chem. Soc., Perkin Trans. 2*, 1222 (1976); P. George, M. Trachtman, C. W. Bock, and A. M. Brett, *Tetrahedron*, **32**, 1357 (1976).

not only balance the bond types, but also match the hybridization of all atoms on both sides of the equation. For example, the stabilization of benzene, relative to 1,3-butadiene, can be calculated by the reaction below, which has 12 sp^2 carbons on each side of the equation.



Isodesmic and homodesmotic reactions can use either experimental thermochemical data or energies obtained by MO or DFT calculations. There have been many specific reaction schemes and computational methods applied to calculation of stabilization energies.⁷ With the above homodesmotic sequence, calculations at the MP4(SDTQ)/6-31G(*d,p*) level give the following stabilization (ΔE) values.⁸

	ΔE	$\Delta E/\pi$ Electron
Cyclobutadiene	-75.1	-18.8
Benzene	25.3	4.3
Cyclooctatetraene(planar)	-28.3	-3.6

The destabilization of cyclobutadiene is estimated to include 33.5 kcal/mol of strain. Planar cyclooctatetraene would also have some strain resulting from expansion of the bond angles. Because the calculations are referenced to butadiene, the stabilization is in addition to the stabilization of butadiene by conjugation. If the stabilization energy of butadiene is assigned as zero, the above reaction gives the resonance energy of benzene as 25.3 kcal/mol. If butadiene is considered to have a delocalization energy of 4.5 kcal/mol (see Section 3.1.2.3), the benzene stabilization energy is 29.8 kcal/mol. B3LYP/6-311+G** calculations on the same homodesmotic reaction led to a stabilization energy of 29.3 kcal/mol.⁹

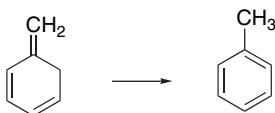
This particular calculation may *underestimate* the relative stabilization, since it uses *trans*-1,3-butadiene as the model, rather than the *cis* geometry that is incorporated into cyclic structures.¹⁰ For example, the homodesmotic reaction below gives a stabilization energy of 30.5 kcal/mol *relative to cyclohexadiene*.¹¹ A feature of this scheme is that it incorporates many of the structural features of the system, such as ring strain, into both sides of the equation so that they should largely cancel. The net stabilization has been called the *aromatic stabilization energy*.



Another refinement of the isodesmic approach to defining aromatic stabilization is to compare methyl-substituted aromatics with the corresponding

7. A. Skanke, R. Hosmane, and J. F. Lieberman, *Acta Chem. Scand.*, **52**, 967 (1998).
8. M. N. Glukhovtsev, R. D. Bach, and S. Laiter, *Theochem*, **417**, 123 (1997).
9. P. v. R. Schleyer, H. Jiao, N. J. R. van Eikema Hommes, V. G. Malkin, and O. L. Malkina, *J. Am. Chem. Soc.*, **119**, 12669 (1997).
10. M. K. Cyranksi, P. v. R. Schleyer, T. M. Krygowski, H. Jiao, and G. Hohlnicher, *Tetrahedron*, **59**, 1657 (2003).
11. P. v. R. Schleyer, M. Manoharan, H. Jiao, and F. Stahl, *Org. Lett.*, **3**, 3643 (2001).

exo-methylene polyene analogs. For example, toluene can be compared with 5-methylene-1,3-cyclohexadiene. This reaction gives a stabilization of 33.2 kcal/mol using B3LYP/6-311+G** calculations.¹²



This sequence is not a suitable one for using experimental data, since the *exo*-methylene analogs are seldom available, but it is practical for computational approaches.

Although the stabilization of aromatic compounds is frequently associated with the delocalization of the π electrons, it is important to recognize that there are other large energy contributions to the difference between localized and delocalized structures, because the *nuclear positions are also different*. The method of separation of nuclear-nuclear, electron-electron, and nuclear-electron forces (see Topic 1.1) has been applied to cyclobutadiene and benzene.¹³ According to this analysis, nuclear-nuclear interactions are destabilizing in both cyclobutadiene and benzene. Electron-electron forces are also destabilizing in benzene, but a very favorable nuclear-electron interaction is responsible for the net stabilization.

Net Stabilization of Delocalized Structure Relative to Localized Model

	Cyclobutadiene	Benzene
V_{ee}	+16.4	-84.4
V_{nn}	-43.4	-78.7
V_{ne}	-1.7	+168.7

These various approaches for comparing the thermodynamic stability of aromatic compounds with reference compounds all indicate that there is a large stabilization of benzene and an even greater destabilization of cyclobutadiene. These compounds are the best examples of aromaticity and antiaromaticity, and in subsequent discussions of other systems we compare their stabilization or destabilization to that of benzene and cyclobutadiene.

8.1.2. Structural Criteria for Aromaticity

Benzene is a perfectly hexagonal molecule with a bond length (1.39 Å) that is intermediate between single and double bonds between sp^2 carbons. Cyclobutadiene, on the other hand, adopts a rectangular shape. This contrasting behavior suggests that *bond length alternation* might be a useful criterion for assessing aromaticity, and several such schemes have been developed. One such system, called HOMA (for harmonic oscillator model for aromaticity), developed by Krygowski and co-workers,¹⁴ takes

¹². P. v. R. Schleyer and F. Puhlhofer, *Org. Lett.*, **4**, 2873 (2002).

¹³. Z. B. Maksic, D. Baric, and I. Petanjek, *J. Phys. Chem. A*, **104**, 10873 (2000).

¹⁴. J. Kruszewski and T. M. Krygowski, *Tetrahedron Lett.*, 3839 (1972).

both bond length alternation and bond stretching into consideration. The aromaticity index HOMA is formulated as

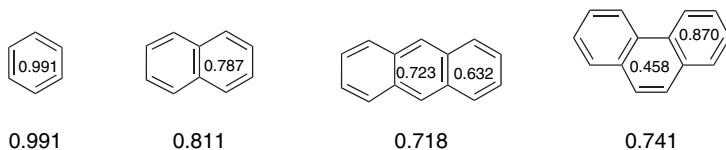
$$\text{HOMA} = 1 - [\alpha(R_{\text{opt}} - R_{\text{av}})^2 + \frac{\alpha}{n} \sum (R_{\text{av}} - R_i)^2] \quad (8.1)$$

where R_{av} is average bond length, R_{opt} is the optimum bond length, R_i is an individual bond length, n is the number of bonds, and α is a constant such that HOMA is equal to zero for a single localized structure. The HOMA equation can be rewritten as

$$\text{HOMA} = 1 - \frac{\alpha}{n} \sum [R_{\text{opt}} - R_i]^2 \quad (8.2)$$

The R_{opt} values are derived from butadiene, which is thereby the implicit standard of the definition. For C–C bonds, $\alpha = 257.7 \text{ \AA}^{-2}$ and $R_{\text{opt}} = 1.388 \text{ \AA}$. Further definition of bond lengths is required for structures with heteroatoms.

In the formulation in Equation (8.1), the first term, the deviation from the optimum length, accounts for the energy associated with bond length effects, and the second term, which reflects deviation from the average, accounts for bond alternation. The HOMA energy and alternation terms have been calculated for many aromatic compounds.¹⁵ The values for benzene, naphthalene, anthracene, and phenanthrene are shown below.¹⁶ Note the decrease as the molecules get larger. HOMA indices can also be assigned to the individual rings in polycyclic structures. A relatively low HOMA is assigned to the center ring in phenanthrene. We will see later that this is in accord with other properties of phenanthrene. In contrast, the center ring in anthracene has a slightly higher index than the terminal rings.



Another aromaticity index based on bond lengths was devised by Bird.¹⁷ The input into the index are bond order values derived from bond lengths. (See Section 1.4.6 to review the relationship between bond length and bond order.) The formulation of the index is

$$I = 100(1 - \frac{V}{V_k})V = \frac{100}{\bar{N}} \sqrt{\frac{\sum (N - \bar{N})^2}{n}} \text{ and } N = \frac{a}{R_2} - b \quad (8.3)$$

where \bar{N} is the arithmetic mean of bond orders. V_k is the value of V for the corresponding localized structures, and a and b are constants for each bond type.

The index I_A is assigned as 100 for benzene. The values are scaled for ring size and ring fusions, and increase with ring size so that naphthalene (142) and anthracene (206) have higher indices than benzene. This method is particularly useful for comparing heterocyclic compounds with hydrocarbons (see Section 8.6).

¹⁵ T. M. Krygowski and M. Cyranski, *Tetrahedron*, **52**, 1713 (1996).

¹⁶ M. K. Cyranski, B. T. Stepien, and T. M. Krygowski, *Tetrahedron*, **56**, 9663 (2000).

¹⁷ C. W. Bird, *Tetrahedron*, **41**, 1409 (1985); C. W. Bird, *Tetrahedron*, **48**, 335 (1992); C. W. Bird, *Tetrahedron*, **52**, 9945 (1996); C. W. Bird, *Tetrahedron*, **54**, 4641 (1998).

8.1.3. Electronic Criteria for Aromaticity

As discussed in the Introduction, Hückel's rule is an electronic criterion for aromaticity, and is based on the configuration of the π electrons. Another characteristic of aromatic compounds is a relatively large HOMO-LUMO gap, which indicates the absence of high-energy, reactive electrons, in agreement with the reduced reactivity of aromatic compounds to electrophilic reagents. This facet of electronic configuration can be expressed in terms of hardness (see p. 96 for the definition of hardness in terms of DFT theory).¹⁸

$$\eta = (\varepsilon_{\text{HOMO}} - \varepsilon_{\text{LUMO}})/2$$

The numerical value of hardness obtained by HMO calculations correlates with the stability of aromatic compounds.¹⁹ The energy gap can also be compared with polyene reference molecules to give "relative hardness." By this measure, the relative hardness of benzene is 0.765β when butadiene is assigned as 0. MNDO calculations have also been used in this context.²⁰

The correlation can be given an experimental basis when hardness is related to molar refractivity²¹:

$$\eta = \frac{19.6}{(R_D)^3} \quad (8.4)$$

Molar refractivity is easily derived from the refractive index. Hardness measured in this way correlates with other aromaticity criteria such as resonance energy per electron for a variety of hydrocarbons and heterocyclic molecules (see p. 747).²²

An experimental measure of the HOMO-LUMO gap is the reduction and oxidation potential of the ring.²³ A range of benzenoid and nonbenzenoid reduction potentials correlates with the LUMO energy, as calculated by a modified HMO method.²⁴

NMR spectroscopy also provides an experimental tool capable of assessing aromaticity. Aromatic compounds exhibit a *diamagnetic ring current*. Qualitatively, this ring current can be viewed as the result of migration of the delocalized π electrons under the influence of the magnetic field in an NMR spectrometer. The ring current results in a large magnetic anisotropy in aromatic compounds. The induced ring current gives rise to a local magnetic field that is opposed to the direction of the applied magnetic field. Nuclei in a region above or below the plane of an aromatic ring are shielded by the induced field and appear at relatively high field in the NMR spectrum, whereas nuclei in the plane of the ring—i.e., the atoms bound directly to the ring—occur at downfield positions. Antiaromatic compounds have a *paramagnetic ring current* and show opposite effects. These chemical shifts are evidence of *magnetic anisotropy*.²⁵ The detailed analysis of ^1H and ^{13}C chemical shifts is complicated.

- ¹⁸. F. De Proft and P. Geerlings, *Chem. Rev.*, **101**, 1451 (2001).
- ¹⁹. Z. Zhou and R. G. Parr, *J. Am. Chem. Soc.*, **111**, 7371 (1989).
- ²⁰. Z. Zhou and H. V. Navangul, *J. Phys. Org. Chem.*, **3**, 784 (1990); Z. Zhou, *Int. Rev. Phys. Chem.*, **11**, 243 (1992).
- ²¹. L. Komorowski, *Structure and Bonding*, **80**, 45 (1993).
- ²². C. W. Bird, *Tetrahedron*, **53**, 3319 (1997).
- ²³. A. J. Fry and P. C. Fox, *Tetrahedron*, **42**, 5255 (1986).
- ²⁴. A. Streitwieser, *J. Am. Chem. Soc.*, **82**, 4123 (1960).
- ²⁵. R. C. Haddon, *J. Am. Chem. Soc.*, **101**, 1722 (1979); J. Aihara, *J. Am. Chem. Soc.*, **103**, 5704 (1981); R. C. Haddon and K. Raghavachari, *J. Am. Chem. Soc.*, **107**, 289 (1985); S. Kuwajima and Z. G. Soos, *J. Am. Chem. Soc.*, **109**, 107 (1987).

The ^1H and ^{13}C shifts are also strongly dependent on carbon hybridization. In aromatic compounds, the ring current makes a significant contribution to the overall chemical shift, but does not appear to be the dominant factor.²⁶ Figure 8.2 is a representation of the shielding and deshielding areas of the benzene ring.

The relationship between chemical shift phenomena and aromaticity can be put on a numerical basis by calculation of the magnetic field at the center of the ring. These values, called the *nucleus independent chemical shift* (NICS), show good correlation with other manifestations of aromaticity.²⁷ Benzenoid hydrocarbons such as benzene, naphthalene, and anthracene show values of about -9 to -10 ppm. Heteroaromatic five-membered rings show somewhat more negative values (pyrrole, -15.1 ; thiophene, -13.6 ; furan, -12.3). Aromatic ions such as cyclopentadienide (-14.3) and cycloheptatrienylum (-7.6) are also negative. Antiaromatic species, including cyclobutadiene ($+27.6$) and borole ($+17.5$) are positive. Saturated compounds such as cyclohexane have values near zero. It is also possible to calculate NICS values for individual rings in a polycyclic system. The NICS value can be affected by other structural features that are not directly related to the aromatic ring current. The maximum for the ring current is located somewhat above the ring and other factors are reduced at this location, so that calculation of the NICS 1.0 Å above and below the ring is useful.²⁸

Several other methods have been devised to analyze the ring current effect. One approach is to isolate the individual orbitals that have π character and use them for the NICS computation.²⁹ Another quantity that relates anisotropic shielding to aromaticity is called the ARCS, *aromatic ring current shielding*.³⁰ As with NICS, it is computed

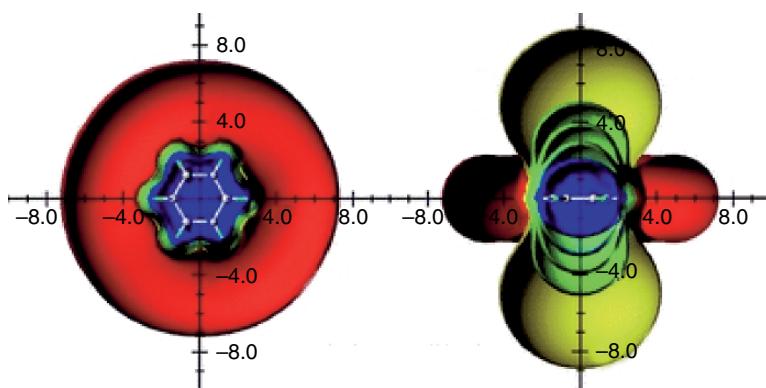


Fig. 8.2. Areas of shielding and deshielding in and perpendicular to the plane of the benzene ring. Reproduced from *J. Chem. Soc., Perkin Trans. 2*, 1893 (2001), by permission of the Royal Society of Chemistry. (See also color insert.)

- ²⁶ U. Fleischer, W. Kutzelnigg, P. Lazzeretti, and V. Muehlenkamp, *J. Am. Chem. Soc.*, **116**, 5298 (1994); S. Klod and E. Kleinpeter, *J. Chem. Soc., Perkin Trans. 2*, 1893 (2001); C. S. Wannere and P. v. R. Schleyer, *Org. Lett.*, **5**, 605 (2003).
- ²⁷ P. v. R. Schleyer, C. Maerker, A. Dransfeld, H. Jiao, and N. J. P. van Eikema Hommes, *J. Am. Chem. Soc.*, **118**, 6317 (1996).
- ²⁸ P. v. R. Schleyer, H. Jiao, N. J. R. van Eikema Hommes, V. G. Malkin, and O. L. Malkina, *J. Am. Chem. Soc.*, **119**, 12669 (1997); P. v. R. Schleyer, M. Manoharan, Z. -X. Wang, B. Kiran, H. Jiao, R. Puchta, and N. J.R. van Eikema Hommes, *Org. Lett.*, **3**, 2465 (2001).
- ²⁹ C. Corminboeuf, T. Heine, and J. Weber, *Phys. Chem. Chem. Phys.*, **5**, 246 (2003).
- ³⁰ J. Juselius and D. Sundholm, *Phys. Chem. Chem. Phys.*, **1**, 3429 (1999).

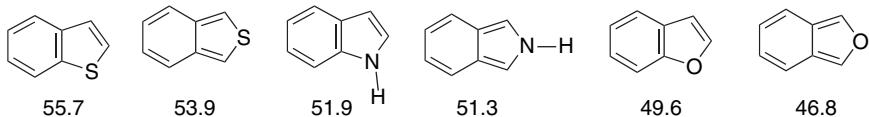
theoretically and defined in such a way that it can be used to compare different rings. The units are nanoamperes (nA), and the calculated ring currents are found to increase in more electron-rich systems, as is the case with NICS. Whereas benzene is 32 nA, pyrrole is 41.4 nA and cyclopentadienide is 72.2 nA. Conversely, it is lower for the cycloheptatrienyl cation (26.1 nA); thiophene (32.1 nA) is very similar to benzene; and nonaromatic compounds such as cyclohexane or 1,4-cyclohexadiene have much smaller values (2.1 and 1.7 nA, respectively).

Another electronic property associated with aromaticity is *magnetic susceptibility*, which is determined by measuring the force exerted on the sample by a magnetic field.³¹ Magnetic susceptibility is closely related to polarizability and is different in the plane and perpendicular to the plane of the ring. It can be determined by various spectroscopic measurements,³² as well as by using an NMR spectrometer.³³ It is observed that aromatic compounds have enhanced magnetic susceptibility, called *exaltation* (Λ), relative to values predicted on the basis of the localized structural components.³⁴

Magnetic Susceptibility Exaltation for Some Aromatic Hydrocarbons

Compound	Λ
Benzene	13.7
Naphthalene	30.5
Anthracene	48.6
Phenanthrene	46.2
Azulene	29.6

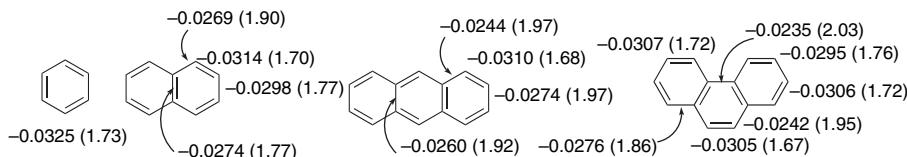
Magnetic susceptibility can also be calculated by computational methods; calculation by the B3LYP method correctly reproduces some of the trends in stability among the benzo[b]- and benzo[c]- derivatives of five-membered heterocycles.³⁵ The benzenoid benzo[b]- isomers are much more stable compounds than the quinoid benzo[c] isomers.



Because all of these electronic aspects of aromaticity are ultimately derived from the electron distribution, we might ask whether representations of electron density reveal any special features in aromatic compounds. The electron density of the π electrons can be mapped through the MESP (molecular electrostatic potential, see Section 1.4.5).³⁶ The MESP perpendicular to the ring is completely symmetrical for benzene, as would be expected for a delocalized structure and is maximal at about

- ³¹. E. A. Boudreaux and R. R. Gupta, in *Physical Methods in Heterocyclic Chemistry*, R. R. Gupta, ed., Wiley-Interscience, New York, 1984, pp. 281–311.
- ³². W. H. Flygare, *Chem. Rev.*, **74**, 653 (1974).
- ³³. K. Frei and H. J. Bernstein, *J. Chem. Phys.*, **37**, 1891 (1962).
- ³⁴. H. J. Dauben, J. D. Wilson, and J. L. Laity, *J. Am. Chem. Soc.*, **90**, 811 (1968); P. v. R. Schleyer and H. Jiao, *Pure Appl. Chem.*, **68**, 209 (1996); P. Friedman and K. F. Ferris, *Int. J. Quantum Chem.*, **24**, 843 (1990).
- ³⁵. B. S. Jursic, *J. Heterocycl. Chem.*, **33**, 1079 (1996).
- ³⁶. C. H. Suresh and S. R. Gadre, *J. Org. Chem.*, **64**, 2505 (1999).

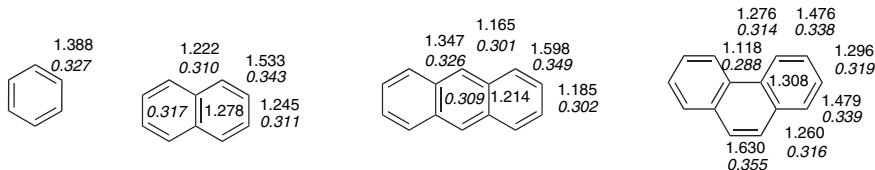
1.73 Å above and below the ring. In naphthalene, there are different values for the different bond types and also shifts in the position of the maxima. The 1,2-bonds, which have higher double-bond character, have more negative MESPs than the 2,3-, 8a-1, or 4a,8a-bonds. The maximum in the MESP is also closer to the ring for these bonds. The trend continues for anthracene and is particularly accentuated for phenanthrene. The 9,10-bond in phenanthrene has the closest maxima with respect to the ring, which suggests considerable localization of the 9,10-bond in phenanthrene.



Value of MESP and distance of maxima.

These data are consistent with both the bond order concept (see p. 76) and the idea that benzenoid structures are preferred to quinoid structures (see p. 724).

Atoms in molecules (AIM) concepts have also been applied to analysis of electron density distribution in benzene and several polycyclic hydrocarbons.³⁷ (See Section 1.4.3 to review AIM electron density indicators.) A correlation was found between the charge density at the bond critical point and bond lengths. Shorter bonds had higher ρ_c and more negative $-L(\nabla^2\rho_c)$, which is also true for other types of bonds. The shorter bonds also have greater ellipticity. Matta and Hernandez-Trujillo found that bond lengths were related to ρ_c for a series of aromatic molecules³⁸ They determined the delocalization indices, which indicate the number of electrons shared by adjacent atoms, for a number of rings. These values are 0.99, 1.39, and 1.89, respectively, for ethane, benzene, and ethene, the numbers reflecting the additional electron density associated with the multiple bonds. These values were also calculated for several fused-ring systems, as shown below. The bond ellipticity was also calculated and is given with the structures (italic numbers). Bond ellipticity increases with bond order, reflecting the accumulation of π -electron density.



These values faithfully capture both structural and reactivity variations among the ring systems. The highest bond orders are found at the 1,2-bond of naphthalene and in anthracene. For phenanthrene, the highest bond order is between the 9,10 positions in the center ring. There is substantially less bond alteration around the periphery of phenanthrene than in anthracene. A pictorial representation of this information is given in Figure 8.3. The overall molecular shape is represented by the 0.001 au isodensity

³⁷ S. T. Howard and T. M. Krygowski, *Can. J. Chem.*, **75**, 1174 (1997).

³⁸ C. F. Matta and J. Hernandez-Trujillo, *J. Phys. Chem. A*, **107**, 7496 (2003).

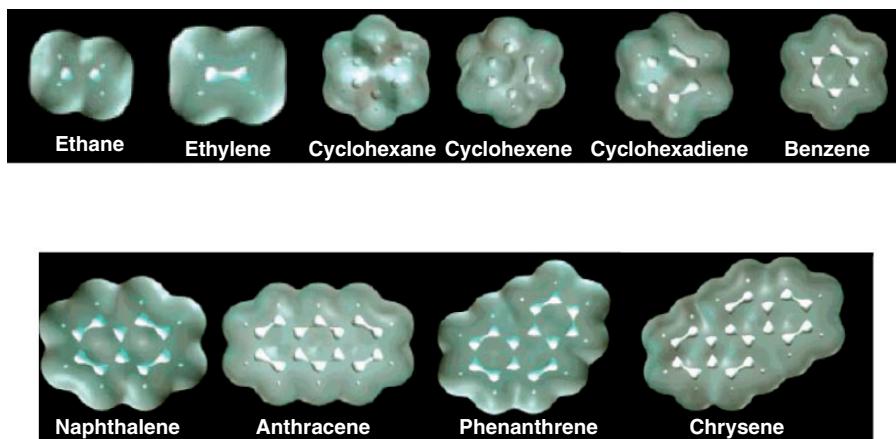
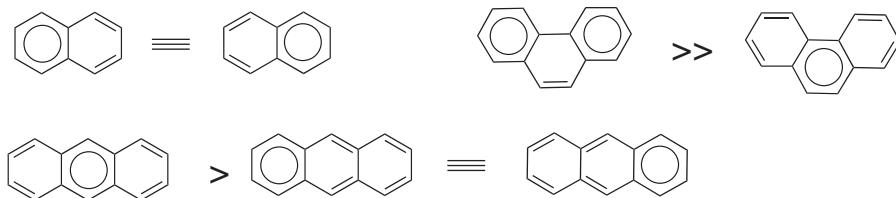


Fig. 8.3. Comparison of electron density as a function of bond order. See text for discussion. Reproduced from *J. Phys. Chem. A*, **107**, 7496 (2003), by permission of the American Chemical Society. (See also color insert.)

surface (gray). The inner lighter surface uses the 0.3274 au surface, which corresponds to the ρ_c for benzene. Bonds with higher ρ_c and higher bond order show merged density at this level. Bonds with lower ρ_c show separation of density at this level between the atoms.

The picture is also consistent with the intuitive idea that the best structure for any given polycyclic molecule is the one with the maximum number of benzene-like rings.³⁹ According to this concept the two rings in naphthalene are identical, but less aromatic than the benzene ring. The external rings in phenanthrene are more aromatic than the central ring, whereas the central ring is more aromatic in anthracene.



8.1.4. Relationship among the Energetic, Structural, and Electronic Criteria of Aromaticity

It has been argued that there are two fundamental aspects of aromaticity, one reflecting the structural and energetic facets and the other related to electron mobility.⁴⁰ Parameters of aromaticity such as bond length and stabilization energy appear to be largely separate from the electronic criteria, such as diamagnetic ring current. However, there is often a correlation between the two kinds of measurements. The

³⁹. E. Clar, *The Aromatic Sextet*, John Wiley & Sons, London, 1972.

⁴⁰. A. R. Katritzky, P. Barczynski, G. Musumarra, D. Pisano, and M. Szafran, *J. Am. Chem. Soc.*, **111**, 7 (1989); A. R. Katritzky, M. Karelson, S. Sild, T. M. Krygowski, and K. Jug, *J. Org. Chem.*, **63**, 5228 (1998); V. I. Minkin, M. N. Glukhovtsev, and B. Ya. Simkin, *Aromaticity and Antiaromaticity*, Wiley, New York, 1994.

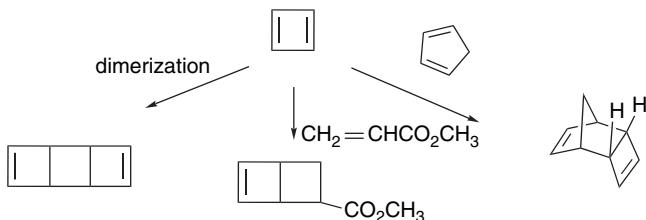
more stabilized compounds exhibit the greatest magnetic susceptibility.⁴¹ The various criteria all correlate, although there may be variation in the degree of correlation for different types of compounds.⁴² Aromaticity is thus best conceived of as a single characteristic owing to structural factors that results in both stabilization and the phenomena associated with electron mobility.

8.2. The Annulenes

The term *annulene* refers to completely conjugated monocyclic polyenes.⁴³ The synthesis and study of annulenes has been extended well beyond the first several members of the series, cyclobutadiene, benzene, and cyclooctatetraene, which were described in the Introduction. The generality and limits of the Hückel rule can be tested by considering the properties of the annulene series. In this section, we consider the properties of the annulenes and related compounds in the context of aromaticity.

8.2.1. Cyclobutadiene

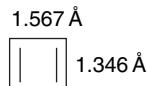
Although several derivatives of cyclobutadiene are known and are discussed shortly, cyclobutadiene itself has been observed only as a *matrix-isolated species*, that is trapped at very low temperature in a frozen inert gas. The first successful synthesis of cyclobutadiene was achieved by release from a stable iron complex.⁴⁴ Various trapping agents react with cyclobutadiene to give Diels-Alder adducts, indicating that it is reactive as both a diene and a dienophile.⁴⁵ Dehalogenation of *trans*-3,4-dibromocyclobutene gave the same reaction products.⁴⁶



In the absence of trapping agents, a characteristic dimer is produced, which is the result of one cyclobutadiene molecule acting as a diene and the other as a dienophile in a Diels-Alder reaction. This dimerization is an extremely fast reaction and limits the lifetime of cyclobutadiene, except at extremely low temperatures.

- ⁴¹ P. v. R. Schleyer, P. K. Freeman, H. Jiao, and B. Goldfuss, *Angew. Chem. Int. Ed. Engl.*, **34**, 337 (1995); C. W. Bird, *Tetrahedron*, **52**, 9945 (1996).
- ⁴² M. K. Cyranski, T. M. Krygowski, A. R. Katritzky, and P. v. R. Schleyer, *J. Org. Chem.*, **67**, 1333 (2002).
- ⁴³ F. Sondheimer, *Pure Appl. Chem.*, **28**, 331 (1971); *Acc. Chem. Res.*, **5**, 81 (1972).
- ⁴⁴ L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Am. Chem. Soc.*, **87**, 3253 (1965).
- ⁴⁵ L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Am. Chem. Soc.*, **88**, 623 (1966); J. C. Barborak, L. Watts, and R. Pettit, *J. Am. Chem. Soc.*, **88**, 1328 (1966); D. W. Whitman and B. K. Carpenter, *J. Am. Chem. Soc.*, **102**, 4272 (1980).
- ⁴⁶ E. K. G. Schmidt, L. Brener, and R. Pettit, *J. Am. Chem. Soc.*, **92**, 3240 (1970).

Cyclobutadiene can also be prepared by photolysis of several different precursors at very low temperature in solid inert gases.⁴⁷ These methods provide cyclobutadiene in a form that is amenable for spectroscopic study. Analysis of the infrared spectrum of the product and deuterated analogs generated from labeled precursors have confirmed the theoretical conclusion that cyclobutadiene is a rectangular molecule.⁴⁸



A number of alkyl-substituted cyclobutadienes have been prepared by related methods.⁴⁹ Increasing alkyl substitution enhances the stability of the compounds. The tetra-*t*-butyl derivative is stable up to at least 150°C, but is very reactive toward oxygen.⁵⁰ This reactivity reflects the high energy of the HOMO. The chemical behavior of the cyclobutadienes is in excellent accord with that expected from the theoretical picture of the structure of these compounds.

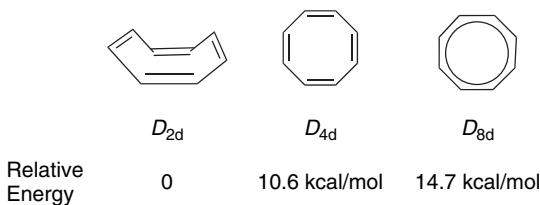
While simple HMO theory assumes a square geometry for cyclobutadiene, most MO methods predict a rectangular structure as the minimum-energy geometry.⁵¹ The rectangular structure is calculated to be strongly destabilized (antiaromatic) with respect to a polyene model.⁵² With HF/6-31G* calculations, for example, cyclobutadiene is found to have a negative resonance energy of -54.7 kcal/mol, relative to 1,3-butadiene. Furthermore, 30.7 kcal of strain is found, giving a total destabilization of 85.4 kcal/mol.⁵³ G2 and MP4/G-31(d,p) calculations arrive at an antiaromatic destabilization energy of about 42 kcal/mol.⁵⁴ A homodesmotic reaction incorporating polyyradicals gives a value of 40.3 as the antiaromatic destabilization at the MP4(SDQ)/6-31G(d,p) level.⁵⁵ Recently, the technique of photoacoustic calorimetry provided the first experimental thermodynamic data on cyclobutadiene. The ΔH_f value of 114 ± 11 kcal/mol that was found leads to a total destabilization of 87 kcal/mol, of which 32 kcal/mol is attributed to ring strain and 55 kcal/mol to antiaromaticity.⁵⁶

- ⁴⁷. G. Maier and M. Scheider, *Angew. Chem. Int. Ed. Engl.*, **10**, 809 (1971); O. L. Chapman, C. L. McIntosh, and J. Pancansky, *J. Am. Chem. Soc.*, **95**, 614 (1973); O. L. Chapman, D. De La Cruz, R. Roth, and J. Pancansky, *J. Am. Chem. Soc.*, **95**, 1337 (1973); C. Y. Lin and A. Krantz, *J. Chem. Soc., Chem. Commun.*, 1111 (1972); G. Maier, H. G. Hartan, and T. Sayrac, *Angew. Chem. Int. Ed. Engl.*, **15**, 226 (1976); H. W. Lage, H. P. Reisenauer, and G. Maier, *Tetrahedron Lett.*, **23**, 3893 (1982).
- ⁴⁸. S. Masamune, F. A. Souto-Bachiller, T. Machiguchi, and J. E. Bertie, *J. Am. Chem. Soc.*, **100**, 4889 (1978).
- ⁴⁹. G. Maier, *Angew. Chem. Int. Ed. Engl.*, **13**, 425 (1974); S. Masamune, *Tetrahedron*, **36**, 343 (1980).
- ⁵⁰. G. Maier, S. Pfriem, U. Schafer, and R. Matusch, *Angew. Chem. Int. Ed. Engl.*, **17**, 520 (1978).
- ⁵¹. J. A. Jafri and M. D. Newton, *J. Am. Chem. Soc.*, **100**, 5012 (1978); W. T. Borden, E. R. Davidson, and P. Hart, *J. Am. Chem. Soc.*, **100**, 388 (1978); H. Kollmar and V. Staemmler, *J. Am. Chem. Soc.*, **99**, 3583 (1977); M. J. S. Dewar and A. Komornicki, *J. Am. Chem. Soc.*, **99**, 6174 (1977); B. A. Hess, Jr., P. Carsky, and L. J. Schaad, *J. Am. Chem. Soc.*, **105**, 695 (1983); H. Kollmar and V. Staemmler, *J. Am. Chem. Soc.*, **100**, 4304 (1978); C. van Wullen and W. Kutzelnigg, *Chem. Phys. Lett.*, **205**, 563 (1993).
- ⁵². M. N. Glukhovtsev, S. Laiter, and A. Pross, *J. Phys. Chem.*, **99**, 6828 (1995).
- ⁵³. B. A. Hess, Jr., and L. J. Schaad, *J. Am. Chem. Soc.*, **105**, 7500 (1983).
- ⁵⁴. M. N. Glukhovtsev, R. D. Bach, and S. Laiter, *Theochem*, **417**, 123 (1997).
- ⁵⁵. C. H. Suresh and N. Koga, *J. Org. Chem.*, **67**, 1965 (2002).
- ⁵⁶. A. A. Deniz, K. S. Peters, and G. J. Snyder, *Science*, **286**, 1119 (1999).

[6]Annulene is benzene. Its properties are so familiar to students of organic chemistry that not much need be said here. It is the parent compound of a vast series of derivatives. As we indicated in Section 8.2.1, benzene exhibits all the properties associated with aromaticity. It shows exceptional thermodynamic stability and its perfectly hexagonal structure sets the standard for bond uniformity. Benzene is much less reactive than conjugated polyenes toward electrophiles, which is in line with the energy of the HOMO of benzene being lower than that for the HOMO of a conjugated polyene. Benzene also exhibits NMR and magnetic susceptibility criteria consistent with aromaticity.

8.2.3. 1,3,5,7-Cyclooctatetraene

The next higher annulene, cyclooctatetraene, is nonaromatic.⁵⁷ It is readily isolable and the chemical reactivity is normal for a polyene. X-ray structure determination shows that the molecule is tub-shaped,¹⁹ and therefore is not a planar system to which the Hückel rule applies. The bond lengths around the ring alternate as expected for a polyene. The C=C bonds are 1.33 Å, whereas the C–C bonds are 1.462 Å in length.⁵⁸ Thermodynamic analysis provides no evidence of any special stability.⁵⁹ There have been both experimental and theoretical studies aimed at estimating the relative stability of the planar form of cyclooctatetraene.⁶⁰ HF/6-31G* calculations find the completely delocalized D_{8h} structure to be about 4.1 kcal higher in energy than the conjugated planar D_{4h} structure, suggesting that delocalization leads to destabilization.⁶¹ Similar results are obtained using MP2/CASSCF calculations.⁶²



These two energies are, respectively, comparable to the experimental activation energies for conformation inversion of the tub conformer and bond shifting, suggesting that the two planar structures might represent the transition states for those processes. The E_a have been measured for several substituted cyclooctatetraenes. According to

⁵⁷. G. Schroeder, *Cyclooctatetraene*, Verlag Chemie, Weinheim, 1965; G. I. Fray and R. G. Saxton, *The Chemistry of Cyclooctatetraene and Its Derivatives*, Cambridge University Press, Cambridge, 1978.

⁵⁸. M. Traetteberg, *Acta Chem. Scand.*, **20**, 1724 (1966).

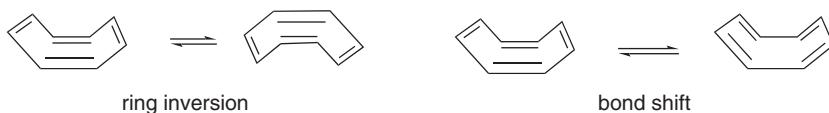
⁵⁹. R. B. Turner, B. J. Mallon, M. Tichy, W. v. E. Doering, W. Roth, and G. Schroeder, *J. Am. Chem. Soc.*, **95**, 8605 (1973).

⁶⁰. L. A. Paquette, *Acc. Chem. Res.*, **26**, 57 (1993).

⁶¹. D. A. Hrovat and W. T. Borden, *J. Am. Chem. Soc.*, **114**, 5879 (1992); P. Politzer, J. S. Murray, and J. M. Seminario, *Int. J. Quantum Chem.*, **50**, 273 (1994).

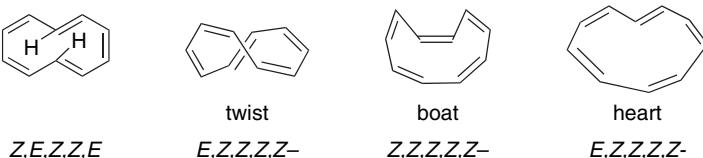
⁶². J. L. Andres, D. Castano, A. Morreale, R. Palmeiro, and R. Gomperts, *J. Chem. Phys.*, **108**, 203 (1998).

in these studies the ring inversion TS is usually about 2 kcal/mol below the bond shift TS.⁶⁰ This result implies a small destabilization of the delocalized structure.



8.2.4. [10]Annulenes—1,3,5,7,9-Cyclodecapentaene Isomers

Larger annulenes permit the incorporation of *trans* double bonds into the rings, and isomeric structures are possible beginning with [10]annulene. According to the Hückel rule, [10]annulene would be aromatic if it were planar. However, all the 1,3,5,7,9-cyclodecapentaene isomers suffer serious steric strain that prevents the planar geometry from being adopted. The *Z,E,Z,Z,E*-isomer, which has minimal bond angle strain, suffers a severe nonbonded repulsion between the two internal hydrogens. The most stable structures are called the twist, boat, and heart.

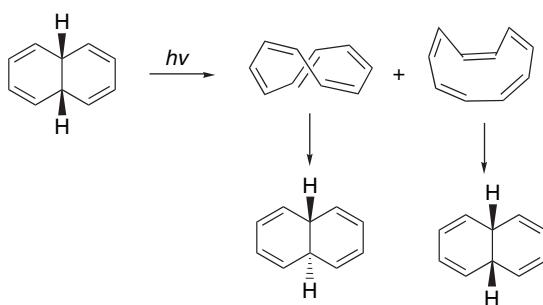


The *Z,Z,Z,Z,Z*-isomer is required by geometry to have bond angles of 144°C to maintain planarity and would therefore be destabilized by distortion of the normal trigonal bond angle. According to CCSD(T)/TZ2P-level calculations, the most stable structure is the twist form of the *E,Z,Z,Z,Z*-isomer.⁶³ This isomer also has the closest agreement between calculated and observed NMR chemical shifts.⁶⁴ All of the isomers prepared to date are quite reactive, but whether the most stable isomer has been observed is uncertain. Two isomeric [10]annulenes, as well as other products, are formed by photolysis of *cis*-9,10-dihydronaphthalene.⁶⁵ Neither compound exhibits properties that would suggest aromaticity. The NMR spectra are consistent with polyene structures. Both compounds are thermally unstable and revert back to stereoisomeric dihydronaphthalenes. The stereochemistry of the products is consistent with assigning the *E,Z,Z,Z,Z-* and *Z,Z,Z,Z,Z*-configurations. These results indicate that [10]annulene is sufficiently distorted from planarity that little aromatic stabilization is achieved.

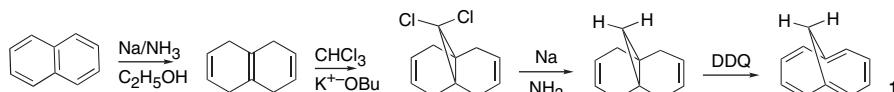
⁶³. R. A. King, T. D. Crawford, J. F. Stanton, and H. F. Schaefer, III, *J. Am. Chem. Soc.*, **121**, 10788 (1999).

⁶⁴. D. R. Price and J. F. Stanton, *Org. Lett.*, **4**, 2809 (2002).

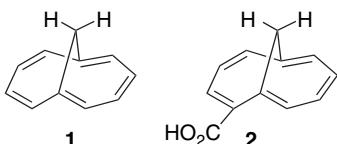
⁶⁵. S. Masamune, K. Hojo, G. Gigam, and D. L. Rabenstein, *J. Am. Chem. Soc.*, **93**, 4966 (1971); S. Masamune and N. Darby, *Acc. Chem. Res.*, **5**, 272 (1972).



A number of structures have been prepared that avoid the steric problems associated with the 1,3,5,7,9-cyclodecapentaenes. 1,6-Methano[10]annulene (**1**) can be prepared from naphthalene in multigram quantities in four steps.⁶⁶



Quite a number of substituted derivatives have also been prepared. In compound **1** the steric problem is avoided with only a modest loss of planarity in the π system.⁶⁷



The results of X-ray crystal structure determinations on **1**⁶⁸ and its carboxylic acid derivative **2**⁶⁹ are shown in Figure 8.4. Both reveal a pattern of bond lengths that is similar to that in naphthalene (see p. 18).⁷⁰

The NMR spectrum of compound **1** shows a diamagnetic ring current of the type expected in an aromatic system.⁷¹ The NICS calculated for **1** is -17.7, which indicates aromaticity.⁷² Both spectroscopic data and MO (MP2/DZV**) and DFT (B3LYP/6-31G) calculations indicate that the ground state of **1** is delocalized.⁷³ Thus while the π system in **1** is not completely planar, it appears to be sufficiently close to provide a delocalized 10-electron π system. A stabilization energy of 17.2 kcal has been obtained on the basis of an experimental heat of hydrogenation.⁷⁴

⁶⁶ E. Vogel, W. Klug, and A. Breuer, *Org. Synth.*, **VI**, 731 (1988).

⁶⁷ E. Vogel and H. D. Roth, *Angew. Chem. Int. Ed. Engl.*, **3**, 228 (1964).

⁶⁸ R. Bianchi, T. Pilati, and M. Simonetta, *Acta Crystallogr., Sect. B*, **B36**, 3146 (1980).

⁶⁹ M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, **48**, 1429 (1965).

⁷⁰ O. Bastainsen and P. N. Skancke, *Adv. Chem. Phys.*, **3**, 323 (1961).

⁷¹ E. Vogel, *Pure Appl. Chem.*, **20**, 237 (1969).

⁷² M. Nendel, K. N. Houk, L. M. Tolbert, E. Vogel, H. Jiao, and P. v. R. Schleyer, *J. Phys. Chem. A*, **102**, 7191 (1998).

⁷³ C. Gellini, P. R. Salvi, and E. Vogel, *J. Phys. Chem. A*, **104**, 3110 (2000); R. Seiler and B. Dick, *Angew. Chem. Int. Ed. Engl.*, **40**, 4020 (2001); L. Catani, C. Gellini, and P. R. Salvi, *J. Phys. Chem. A*, **102**, 1945 (1998).

⁷⁴ W. R. Roth, M. Bohm, H. W. Lennartz, and E. Vogel, *Angew. Chem. Int. Ed. Engl.*, **22**, 1007 (1983); W. R. Roth, F.-G. Klarner, G. Siepert, and H.-W. Lennartz, *Chem. Ber. Recueil.*, **125**, 217 (1992).

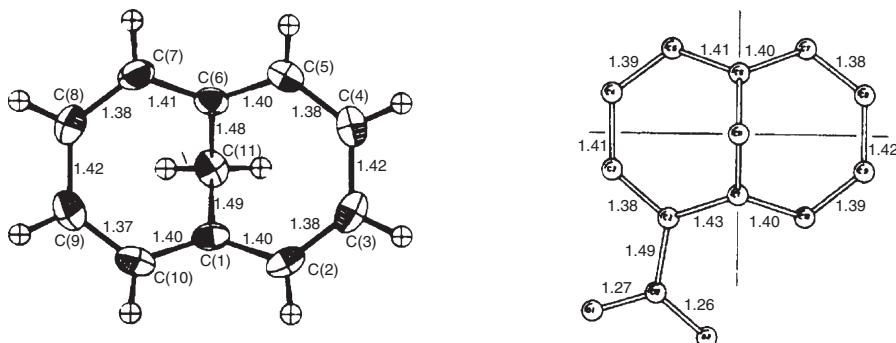
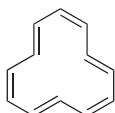


Fig. 8.4. X-ray crystal structure of 1,6-methanocyclodeca-1,3,5,7,9-pentaene (left) and 1,6-methanocyclodeca-1,3,5,7,9-pentaene-2-carboxylic acid (right). Reproduced from *Acta Crystallogr. B*, **36**, 3146 (1980) and *Helv. Chim. Acta*, **48**, 1429 (1965), by permission of the International Union of Crystallography and Wiley-VCH, respectively.

The deviation from planarity that is present in a structure such as **1** raises the question of how severely a conjugated system can be distorted from the ideal coplanar alignment of *p* orbitals and still retain aromaticity. This problem has been analyzed by determining the degree of rehybridization necessary to maximize *p*-orbital overlap in **1**.⁷⁵ A quantitative VB treatment also finds the periphery of conjugated bonds to be delocalized and the orbitals are quite similar to those in naphthalene.⁷⁶ Thus a relatively small amount of rehybridization greatly improves orbital overlap in the twisted system and stabilizes the structure.

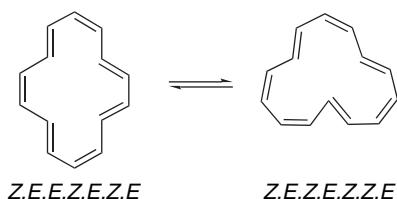
8.2.5. [12], [14], and [16]Annulenes

[12]Annulene is a very unstable compound that undergoes cyclization to bicyclic isomers and can be kept only at very low temperature.⁷⁷ The NMR spectrum has been studied at low temperature.⁷⁸ Apart from indicating the *Z,E,Z,E,Z,E*-double-bond geometry shown in the structure, the spectrum reveals a *paramagnetic ring current*, the opposite from what is observed for aromatic systems. This feature is characteristic of the [4*n*]annulenes and has been useful in characterizing the aromaticity or lack of it in annulenes.⁷⁹



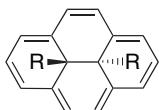
[14]Annulene was first prepared in 1960.⁸⁰ Its NMR spectrum has been investigated and shows that two geometric isomers are in equilibrium.⁸¹

- ^{75.} R. C. Haddon, *Acc. Chem. Res.*, **21**, 243 (1988).
- ^{76.} M. Sironi, M. Raimondi, D. L. Cooper, and J. Gerratt, *Theochem*, **338**, 257 (1995).
- ^{77.} J. F. M. Oth, H. Rottele, and G. Schroeder, *Tetrahedron Lett.*, 61 (1970).
- ^{78.} J. F. M. Oth, J.-M. Gilles, and G. Schroeder, *Tetrahedron Lett.*, 67 (1970).
- ^{79.} R. C. Haddon, *Tetrahedron*, **28**, 3613, 3635 (1972).
- ^{80.} F. Sondheimer and Y. Gaoni, *J. Am. Chem. Soc.*, **82**, 5765 (1960).
- ^{81.} J. F. M. Oth, *Pure Appl. Chem.*, **25**, 573 (1971).



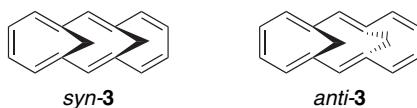
The spectrum also reveals a significant diamagnetic (aromatic) ring current. The internal hydrogens [C(3), C(6), C(10), C(13)] are very far upfield ($\delta = -0.61$ ppm).³⁶ The interconversion of the two forms involves a configurational change from *E* to *Z* of at least one double bond, and the E_a for this process is about 10 kcal/mol. The crystal structure for [14]annulene shows the *Z,E,E,Z,E,Z,E*-form to be present in the solid.⁸² The bond lengths around the ring range from 1.35 to 1.41 Å, but do not show the alternating pattern of short and long bonds expected for a localized polyene. There is some distortion from planarity, especially at carbon atoms 3, 6, 10, and 13, which is caused by nonbonded repulsions between the internal hydrogens. MP2/6-31G* and B3LYP/6-31G* calculations find the delocalized structure as the only minimum.⁸³

A 14-electron π system can be generated in circumstances in which the steric problem associated with the internal hydrogens of [14]annulene can be avoided. This can be achieved in 10b,10c-dihydropyrene systems, in which the annulene ring is built around a saturated core.



Several derivatives of this ring system have been synthesized.⁸⁴ The properties of these compounds indicate that the conjugated system has aromatic character. They exhibit NMR shifts characteristic of a diamagnetic ring current. Typical aromatic substitution reactions can be carried out.⁸⁵ An X-ray crystal structure ($R = C_2H_5$) shows that the bond lengths are in the aromatic range (1.39–1.40 Å), and there is no strong alternation around the ring.⁸⁶ The peripheral atoms are not precisely planar, but the maximum deviation from the average plane is only 0.23 Å. The dimethyl derivative is essentially planar with bond lengths between 1.38 and 1.40 Å.

Another family of 14 π -electron systems is derived from structure **3**.⁸⁷



⁸² C. C. Chiang and I. C. Paul, *J. Am. Chem. Soc.*, **94**, 4741 (1972).

⁸³ C. H. Choi, M. Kertesz, and A. Karpfen, *J. Am. Chem. Soc.*, **119**, 11994 (1997).

⁸⁴ (a) R. H. Mitchell and V. Boekelheide, *J. Am. Chem. Soc.*, **96**, 1547 (1974); (b) V. Boekelheide and T. A. Hylton, *J. Am. Chem. Soc.*, **92**, 3669 (1970); (c) H. Blaschke, C. E. Ramey, I. Calder, and V. Boekelheide, *J. Am. Chem. Soc.*, **92**, 3675 (1970); (d) V. Boekelheide and J. B. Phillips, *J. Am. Chem. Soc.*, **89**, 1695 (1967); (e) R. H. M. Mitchell, V. S. Iyer, N. Khalifa, R. Mahadevan, S. Venugopalan, S. A. Weerawarna, and P. Zhou, *J. Am. Chem. Soc.*, **117**, 1514 (1995).

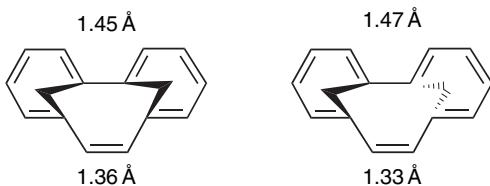
⁸⁵ J. B. Phillips, R. J. Molyneux, E. Sturm, and V. Boekelheide, *J. Am. Chem. Soc.*, **89**, 1704 (1967).

⁸⁶ A. W. Hanson, *Acta Crystallogr.*, **23**, 476 (1967).

⁸⁷ E. Vogel, *Pure Appl. Chem.*, **28**, 355 (1971).

The *syn* isomer can achieve a conjugated system with angles of up to 35° between adjacent *p* orbitals. The *anti* isomer is much more twisted.⁸⁸ An X-ray crystal structure determination has been done on the *syn* isomer and is illustrated in Figure 8.5. It shows C–C bond lengths between 1.368 and 1.418 Å for the conjugated system.⁸⁹ The spectroscopic properties of the *syn* isomer are consistent with considering it to be a delocalized annulene.⁹⁰ B3LYP/6-31G* calculations indicate that both the *syn* and *anti* structures are stabilized by delocalization, the *syn* (17.6 kcal/mol) more so than the *anti* (8.1 kcal).⁹¹

An isomeric system is related to the benzenoid hydrocarbon phenanthrene. Both the *syn* and *anti* stereoisomers have been synthesized.⁹²



The *syn* isomer shows evidence of a diamagnetic ring current, from both the relatively low field position of the vinylic hydrogens and the upfield shift of the methylene hydrogens. The *anti* isomer shows much less pronounced shifts. The X-ray crystal structure (Figure 8.6) of the *syn* isomer shows a moderate level of bond alternation, ranging from 1.36 to 1.45 Å. In the *anti* isomer bond alternation is more pronounced with the double bond in the center ring being essentially a localized double bond.

The Hückel rule predicts nonaromaticity for [16]annulene. The compound has been synthesized and characterized.⁹³ The bond lengths show significant alternation in length (C=C, 1.34 Å; C–C, 1.46 Å), and the molecule is less planar

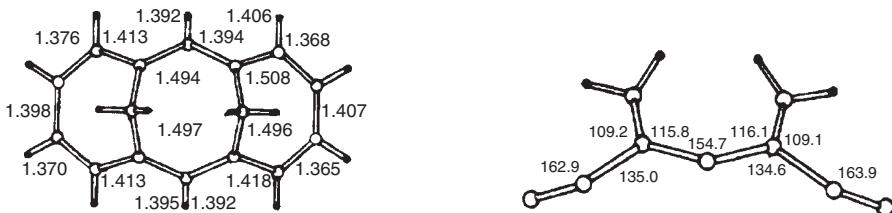


Fig. 8.5. Carbon framework from X-ray crystal structure of *syn*-tricyclo[8.4.1.1^{3,8}]hexadeca-1,3,5,7,9,11,13-heptaene (left). Side view showing deviation from planarity of the annulene ring (right). Reproduced from *Acta Crystallogr. B*, **33**, 940 (1977), by Permission of the International Union of Crystallography.

- ⁸⁸. E. Vogel, J. Sombroek, and W. Wagemann, *Angew. Chem. Int. Ed. Engl.*, **14**, 564 (1975); E. Vogel, U. Haberland, and H. Gunther, *Angew. Chem. Int. Ed. Engl.*, **9**, 513 (1970).
- ⁸⁹. R. Destro, T. Pilati, and M. Simonetta, *Acta Crystallogr., B*, **33**, 940 (1977).
- ⁹⁰. J. Dewey, H. M. Deger, W. Froehlich, B. Dick, K. A. Klingensmith, G. Hohlneicher, E. Vogel, and J. Michl, *J. Am. Chem. Soc.*, **102**, 6412 (1980).
- ⁹¹. M. Nendel, K. N. Houk, L. M. Tolbert, E. Vogel, H. Jiao, and P. v. R. Schleyer, *Angew. Chem. Int. Ed. Engl.*, **36**, 748 (1997).
- ⁹². E. Vogel, W. Puttmann, W. Duchatsch, T. Schieb, H. Schmickler, and J. Lex, *Angew. Chem. Int. Ed. Engl.*, **25**, 720 (1986); E. Vogel, T. Schieb, W. H. Schulz, K. Schmidt, H. Schmickler, and J. Lex, *Angew. Chem. Int. Ed. Engl.*, **25**, 723 (1986).
- ⁹³. I. Calder, Y. Gaoni, and F. Sondheimer, *J. Am. Chem. Soc.*, **90**, 4946 (1968); G. Schroeder and J. F. M. Oth, *Tetrahedron Lett.*, 4083 (1966).

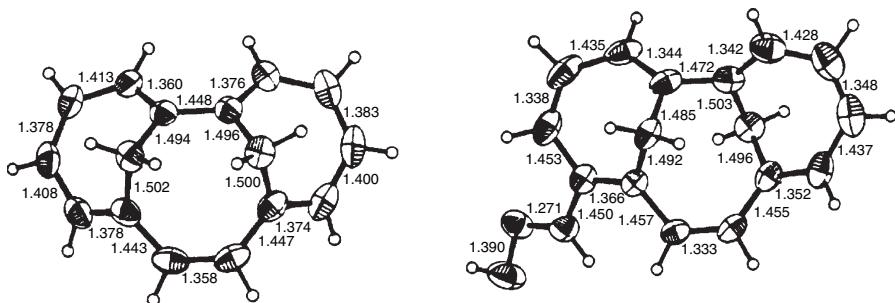
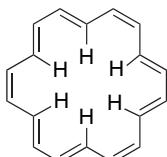


Fig. 8.6. X-ray structure of *syn*-tricyclo[8.4.1.1^{4,9}]hexadeca-2,4,6,8,10,12,14-heptaene (left). X-ray crystal structure of *anti* isomer of tricyclo[8.4.1.1^{4,9}]hexadeca-2,4,6,8,10,12,14-heptaene-5-carbaldehyde oxime (right). Reproduced from *Angew. Chem. Int. Ed. Engl.*, **25**, 720, 723 (1986), by permission of Wiley-VCH.

than [14]annulene.⁹⁴ Experimental combustion data indicate that [16]annulene is less stable than cyclooctatetraene.⁹⁵ Computational studies and NMR spectra of deuterated [16]annulene indicate that there are several conformations that differ in relative placement of the internal hydrogens.⁹⁶ These structural data are consistent with regarding [16]annulene as being nonaromatic.

8.2.6. [18]Annulene and Larger Annulenes

[18]Annulene offers a particularly significant test of the Hückel rule. The internal cavity in [18]annulene is large enough to minimize steric interaction between the internal hydrogens in a geometry that is free of angle strain. Most MO calculations find the delocalized structure to be more stable than the polyene.⁹⁷ Both MP/6-31G* and B3LYP/6-311G*calculations find a delocalized structure with D_{6h} symmetry as the minimum energy. The bond lengths are 1.39–1.42 Å, and a stabilization of 18 kcal/mol is indicated.⁹⁸

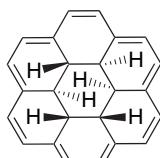


The properties of [18]annulene are consistent with its being aromatic. The X-ray crystal structure shows the molecule to be close to planarity, with the maximum deviation from the plane being 0.085 Å.⁹⁹ The bond lengths are in the range 1.385–1.405 Å, and

- ^{94.} S. M. Johnson and I. C. Paul, *J. Am. Chem. Soc.*, **90**, 6555 (1968).
- ^{95.} G. R. Stevenson and B. E. Forch, *J. Am. Chem. Soc.*, **102**, 5985 (1980).
- ^{96.} J. M. Hernando, J. J. Quirante, and F. Enriquez, *Collect. Czech. Chem. Commun.*, **57**, 1 (1992); C. D. Stevenson and T. L. Kurth, *J. Am. Chem. Soc.*, **122**, 722 (2000).
- ^{97.} J. M. Shulman and R. L. Disch, *Theochem.*, **80**, 213 (1991); K. Yoshizawa, T. Kato, and T. Yamabe, *J. Phys. Chem.*, **100**, 5697 (1996).
- ^{98.} K. K. Baldridge and J. S. Siegel, *Angew. Chem. Int. Ed. Engl.*, **36**, 745 (1997); C. H. Choi, M. Kertesz, and A. Karpfen, *J. Am. Chem. Soc.*, **119**, 11994 (1997).
- ^{99.} J. Bregman, F. L. Hirshfeld, D. Rabinovich, and G. M. J. Schmidt, *Acta Crystallogr.*, **19**, 227 (1965); F. L. Hirshfeld and D. Rabinovich, *Acta Crystallogr.*, **19**, 235 (1965); S. Gorter, E. Rutten-Kulemans, M. Krever, C. Romers, and D. W. J. Cruickshank, *Acta Cryst.*, **B51**, 1036 (1995).

the pattern is short, short, long, rather than alternating. The NMR spectrum indicates an aromatic ring current.¹⁰⁰ The chemical reactivity of the molecule also justifies its classification as aromatic.¹⁰¹

There are also examples of [18]annulene systems constructed around a saturated central core, such as in compound **4**.¹⁰² In this compound, the internal protons are at very high field (-6 to -8 ppm), whereas the external protons are far downfield (~ 9.5 ppm).

**4**

The chemical shift data can be used as the basis for calculating the diamagnetic ring current by comparing the value with the maximum ring current expected for a completely delocalized π system. By this criterion, the flexible [18]annulene maintains only about half (0.56) of the maximum ring current, whereas the rigid ring in **4** gives a value of 0.88, indicating more effective conjugation in this system.

The synthesis of annulenes has been carried forward to larger rings as well. [20]Annulene,¹⁰³ [22]annulene,¹⁰⁴ and [24]annulene¹⁰⁵ have all been reported. The NMR spectra of these compounds are consistent with regarding [22]annulene as aromatic, whereas the [20] and [24] analogs are not. The dominant structure for [24]annulene has a repeating *Z,E,E*-motif of double bonds. The internal hydrogens are at lower field in the ^1H -NMR spectrum than the external ones, which is consistent with a paramagnetic ring current. There is another minor conformation that has the same configuration of the double bonds. There is also evidence for a bond shift process that interchanges single and double bonds. This process occurs with a ΔG^\ddagger of about 10 kcal/mol.¹⁰⁶ Although the properties of these molecules have not been studied as completely as for the smaller systems, they are consistent with the predictions of the Hückel rule.

¹⁰⁰ Y. Gaoni, A. Melera, F. Sondheimer, and R. Wolovsky, *Proc. Chem. Soc.*, 397 (1965).

¹⁰¹ I. C. Calder, P. J. Garratt, H. C. Longuet-Higgins, F. Sondheimer, and R. Wolovsky, *J. Chem. Soc. C*, 1041 (1967).

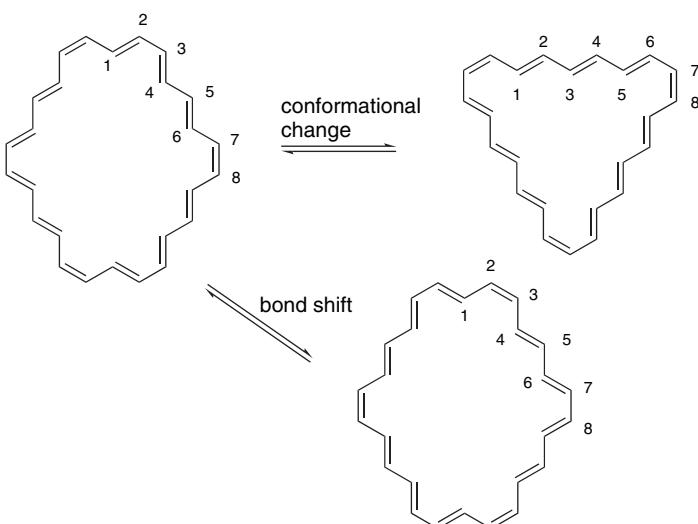
¹⁰² T. Otsubo, R. Gray, and V. Boekelheide, *J. Am. Chem. Soc.*, **100**, 2449 (1978).

¹⁰³ B. W. Metcalf and F. Sondheimer, *J. Am. Chem. Soc.*, **93**, 6675 (1971).

¹⁰⁴ R. M. McQuilkin, B. W. Metcalf, and F. Sondheimer, *J. Chem. Soc., Chem. Commun.*, 338 (1971).

¹⁰⁵ I. C. Calder and F. Sondheimer, *J. Chem. Soc., Chem. Commun.*, 904 (1966).

¹⁰⁶ J. F. M. Oth and Y. de J. de Zelicourt, *Helv. Chim. Acta*, **82**, 435 (1999).



Theoretical calculations indicate that the tendency to be aromatic decreases as ring size increases.¹⁰⁷ For example, the NICS value decreases from -15.0 and -14.7 for [14] and [18]annulene, respectively, to -5.6 at [42]annulene and -1.2 at [66]annulene. The delocalized structures are computed to be more stable, however, leveling off at $22\text{--}23$ kcal/mol at [30]annulene.¹⁰⁸ Of course, on a per electron basis, this means a decrease in relative stability.

8.2.7. Other Related Structures

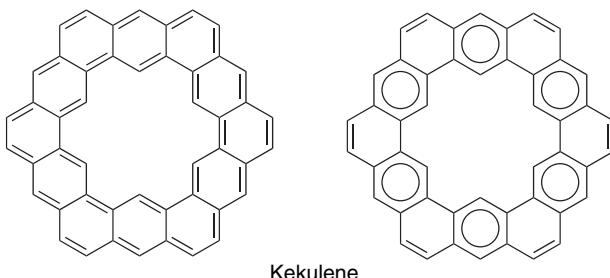
Both clever synthesis and energetic processes leading to stable compounds have provided other examples of structures for which aromaticity might be important. Kekulene was synthesized in 1978.¹⁰⁹ How aromatic is this substance? By both energy and magnetic criteria, it appears that it is primarily benzenoid in character. Its energy is close to that expected from isodesmic reactions summing smaller aromatic components. Magnetic criteria, too, indicate that it is similar to the smaller polycyclic benzenoid hydrocarbons, such as phenanthrene and anthracene.¹¹⁰ Kekulene seems best represented by a structure that emphasizes the aromaticity of alternating rings, similar to the structure of phenanthrene (see p. 772). (See Problem 8.15 to consider this issue more thoroughly.)

¹⁰⁷ C. H. Choi and M. Kertesz, *J. Chem. Phys.*, **108**, 6681 (1998).

¹⁰⁸ C. S. Wannere and P. v. R. Schleyer, *Org. Lett.*, **5**, 865 (2003).

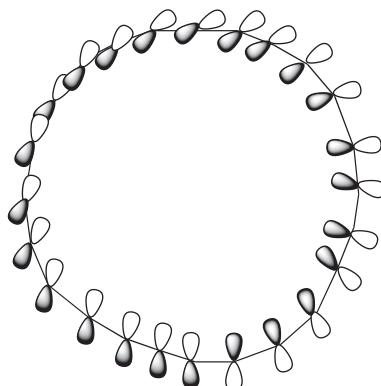
¹⁰⁹ H. A. Staab and F. Diedrich, *Angew. Chem. Int. Ed. Engl.*, **17**, 372 (1978); H. A. Staab and F. Diedrich, *Chem. Ber.*, **116**, 3487 (1983).

¹¹⁰ H. Jiao and P. v. R. Schleyer, *Angew. Chem. Int. Ed. Engl.*, **35**, 2383 (1996).



Fullerene, C_{60} , is a spherical form of carbon that is produced by processes such as laser vaporization of graphite.¹¹¹ The structure consists of hexagons and pentagons, corresponding to the pattern of a soccer ball. There is bond length variation with the bonds shared by the hexagonal rings being shorter ($1.40 \pm 0.01 \text{ \AA}$) than those of the pentagons ($1.46 \pm 0.01 \text{ \AA}$). Unlike benzene, with its two-Kekulé structure, there is only one valence bond structure for C_{60} . It has double bonds at all hexagon-hexagon edges and single bonds at the pentagonal edges. An isodesmic energy computation suggests that the π system is substantially less stable than for benzene on an atom-by-atom comparison.¹¹² Calculated chemical shift parameters suggest that the five-membered rings are antiaromatic, whereas the hexagonal rings are aromatic.¹¹³ Thus it appears that fullerene is a delocalized molecule, but with both stabilizing and destabilizing components, which are partially compensating in terms of stabilization energy.

It was pointed out that a different array of atomic orbitals might be conceived of in large conjugated rings. The array, called a *Möbius twist*, results in there being one point in the ring at which the atomic orbitals have a phase reversal (node).¹¹⁴



If the ring were sufficiently large that the twist between individual orbitals was small, such a system would not necessarily be less stable than the normal array of atomic orbitals. This same analysis points out that in such an array the Hückel rule is reversed and aromaticity is predicted for the $4n$ π -electron systems.

- ¹¹¹. H. W. Kroto, J. P. Heath, S. C. O'Brien, R. F. Curl, and R. E. Smalley, *Nature*, **318**, 162 (1985).
- ¹¹². P. W. Fowler, D. J. Collins, and S. J. Austin, *J. Chem. Soc., Perkin Trans. 2*, 275 (1993).
- ¹¹³. P. v. R. Schleyer, C. Maerker, A. Dransfeld, H. Jiao, and N. J. R. van Eikema Hommes, *J. Am. Chem. Soc.*, **118**, 6317 (1996).
- ¹¹⁴. E. Helibronner, *Tetrahedron Lett.*, 1923 (1964).

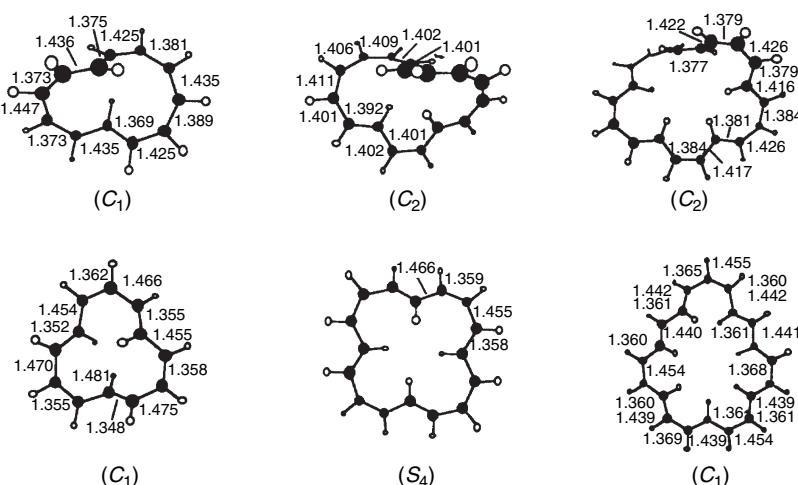


Fig. 8.7. Most stable (top) and most aromatic (bottom) Möbius structures for [12], [16], and [20]annulene. Reproduced from *Org. Lett.*, **4**, 3431 (2002), by permission of the American Chemical Society.

The possibility of Möbius conjugation in [12], [16], and [20]annulene has been explored using B3LYP/6-31G* calculations.¹¹⁵ The most stable and most aromatic structures are shown in Figure 8.7. The most aromatic Möbius isomer of [12]annulene is found about 4.4 kcal/mol above the most stable structure. It shows an NICS of -14.6 and relatively little bond length alternation, despite angles deviating as much as 53.6° from the alignment of the *p* orbitals. The most stable structure does not have aromatic characteristics, showing a positive NICS. For [16]annulene, the most aromatic Möbius structure is 15.8 kcal/mol above the most stable structure. The most aromatic structure for [20]annulene is 6.2 kcal/mol above the most stable structure. Thus, although it appears that there are energy minima corresponding to Möbius structures, they all lie above nonaromatic structures in energy.

Comparison of Properties of “Most Stable” and “Most Aromatic” Structure for [12], [16], and [20]annulenes

	[12]		[16]		[20]	
	Most stable	Best Möbius	Most stable	Best Möbius	Most stable	Best Möbius
Relative energy ^a	0.0	4.4	0.0	15.8	0.0	6.2
Δ in bond length ^b	0.133	0.078	0.097	0.019	0.095	0.049
NICS	+3.2	-14.6	+10.9	-14.5	+12.1	-10.2
χ	-65.0	-101.5	-63.9	-176.8	-75.6	-170.8
Max angle of twist	62.4°	53.6°	32.6°	29.1°	29.5°	29.9°

a. kcal/mol.

b. Difference between shortest and longest bond lengths in Å.

So far, no ground state molecule in which the twisted conjugation exists has been made. Whatever stabilization is associated with aromaticity in the Möbius structures is

¹¹⁵ C. Castro, C. Isborn, W. L. Karney, M. Mauksch, and P. v. R. Schleyer, *Org. Lett.*, **4**, 3431 (2002).

counterbalanced by bond angle and other strain, so the prediction of Möbius aromaticity remains to be verified experimentally. Its correctness is strongly suggested, however, by the fact that transition structures with twisted orbital arrays appear to be perfectly acceptable in many organic reactions.¹¹⁶ We return to this topic in Section 10.1. The rules for aromaticity can be generalized to include Möbius orbital arrays:

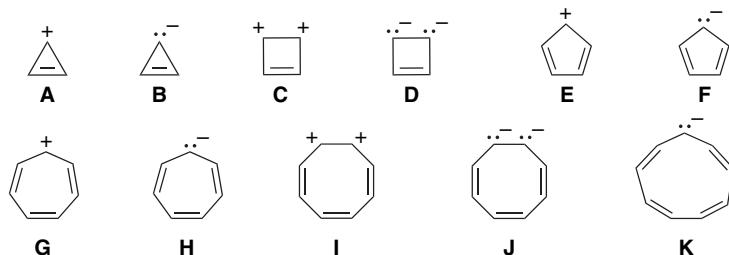
Hückel Orbital Array	Möbius Orbital Array
$4n + 2 = \text{Aromatic}$	$4n = \text{Aromatic}$
$4n = \text{Antiaromatic}$	$4n + 2 = \text{Antiaromatic}$

8.3. Aromaticity in Charged Rings

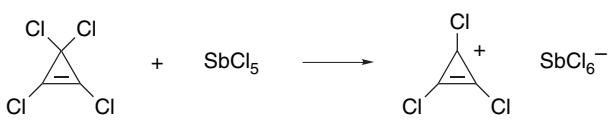
There are striking stability relationships owing to aromaticity in charged ring systems. The HMO energy levels that apply to fully conjugated planar three- to nine-membered rings were shown earlier in Figure 8.1 (p. 714). These energy levels are applicable to ions as well as to the neutral annulenes. A number of cations and anions that are completely conjugated planar structures are shown in Scheme 8.1. Among these species, the Hückel rule predicts aromatic stability for cyclopropenium ion (**A**), cyclobutadiene dication (**C**), cyclobutadiene dianion (**D**), cyclopentadienide anion (**F**), cycloheptatrienyl cation (tropylium ion, **G**), the dications and dianions derived from cyclooctatetraene (**I**, **J**) and the cyclononatetraenide anion (**K**). The other species shown, which have $4n \pi$ electrons, are expected to be quite unstable. These include cyclopropenide anion (**B**), cyclopentadienyl cation (**E**), and cycloheptatrienide (**H**). Let us examine what is known about the chemistry of some of these systems.

There is a good deal of information about the cyclopropenium ion that supports the idea that it is exceptionally stable. It and a number of derivatives can be generated by ionization procedures.

Scheme 8.1. Conjugated Cyclic Cations and Anions



¹¹⁶ H. E. Zimmerman, *J. Am. Chem. Soc.*, **88**, 1566 (1966); H. E. Zimmerman, *Acc. Chem. Res.*, **4**, 272 (1971).



Ref. 117



Ref. 118

The 1,2,3-tri-*t*-butylcyclopropenium cation is so stable that the perchlorate salt can be recrystallized from water.¹¹⁹ An X-ray study of triphenylcyclopropenium perchlorate has verified the existence of the carbocation as a discrete ion.¹²⁰ Quantitative estimation of the stability of the unsubstituted cyclopropenium ion can be made in terms of its pK_{R^+} value of -7.4 , which is intermediate between such highly stabilized ions as triphenylmethyl cation and the *bis*-(4-methoxyphenyl)methyl cation.¹²¹ (See Section 4.4.1 for the definition of pK_{R^+}). An HF/6-31G* MO calculation on the following isodesmic reaction:



yields a ΔH of $+38.2$ kcal/mol, whereas experimental data on the heats of formation of the various species give $\Delta H = +31$ kcal/mol.¹²² Both values imply that the cyclopropenium ion is much more stable than the allyl cation. G2 calculations indicate total aromatic stabilization of 59.1 kcal/mol based on the reaction¹²³



A radical-based homodesmotic reaction gives a value of 30.4 kcal/mol, which compares with 29.1 kcal/mol for benzene by the same approach.¹²⁴ The gas phase heterolytic bond dissociation energy to form cyclopropenium ion from cyclopropene is 225 kcal/mol. This compares with 256 kcal/mol for formation of the allyl cation from propene and 268 kcal/mol for the 1-propyl cation from propane.¹²⁵ It is clear that the cyclopropenyl cation is highly stabilized.

In contrast, the less strained four π -electron cyclopentadienyl cation is quite unstable, being calculated to have a negative stabilization of 56.7 kcal/mol.¹²⁶ The

¹¹⁷ S. W. Tobey and R. West, *J. Am. Chem. Soc.*, **86**, 1459 (1964); R. West, A. Sado, and S. W. Tobey, *J. Am. Chem. Soc.*, **88**, 2488 (1966).

¹¹⁸ R. Breslow, J. T. Groves, and G. Ryan, *J. Am. Chem. Soc.*, **89**, 5048 (1967).

¹¹⁹ J. Ciabattoni and E. C. Nathan, III, *J. Am. Chem. Soc.*, **91**, 4766 (1969).

¹²⁰ M. Sundaralingam and L. H. Jensen, *J. Am. Chem. Soc.*, **88**, 198 (1966).

¹²¹ R. Breslow and J. T. Groves, *J. Am. Chem. Soc.*, **92**, 984 (1970).

¹²² L. Radom, P. C. Hariharan, J. A. Pople, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **98**, 10 (1976).

¹²³ M. N. Glukhovtsev, S. Laiter, and A. Pross, *J. Phys. Chem.*, **100**, 17801 (1996).

¹²⁴ C. H. Suresh and N. Koga, *J. Org. Chem.*, **67**, 1965 (2002).

¹²⁵ F. P. Lossing and J. L. Holmes, *J. Am. Chem. Soc.*, **106**, 6917 (1984).

¹²⁶ P. v. R. Schleyer, P. K. Freeman, H. Jiao, and B. Goldfuss, *Angew. Chem. Int. Ed. Engl.*, **34**, 337 (1995); B. Reidl and P. v. R. Schleyer, *J. Comput. Chem.*, **19**, 1402 (1998).

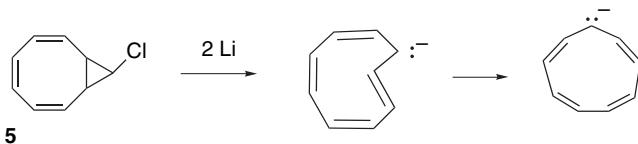
cyclopentadienyl cation is also calculated to be antiaromatic by magnetic susceptibility and chemical shift criteria.¹²⁷ Its pK_{R+} has been estimated as -40, using an electrochemical cycle.¹²⁸ The heterolytic bond dissociation energy to form the cation from cyclopentadiene is 258 kcal/mol, which is substantially more than for formation of an allylic cation from cyclopentene but only slightly more than the 252 kcal/mol required for formation of an unstabilized secondary carbocation.¹²⁵ The high energy of the cyclopentadienyl cation is also indicated by ionization studies in solution. A rate retardation of 10^{-14} relative to cyclopentyl analogs has been estimated from solvolytic rate data.¹²⁹ Solvolysis of cyclopentadienyl halides assisted by silver ion is extremely slow, even though the halide is doubly allylic.¹³⁰ When cyclopentadienyl bromide and antimony pentafluoride react at -78°C, an EPR spectrum is observed, which indicates that the cyclopentadienyl cation is a triplet.¹³¹ Similar studies indicate that the pentaisopropyl¹³² and pentachlorocyclopentadienyl cation are also triplets, but the ground state of the pentaphenyl derivative is a singlet.

The relative stability of the anions derived from cyclopropene and cyclopentadiene by deprotonation is just the reverse of the situation for the cations. Cyclopentadiene is one of the most acidic hydrocarbons known, with a pK_a of 16.0.¹³³ The pK_a 's of triphenylcyclopropene and trimethylcyclopropene have been estimated as 50 and 62, respectively, using electrochemical cycles¹³⁴ (see Section 6.1). The unsubstituted compound would be expected to fall somewhere between and thus must be about 40 powers of 10 less acidic than cyclopentadiene. MP2/6-311+G(2df,2pd) and B3LYP/6-311+G(2df,2pd) calculations indicate a small destabilization of the cyclopropenyl anion, relative to the cyclopropyl anion.¹³⁵ Thus the six π -electron cyclopentadienide anion is enormously stabilized relative to the four π -electron cyclopropenide ion, in agreement with the Hückel rule.

The Hückel rule predicts aromaticity for the six π -electron cation derived from cycloheptatriene by hydride abstraction and antiaromaticity for the planar eight π -electron anion that would be formed by deprotonation. The cation is indeed very stable, with a pK_{R+} of +4.7.¹³⁶ Salts containing the cation can be isolated as a result of a variety of preparative procedures.¹³⁷ On the other hand, the pK_a of cycloheptatriene has been estimated at 36.¹³⁴ This value is similar to normal 1,4-dienes and does not indicate strong destabilization. The seven-membered eight π -electron anion is probably nonplanar. This would be similar to the situation in the nonplanar eight π -electron hydrocarbon, cyclooctatetraene.

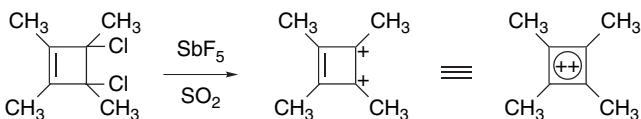
- ¹²⁷. H. Jiao, P. v. R. Schleyer, Y. Mo, M. A. McAllister, and T. T. Tidwell, *J. Am. Chem. Soc.*, **119**, 7075 (1997).
- ¹²⁸. R. Breslow and S. Mazur, *J. Am. Chem. Soc.*, **95**, 584 (1975).
- ¹²⁹. A. D. Allen, M. Sumonja, and T. T. Tidwell, *J. Am. Chem. Soc.*, **119**, 2371 (1997).
- ¹³⁰. R. Breslow and J. M. Hoffman, Jr., *J. Am. Chem. Soc.*, **94**, 2110 (1972).
- ¹³¹. M. Saunders, R. Berger, A. Jaffe, J. M. McBride, J. O'Neill, R. Breslow, J. M. Hoffman, Jr., C. Perchonock, E. Wasserman, R. S. Hutton, and V. J. Kuck, *J. Am. Chem. Soc.*, **95**, 3017 (1973).
- ¹³². H. Sitzmann, H. Bock, R. Boese, T. Dezember, Z. Havlas, W. Kaim, M. Moschersch, and L. Zanathy, *J. Am. Chem. Soc.*, **115**, 12003 (1993).
- ¹³³. A. Streitwieser, Jr., and L. L. Nebenzahl, *J. Am. Chem. Soc.*, **98**, 2188 (1976).
- ¹³⁴. R. Breslow and W. Chu, *J. Am. Chem. Soc.*, **95**, 411 (1973).
- ¹³⁵. G. N. Merrill and S. R. Kass, *J. Am. Chem. Soc.*, **119**, 12322 (1997).
- ¹³⁶. W. v. E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **76**, 3203 (1954).
- ¹³⁷. T. Nozoe, *Prog. Org. Chem.*, **5**, 132 (1961); K. M. Harmon, in *Carbonium Ions*, Vol. IV, G. A. Olah and P. v. R. Schleyer, eds., Wiley-Interscience, New York, 1973, Chap. 2.

The cyclononatetraenide anion is generated by treatment of the halide **5** with lithium metal.¹³⁸



An isomeric form of the anion that is initially formed is converted to the all-*cis* system rapidly at room temperature.¹³⁹ Data on the equilibrium acidity of the parent hydrocarbon are not available, so the stability of the anion cannot be judged quantitatively. The NMR spectrum of the anion, however, is indicative of aromatic character.^{139b}

Several doubly charged ions are included in Scheme 8.1; some have been observed experimentally. Ionization of 3,4-dichloro-1,2,3,4-tetramethylcyclobutene in SbF₅-SO₂ at -75°C results in an NMR spectrum attributed to the tetramethyl derivative of the cyclobutadienyl dication.¹⁴⁰



It is difficult to choose a reference compound against which to judge the stability of the dication. That it can be formed at all, however, is suggestive of special stabilization associated with the two π -electron system. The dianion formed by adding two electrons to the π system of cyclobutadiene also meets the $4n + 2$ criterion. In this case, however, four of the six electrons would occupy HMO nonbonding orbitals, so high reactivity could be expected. There is some evidence that this species may have a finite existence.¹⁴¹ Reaction of 3,4-dichlorocyclobutene with sodium naphthalenide, followed a few minutes later by methanol-O-*d* gives a low yield of 3,4-di-deutero-cyclobutene. The inference is that the dianion [C₄H₄²⁻] is present, but there has not yet been direct experimental observation of this species. Cyclooctatetraene is reduced by alkali metals to a dianion.



The NMR spectrum is indicative of a planar aromatic structure.¹⁴² The NICS value (MP2/6-31G*) is -19.9.¹⁴³ It has been demonstrated that the dianion is more stable

¹³⁸. T. J. Katz and P. J. Garratt, *J. Am. Chem. Soc.*, **86**, 5194 (1964); E. A. LaLancette and R. E. Benson, *J. Am. Chem. Soc.*, **87**, 1941 (1965).

¹³⁹. (a) G. Boche, D. Martens, and W. Danzer, *Angew. Chem. Inter. Ed. Engl.*, **8**, 984 (1969); (b) S. Fliszar, G. Cardinal, and M. Bernaldin, *J. Am. Chem. Soc.*, **104**, 5287 (1982); S. Kuwajima and Z. G. Soos, *J. Am. Chem. Soc.*, **108**, 1707 (1986).

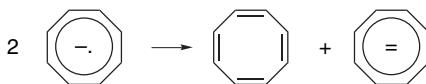
¹⁴⁰. G. A. Olah, J. M. Bollinger, and A. M. White, *J. Am. Chem. Soc.*, **91**, 3667 (1969); G. A. Olah and G. D. Mateescu, *J. Am. Chem. Soc.*, **92**, 1430 (1970).

¹⁴¹. J. S. McKennis, L. Brener, J. R. Schweiger, and R. Pettit, *J. Chem. Soc., Chem. Commun.*, 365 (1972).

¹⁴². T. J. Katz, *J. Am. Chem. Soc.*, **82**, 3784 (1960).

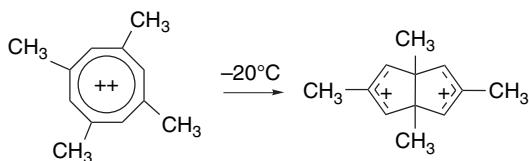
¹⁴³. P. v. R. Schleyer, C. Maerker, A. Dransfeld, H. Jiao, and J. R. van Eikema Hommes, *J. Am. Chem. Soc.*, **118**, 6317 (1996).

than the radical anion formed by one-electron reduction, since the radical anion disproportionates to cyclooctatetraene and the dianion.

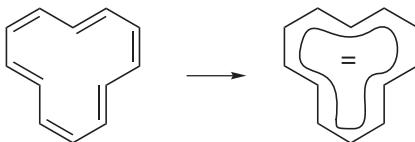


The crystal structure of the potassium salt of 1,3,5,7-tetramethylcyclooctatetraene dianion has been determined by X-ray diffraction.¹⁴⁴ The eight-membered ring is planar, with “aromatic” C–C bond lengths of about 1.41 Å without significant alternation. Spectroscopic and structural studies lead to the conclusion that the cyclooctatetraene dianion is a stabilized delocalized structure.

A dication derived from 1,3,5,7-tetramethylcyclooctatetraene is formed at -78°C in SO_2Cl by reaction with SbF_5 . Both the proton and carbon NMR spectra indicate that the ion is a symmetrical, diamagnetic species, and the chemical shifts are consistent with an aromatic anisotropy. At about -20°C , this dication undergoes a chemical transformation to a more stable diallylic dication.¹⁴⁵



Reduction of the nonaromatic polyene [12]annulene, either electrochemically or with lithium metal, generates a 14 π -electron dianion.¹⁴⁶



The NMR spectrum of the resulting dianion shows chemical shifts indicative of aromatic character, even though steric interactions among the internal hydrogens must prevent complete coplanarity. In contrast to the neutral [12]annulene, which is thermally unstable above -50°C , the dianion remains stable at 30°C . The dianion of [16]annulene has also been prepared, and shows properties consistent with its being regarded as aromatic.¹⁴⁷

The pattern of experimental results on charged species with cyclic conjugated systems is summarized in Table 8.1. It is consistent with the applicability of Hückel’s rule to charged, as well as neutral, conjugated planar cyclic structures.

¹⁴⁴. S. Z. Goldberg, K. N. Raymond, C. A. Harmon, and D. H. Templeton, *J. Am. Chem. Soc.*, **96**, 1348 (1974).

¹⁴⁵. G. A. Olah, J. S. Staral, G. Liang, L. A. Paquette, W. P. Melega, and M. J. Carmody, *J. Am. Chem. Soc.*, **99**, 3349 (1977).

¹⁴⁶. J. F. M. Oth and G. Schroeder, *J. Chem. Soc. B*, 904 (1971).

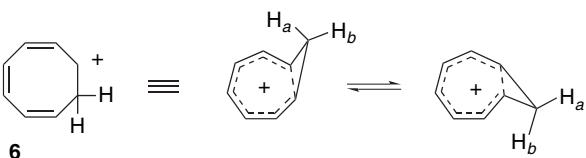
¹⁴⁷. J. F. M. Oth, G. Anthoine, and J. -M. Gilles, *Tetrahedron Lett.*, 6265 (1968).

Table 8.1. Hückel's Rule Relationships for Charged Species

Compound	π Electrons
Aromatic	
Cyclopropenylum ion	2
Cyclopentadienide anion	6
Cycloheptatrienylum ion	6
Cyclooctatetraene dianion	10
Cyclononatetraenide anion	10
[12]Annulene dianion	14
Antiaromatic	
Cyclopropenide anion	4
Cyclopentadienylium ion	4
Nonaromatic	
Cycloheptatrienide anion	8

8.4. Homoaromaticity

Homoaromaticity is a term used to describe systems in which a stabilized cyclic conjugated system is formed by bypassing one saturated atom.¹⁴⁸ One would expect the resulting stabilization to be reduced because of poorer overlap of the orbitals, but the properties of several such cationic species suggest that there is substantial stabilization. The cyclooctatrienyl cation (homotropylium **6**) is an example.



A significant feature of the NMR spectrum of this cation is the fact that the protons *a* and *b* exhibit sharply different chemical shifts. Proton *a* is 5.8 ppm upfield of *b*, indicating the existence of a diamagnetic ring current.¹⁴⁹ The fact that the two protons exhibit separate signals also establishes that there is a substantial barrier for the conformational process that interchanges H_{*a*} and H_{*b*}. The Δ*G*[‡] for this process is 22.3 kcal/mol.¹⁵⁰ MO (MP3/6-31G*) calculations that include the effects of electron correlation indicate that the homoconjugated structure is a good description of the cation and find that there is a strong aromatic ring current.¹⁵¹ MP4(SDQ)/6-31G(*d*) calculations were used to compare the homoaromatic structure with a planar model. The computations indicate that the total energy difference between the two structures includes a homoaromatic stabilization of about 4 kcal/mol and that additional strain in

¹⁴⁸. S. Winstein, *Q. Rev. Chem. Soc.*, **23**, 141 (1969); L. A. Paquette, *Angew. Chem. Int. Ed. Engl.*, **17**, 106 (1978); R. V. Williams, *Adv. Phys. Org. Chem.*, **29**, 273 (1994); R. V. Williams, *Chem. Rev.*, **101**, 1185 (2001).

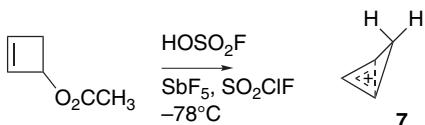
¹⁴⁹. (a) P. Warner, D. L. Harris, C. H. Bradley, and S. Winstein, *Tetrahedron Lett.*, 4013 (1970); C. E. Keller and R. Pettit, *J. Am. Chem. Soc.*, **88**, 604, 606 (1966); R. F. Childs, *Acc. Chem. Res.*, **17**, 347 (1984); (b) R. C. Haddon, *J. Am. Chem. Soc.*, **110**, 1108 (1988).

¹⁵⁰. S. Winstein, C. G. Kreiter, and J. I. Brauman, *J. Am. Chem. Soc.*, **88**, 2047 (1966).

¹⁵¹. R. C. Haddon, *J. Am. Chem. Soc.*, **110**, 1108 (1988).

the planar structure accounts for most of the difference.¹⁵² A higher estimate of the homoaromatic stabilization of 13.4 kcal/mol results from a calculation that assigns the difference in strain as 10.1 kcal/mol.¹⁵³

The cyclobutenyl cation **7** is the homoaromatic analog of the very stable cyclopropenium cation. This ion can be prepared from 3-acetoxycyclobutene using “superacid” conditions.¹⁵⁴



The homoaromatic cyclobutenyl cation is calculated to be 10.3 kcal/mol less stable than the isomeric methylcyclopropenyl ion, but the barrier for interconversion is high.¹⁵⁵ The temperature-dependent NMR spectrum of the ion can be analyzed to show that there is a barrier (8.4 kcal/mol) for the ring flip that interchanges the two hydrogens of the methylene group. The ¹³C-NMR chemical shift is also compatible with the homoaromatic structure. MO (MP3/6-31G*) calculations are successful in reproducing the structural and spectroscopic characteristics of the cation and are consistent with a homoaromatic structure.¹⁵⁶ Analysis of electron density did not find a bond critical point between C(1) and C(3), but the electron density is equivalent to a bond order of about 0.45. The electron density contours are shown in Figure 8.8.

The existence of stabilizing homoconjugation in anions has been more difficult to establish. Much of the discussion has revolved about anion **8**. The species was proposed to have aromatic character on the basis of the large upfield shift of the CH₂ group, which would lie in the shielding region generated by a diamagnetic ring current.¹⁵⁷ The ¹³C-NMR spectrum can also be interpreted in terms of homoaromaticity.¹⁵⁸ Both

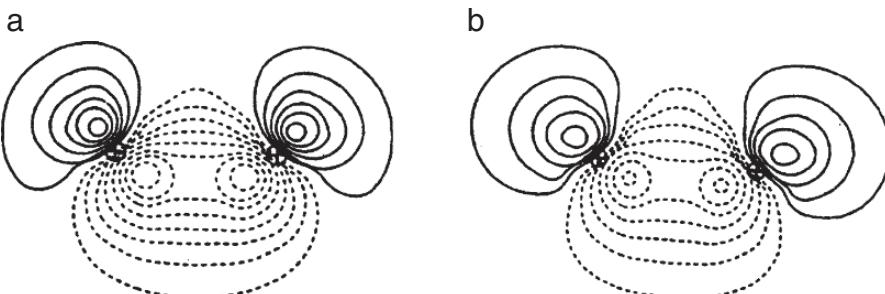


Fig. 8.8. Electron density contours for C(1)–C(3) bridging in homoaromatic cations: (a) cyclobutenyl cation; (b) cyclooctatrienylium ion. Reproduced from *J. Phys. Org. Chem.*, **6**, 445 (1993).

- ¹⁵² D. Cremer, F. Reichel, and E. Kraka, *J. Am. Chem. Soc.*, **113**, 9459 (1991).
- ¹⁵³ B. Reindl, T. Clark, and P. v. R. Schleyer, *J. Phys. Chem. A*, **102**, 8953 (1998).
- ¹⁵⁴ G. A. Olah, J. S. Staral, R. J. Spear, and G. Liang, *J. Am. Chem. Soc.*, **97**, 5489 (1975).
- ¹⁵⁵ A. Cunje, C. F. Rodriguez, M. H. Lien, and A. C. Hopkinson, *J. Org. Chem.*, **61**, 5212 (1996).
- ¹⁵⁶ R. C. Haddon and K. Raghavachari, *J. Am. Chem. Soc.*, **105**, 1188 (1983); M. Schindler, *J. Am. Chem. Soc.*, **109**, 1020 (1987); S. Sieber, P. v. R. Schleyer, A. H. Otto, J. Gauss, F. Reichel, and D. Cremer, *J. Phys. Org. Chem.*, **6**, 445 (1993).
- ¹⁵⁷ S. Winstein, M. Ogliaruso, M. Sakai, and J. M. Nicholson, *J. Am. Chem. Soc.*, **89**, 3656 (1967).
- ¹⁵⁸ M. Cristl, H. Leininger, and D. Brueckner, *J. Am. Chem. Soc.*, **105**, 4843 (1983).

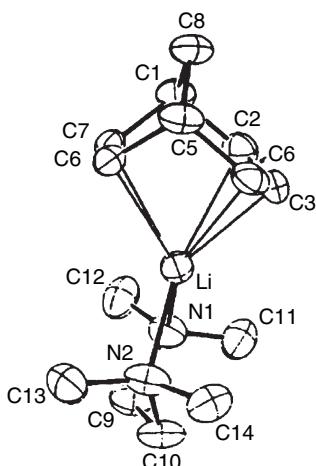
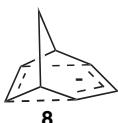


Fig. 8.9. Crystal structure of the TMEDA complex of lithium bicyclo[3.2.1]octa-2,6-dienide. Reproduced from *Angew. Chem. Int. Ed. Engl.*, **25**, 468 (1986), by permission of Wiley-VCH.

gas phase and solution measurements suggest that the parent hydrocarbon is more acidic than would be anticipated if there were no special stabilization of the anion.¹⁵⁹ An X-ray crystal structure of the lithium salt has been done.¹⁶⁰ The structure is a monomeric TMEDA complex (Fig. 8.9). The lithium is not symmetrically disposed toward the anion but is closer to one carbon of the allyl system. There is no indication of flattening of the homoconjugated atoms and the C(6)–C(7) bond distance is in the normal double-bond range (1.354 Å).

In contrast to the homoaromatic cations **6** and **7**, MO calculations fail to reveal substantial stabilization of the anion **8**.¹⁶¹ There does not seem to be any diamagnetic ring current associated with the anion.¹⁶² The weight of the evidence seems to be against significant homoaromatic stabilization in **8**.



8.5. Fused-Ring Systems

Many completely conjugated hydrocarbons can be built up from benzene, the other annulenes and related structural fragments. Scheme 8.2 gives the structures, names, and stabilization energies of a variety of such hydrocarbons. Derivatives of

¹⁵⁹ R. E. Lee and R. R. Squires, *J. Am. Chem. Soc.*, **108**, 5078 (1986); W. N. Washburn, *J. Org. Chem.*, **48**, 4287 (1983).

¹⁶⁰ N. Hertkorn, F. H. Kohler, G. Mueller, and G. Reber, *Angew. Chem. Int. Ed. Engl.*, **25**, 468 (1986).

¹⁶¹ J. B. Grutzner and W. L. Jorgenson, *J. Am. Chem. Soc.*, **103**, 1372 (1981); E. Kaufman, H. Mayr, J. Chandrasekhar, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **103**, 1375 (1981); R. Lindh, B. O. Roos, G. Jonsall, and P. Ahlberg, *J. Am. Chem. Soc.*, **108**, 6554 (1986).

¹⁶² N. H. Werstiuk and J. Ma, *Can. J. Chem.*, **77**, 752 (1999).

Scheme 8.2. Stabilization Energies of Some Polycyclic Hydrocarbons^a

HMO	Benzene 2.00	Naphthalene 3.698	Anthracene 5.31	Naphthacene 6.93
HMO'	0.39	0.55	0.66	0.76
RE	0.38	0.59	0.71	0.83
SCF-MO	0.869 eV	1.323 eV	1.600 eV	1.822 eV
HMO	Phenanthrene 5.44	Triphenylene 7.27	Pyrene 6.50	Perylene 8.24
HMO'	0.72	1.01	0.82	0.96
RE	0.85	1.13	0.95	1.15
SCF-MO	1.933 eV	2.654 eV	2.10 eV	2.619 eV
HMO	Butalene 1.66	Pentalene 2.45	Azulene 3.25	Heptalene 3.61
HMO'	-0.48	-0.14	0.23	-0.04
RE	-0.34	-0.09	0.27	-0.01
SCF-MO	-0.28 eV	-0.006 eV	0.169 eV	-0.004 eV
HMO	Methylene-cyclopropene 0.96	Fulvene 1.46	Calicene —	Fulvalene 2.80
HMO'	0.02	-0.012	0.34	-0.33
RE		-0.01	0.39	-0.29
SCF-MO				
HMO	Benzocyclobutadiene 2.38	—	Biphenylene 4.50	4.61
HMO'	-0.22	-0.22	0.32	0.47
RE	-0.16	—	0.42	0.57
SCF-MO	—	—	1.346 eV	1.335 eV
HMO'	s-indacene 0.110	as-indacene -0.249		

- a. Stabilization energies are from the following sources: HMO: C. A. Coulson, A. Streitwieser, Jr., M. D. Poole, and J. I. Brauman, *Dictionary of π -Electron Calculations*, W. H. Freeman, San Francisco, 1965.
 HMO': B. A. Hess, Jr., and L. J. Schaad, Jr., *J. Am. Chem. Soc.*, **93**, 305, 2413 (1971); *J. Org. Chem.*, **36**, 3418 (1971); *J. Org. Chem.*, **37**, 4179 (1972).
 RE: A. Moyano and J. C. Paniagua, *J. Org. Chem.*, **51**, 2250 (1986).
 SCF-MO: M. J. S. Dewar and C. de Llano, *J. Am. Chem. Soc.*, **91**, 789 (1969); 1 eV = 23 kcal/mol.

these hydrocarbons having heteroatoms in place of one or more carbon atoms constitute another important class of organic compounds and are discussed in Section 8.6. It is of interest to be able predict the stability of such fused-ring compounds. Because Hückel's rule applies only to monocyclic systems, it cannot be applied to the fused-ring compounds, but there have been many efforts to develop relationships that would predict their stability. The underlying concepts are the same as for monocyclic systems; stabilization results from a particularly favorable arrangement of MOs, whereas instability is associated with unpaired electrons or electrons in high-energy orbitals.

The same approximations discussed in Section 1.5 permit calculation of the HMO for conjugated systems of the type shown in Scheme 8.2, and many of the results have been tabulated.¹⁶³ However, attempts to correlate stability with the Hückel delocalization energy relative to isolated double bonds give poor correlation with the observed chemical properties of the compounds.

Much better agreement between calculated stabilization energy and experimental chemical properties is achieved when a polyene is chosen as the reference state.¹⁶⁴ A series of energy terms corresponding to the structural units in the reference polyene was established empirically by Hess and Schaad.¹⁶⁵ The difference between the energy of the conjugated hydrocarbon by HMO calculations and the sum of the appropriate structural units gives a stabilization energy. For azulene, for example, the HMO calculation gives an energy of $10\alpha + 13.36\beta$. The energy for the polyene reference is obtained by summing contributions for the component bond types: $3(\text{CH}=\text{CH}) + 2(\text{HC}=\text{C}) + 3(\text{HC}-\text{CH}) + 1(\text{C}-\text{C}) = 13.13\beta$. The difference, 0.23β , is the stabilization or resonance energy assigned to azulene by this method. For comparison of nonisomeric molecules, the Hess-Schaad treatment uses resonance energy per electron, which is obtained by dividing the calculated stabilization energy by the number of π electrons. Although the resulting stabilization energies are based on a rudimentary HMO calculation, they are in good qualitative agreement with observed chemical stability. The stabilizations have been calculated for most of the molecules in Scheme 8.2 and are listed as HMO'.

The energy parameters assigned to the reference polyene used by Hess and Schaad were developed on an empirical basis. Subsequently Moyano and Paniagua developed an alternative set of reference bond energies on a theoretical basis,¹⁶⁶ and these values are shown along with the Hess-Schaad values in Table 8.2. The stabilizations calculated for the various hydrocarbons using this point of reference in Scheme 8.2 are those listed as RE (for resonance energy). The Hess-Schaad HMO' and the RE values are in generally good agreement with observed stability. Both calculations give negative stabilization for benzocyclobutadiene, for example.¹⁶⁷

The values listed in Scheme 8.2 as SCF-MO are from an early semiempirical SCF calculation, which was the first instance in which a polyene was chosen as the reference state.¹⁶⁴

¹⁶³ E. Heilbronner and P. A. Straub, *Hückel Molecular Orbitals*, Springer-Verlag, Berlin, 1966; C. A. Coulson and A. Streitwieser, *Dictionary of π -Electron Calculations*, W. H. Freeman, San Francisco, 1965.

¹⁶⁴ M. J. S. Dewar and C. de Llano, *J. Am. Chem. Soc.*, **91**, 789 (1969).

¹⁶⁵ B. A. Hess, Jr., and L. J. Schaad, *J. Am. Chem. Soc.*, **93**, 305, 2413 (1971); *J. Org. Chem.*, **36**, 3418 (1971); *J. Org. Chem.*, **37**, 4179 (1972).

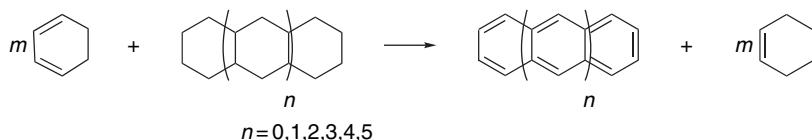
¹⁶⁶ A. Moyano and J. C. Paniagua, *J. Org. Chem.*, **51**, 2250 (1986).

¹⁶⁷ There are a number of other systems for comparing the stability of conjugated cyclic compounds with reference polyenes. For example, see L. J. Schaad and B. A. Hess, Jr., *Pure Appl. Chem.*, **54**, 1097 (1982); J. Aihara, *Pure Appl. Chem.*, **54**, 1115 (1982); K. Jug, *J. Org. Chem.*, **48**, 1344 (1983); W. Gründler, *Monatsch. Chem.*, **114**, 155 (1983).

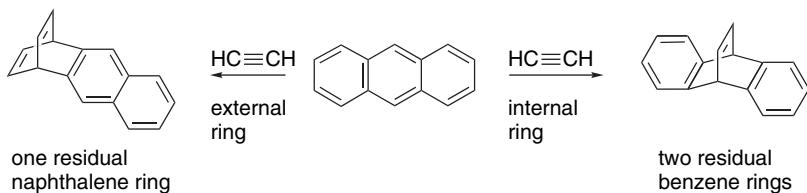
Table 8.2. Energy Values for Reference Bond Types

Bond type	Hess-Schaad value (β)	Bond type	Moyano-Paniagua value (β)
$\text{H}_2\text{C}=\text{CH}$	2.000	$\text{H}_2\text{C}=\text{CH}-\text{CH}=$	2.2234
$\text{HC}=\text{CH}$	2.070	$\text{H}_2\text{C}=\text{CH}-\text{C}=$	2.2336
$\text{H}_2\text{C}=\text{C}$	2.000	$=\text{CH}-\text{CH}=\text{CH}-\text{CH}=$	2.5394
$\text{HC}=\text{C}$	2.108	$=\text{CH}-\text{CH}=\text{CH}-\text{C}=$	2.5244
$\text{C}=\text{C}$	2.172	$=\text{C}-\text{CH}=\text{CH}-\text{C}=$	2.4998
$\text{HC}-\text{CH}$	0.466	$\text{H}_2\text{C}=\text{C}-$	2.4320
$\text{HC}-\text{C}$	0.436	$-\text{CH}=\text{CH}-$	2.7524
$\text{C}-\text{C}$	0.436	$-\text{C}=\text{C}-$	2.9970

All these approaches agree that benzene and the structures that can be built up by fusing benzenoid rings together are strongly stabilized relative to the reference polyenes. The larger rings tend to have lower resonance energies per π electron than does benzene. This feature is in agreement with experimental trends in reactivity.¹⁶⁸ Schleyer and co-workers have applied some of the criteria of aromaticity to this series of compounds.¹⁶⁹ With application of the isodesmic equation below, the stabilization per electron was found to increase on going from benzene to naphthalene and then to remain approximately constant.



Another manifestation of aromatic stability is resistance to addition reactions. For example, the E_a and ΔH for cycloaddition with ethyne were calculated, and the results are shown as in Table 8.3. The internal rings have greater exothermicity and lower E_a .



A similar trend is observed for the rates of Diels-Alder addition reactions of anthracene, naphthacene, and pentacene, in which three, four, and five rings, respectively, are linearly fused. The rate data are shown in Table 8.4. The same trend can be seen in the E_a and the gain in resonance energy when cycloreversion of the adducts **9–12** yields the aromatic compound, as shown in Scheme 8.3.

¹⁶⁸ D. Biermann and W. Schmidt, *J. Am. Chem. Soc.*, **102**, 3163, 3173 (1980).

¹⁶⁹ P. v. R. Schleyer, M. Manoharan, H. Jiao, and F. Stahl, *Org. Lett.*, **3**, 3643 (2001).

Table 8.3. Calculated Barriers and Reaction Energy for Cycloaddition of Ethyne with Polycyclic Hydrocarbons

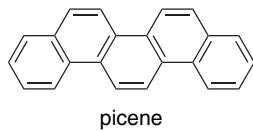
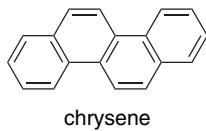
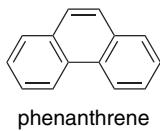
Compound	E_a	ΔH
Benzene	43.8	6.1
Naphthalene	36.8	-8.7
Anthracene (external ring)	34.3	-13.9
Anthracene (center ring)	29.4	-26.2
Naphthacene (external ring)	33.3	-16.1
Naphthacene (internal ring)	26.8	-32.6
Pentacene (external ring)	32.7	-17.3
Pentacene (internal ring)	25.5	-35.4
Pentacene (center ring)	24.0	-39.5

Table 8.4. Rates of Diels-Alder Additions of Linear Polycyclic Aromatic Hydrocarbons^a

Dienophile	$k(M^{-1}s^{-1})$ in toluene at 80°C		
	Anthracene	Naphthacene	Pentacene
Benzoquinone		44	181
Maleic anhydride	5	294	4710
<i>N</i> -Phenylmaleimide	10	673	19,280

a. V. D. Samuilov, V. G. Uryadov, L. F. Uryadova, and A. J. Konolova, *Zh. Org. Khim.* (Engl. Trans.), **21**, 1137 (1985).

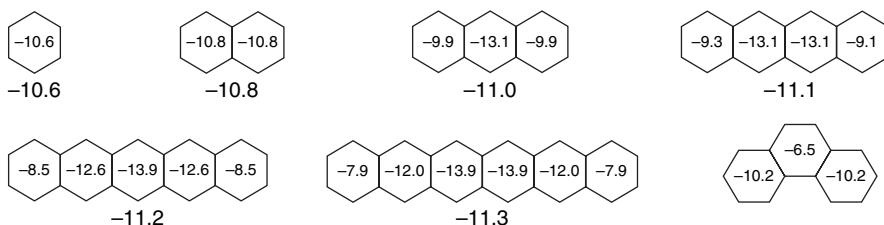
Benzene rings can also be fused in angular fashion, as in phenanthrene, chrysene, and picene. These compounds, while quite reactive toward additions in the center ring, retain most of the REPE stabilization of benzene and naphthalene.¹⁷⁰

**Scheme 8.3. Correlation between E_a for Retro-Diels-Alder Reaction and Change in Resonance Stabilization of Polycyclic Hydrocarbons**

	9	\downarrow	benzene	
	10	\downarrow	naphthalene	
	11	\downarrow		anthracene
	12	\downarrow		naphthacene
E_a (kcal/mol)	16		29	31
ΔRE (kcal/mol)	40		17	11

¹⁷⁰ K. B. Wiberg, *J. Org. Chem.*, **62**, 5720 (1997).

The NICS values for the linear polycyclic arenes show a pattern of increasing negativity (aromaticity) toward the center ring. In contrast, for phenanthrene, the center ring has the lowest NICS, consistent with the more localized nature of this ring.¹⁷¹



Average (beneath the structure) and individual ring (inside each ring) NICS values for polycyclic hydrocarbons. Except for phenanthrene the values are 1 Å above the ring.

The HOMO-LUMO gap decreases as the number of fused rings increases. The decreasing gap is reflected in the hardness values shown in Scheme 8.4, as assigned by Zhou and Parr.¹⁷² The values for phenanthrene and acenaphthene, which have more localized double bonds, are 0.315 and 0.151, respectively. Similarly, the nonbenzenoid hydrocarbon azulene is calculated to be softer.

There is evidence that aromatic circuits can exist within a larger conjugated unit resulting in an aromatic segment in conjugation with a “localized” double bond. For example, in acenaphthene, the double bond in the five-membered ring is both structurally and chemically similar to a normal localized double bond. The resonance energy given in Scheme 8.2, 0.57β , is slightly less than that for naphthalene (0.59β). The additional double bond of acenaphthene has only a small effect on the stability of the conjugated system. The molecular structure determined at 80 K by neutron diffraction shows bond lengths for the aromatic portion that are quite similar to those

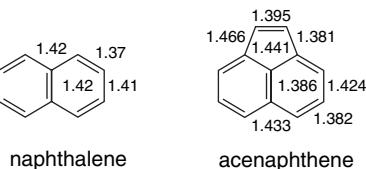
Scheme 8.4. HOMO-LUMO Gaps and Hardness for Polycyclic Hydrocarbons

HMO gap (β)	2.000	1.3360	0.8284	0.5900
Rel Hardness	0.482	0.264	0.151	0.088
HMO gap (β)	0.8775	0.9221	1.2104	
Rel Hardness	0.253	0.206	0.315	

¹⁷¹. P. v. R. Schleyer, M. Manoharan, H. Jiao, and F. Stahl, *Org. Lett.*, **3**, 3643 (2001).

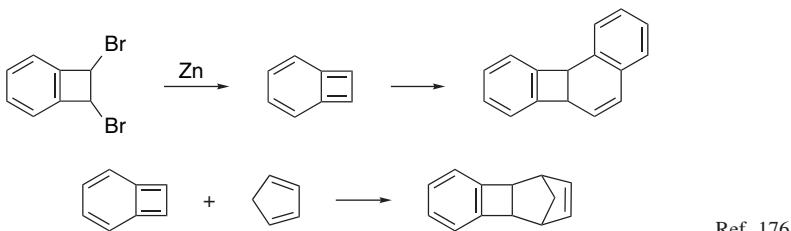
¹⁷². Z. Zhou and R. G. Parr, *J. Am. Chem. Soc.*, **111**, 7371 (1989).

of naphthalene.¹⁷³ The double bond is somewhat longer than a normal double bond, but this may reflect the strain imposed on it by the naphthalene framework.

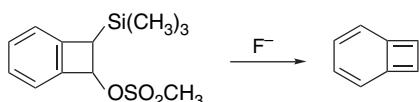


The predictions of relative stability by the various approaches diverge more widely when nonbenzenoid systems are considered. The simple Hückel method using total π delocalization energies relative to an isolated double-bond reference energy ($\alpha + \beta$) fails. This approach predicts stabilization of the same order of magnitude for such unstable systems as pentalene and fulvalene as it does for much more stable aromatics. The HMO', RE, and SCF-MO methods, which use polyene reference energies, do much better. All show drastically reduced stabilization for such systems and, in fact, indicate destabilization of systems such as butalene and pentalene (Scheme 8.2).

It is of interest to consider at this point some of the specific molecules in Scheme 8.2 and compare their chemical properties with the calculated stabilization energies. Benzocyclobutadiene has been generated in a number of ways, including dehalogenation of dibromobenzocyclobutene.¹⁷⁴ Chemically, benzocyclobutadiene reacts as a polyene having a quinodimethane structure and is a reactive diene in Diels-Alder cycloadditions, dimerizing or polymerizing readily.¹⁷⁵



Generation of benzocyclobutadiene by fluoride-induced elimination has permitted the NMR spectrum to be observed under flow conditions.¹⁷⁷ All the peaks are somewhat upfield of the aromatic region, suggesting polyene character.



¹⁷³ R. A. Wood, T. R. Welberry, and A. D. Rae, *J. Chem. Soc., Perkin Trans. 2*, 451 (1985).

¹⁷⁴ M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **78**, 500 (1956); *J. Am. Chem. Soc.*, **79**, 1701 (1957).

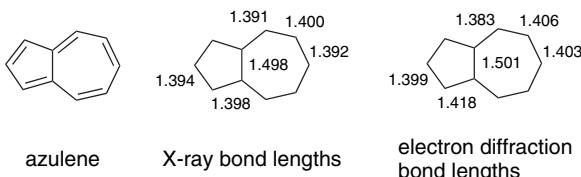
¹⁷⁵ (a) M. P. Cava and M. J. Mitchell, *Cyclobutadiene and Related Compounds*, Academic Press, New York, 1967, pp. 192–216; (b) M. K. Shepherd, *Cyclobutarenes: Chemistry of Benzocyclobutene, Biphenylene and Related Compounds*, Elsevier, New York, 1991; W. S. Trahanovsky and K. B. Arvidson, *J. Org. Chem.*, **61**, 9528 (1996); P. Gandhi, *J. Sci. Ind. Res.*, **41**, 495 (1982); M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **80**, 2255 (1958); M. P. Cava and M. J. Mitchell, *J. Am. Chem. Soc.*, **81**, 5409 (1959); A. K. Sadana, R. K. Saini, and W. E. Billups, *Chem. Rev.*, **103**, 1539 (2003).

¹⁷⁶ M. P. Cava and M. J. Mitchell, *J. Am. Chem. Soc.*, **81**, 5409 (1959).

¹⁷⁷ W. S. Trahanovsky and D. R. Fischer, *J. Am. Chem. Soc.*, **112**, 4971 (1990).

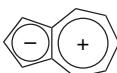
The ring current in benzocyclobutadiene has been analyzed in detail.¹⁷⁸ The main ring current is associated with the four-membered ring and is paramagnetic. This is consistent with the calculated NICS values, which are -2.5 for the six-membered ring and 22.5 for the four-membered ring.¹⁷⁹ The fusion of the cyclobutadiene ring to benzene greatly diminishes the aromatic character of the benzenoid ring. The implication of a nonaromatic structure is that the combination of ring strain and the antiaromaticity associated with the four-membered ring results in a localized system.¹⁸⁰

Azulene is one of the few nonbenzenoid hydrocarbons that appear to have appreciable aromatic stabilization. There is some divergence on this point between the SCF-MO and HMO' results in Scheme 8.2. The latter estimates a resonance energy about half that for the isomeric naphthalene, whereas the SCF-MO method assigns a resonance energy that is only about one-seventh that of naphthalene. Naphthalene is thermodynamically more stable than azulene by about 38.5 kcal/mol. Molecular mechanics calculations attribute about 12.5 kcal/mol of the difference to strain and about 26 kcal/mol to greater resonance stabilization of naphthalene.¹⁸¹ Based on heats of hydrogenation, the stabilization energy of azulene is about 16 kcal/mol.¹⁸² The parent hydrocarbon and many of its derivatives are well-characterized compounds with considerable stability. The structure of azulene has been determined by both X-ray crystallography and electron-diffraction measurements.¹⁸³ The peripheral bond lengths are in the aromatic range and show no regular alternation. The bond shared by the two rings is significantly longer, indicating that it has predominantly single-bond character, which indicates that the conjugated system more closely resembles [10]annulene than naphthalene. Theoretical calculations indicate that the molecule has C_{2v} symmetry, suggesting delocalization of the π electrons.¹⁸⁴



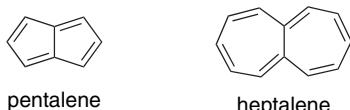
An interesting structural question involves the contribution of a dipolar structure that pictures the molecule as the fusion of a cyclopentadienide anion and a cycloheptatrienyl cation.

- ¹⁷⁸. A. Soncini, R. W. A. Havenith, P. W. Fowler, L. W. Jenneskens, and E. Steiner, *J. Org. Chem.*, **67**, 4753 (2002); R. W. A. Havenith, F. Lugli, P. W. Fowler, and E. Steiner, *J. Phys. Chem. A*, **106**, 5703 (2002).
- ¹⁷⁹. P. v. R. Shleyer, C. Maerker, A. Dransfeld, H. Jiao, and N. J. R. van Eikema Hommes, *J. Am. Chem. Soc.*, **118**, 6317 (1996).
- ¹⁸⁰. P. B. Karadakov, J. Gerratt, D. L. Cooper, M. Raimondi, and M. Sironi, *Int. J. Quantum Chem.*, **60**, 545 (1996); M. O. Jensen, T. Thorsteinsson, and A. E. Hansen, *Intl. J. Quantum Chem.*, **90**, 616 (2002).
- ¹⁸¹. N. L. Allinger and Y. H. Yu, *Pure Appl. Chem.*, **55**, 191 (1983).
- ¹⁸². W. R. Roth, M. Boehm, H. W. Lennartz, and E. Vogel, *Angew. Chem. Int. Ed. Engl.*, **22**, 1007 (1983).
- ¹⁸³. A. W. Hanson, *Acta Crystallogr.*, **19**, 19 (1965); O. Bastiansen and J. L. Derissen, *Acta Chem. Scand.*, **20**, 1319 (1966).
- ¹⁸⁴. (a) C. Glidewell and D. Lloyd, *Tetrahedron*, **40**, 4455 (1984); (b) R. C. Haddon and K. Raghavachari, *J. Am. Chem. Soc.*, **104**, 3516 (1982); (c) S. Grimme, *Chem. Phys. Lett.*, **201**, 67 (1993); (d) S. J. Mole, X. Zhou, J. G. Wardeska, and R. Liu, *Spectrochim. Acta A*, **52**, 1211 (1996); (e) B.-C. Wang, Y.-S. Lin, J.-C. Chang, and P.-Y. Wang, *Can. J. Chem.*, **78**, 224 (2000); (f) I. Bandyopadhyay, *Theochem*, **618**, 59 (2002).

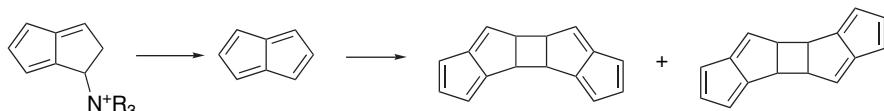


Azulene does have an appreciable dipole moment (0.8 D).¹⁸⁵ B3LYP/6-31G* and MP2/6-31G* computations calculate the dipole moment as about 1.0 D.^{184c,d} The essentially single-bond nature of the shared bond indicates, however, that the conjugation is principally around the periphery of the molecule.

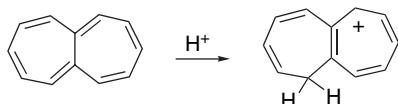
The significant resonance stabilization of azulene can be contrasted with pentalene and heptalene, both of which are indicated to be destabilized relative to a reference polyene.



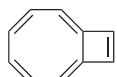
Preparation of pentalene is followed by immediate dimerization.¹⁸⁶ Low-temperature photolysis produces a new species believed to be pentalene, but the compound reverts to dimer at -100°C . The matrix-isolated monomer has been characterized spectroscopically,¹⁸⁷ and the results are in accord with the predicted lack of stabilization.¹⁸⁸



Heptalene readily polymerizes and is sensitive to oxygen. The NMR spectrum does not indicate the presence of an aromatic ring current. The conjugate acid of heptalene, however, is very stable (even at pH 7 in aqueous solution), reflecting the stability of the cation, which is a substituted tropylum ion.¹⁸⁹



Another structure with a ten electron conjugated system is bicyclo[6.2.0]deca-1,3,5,7,9-pentaene. The crystal structure of the 9,10-diphenyl derivative shows the conjugated system to be nearly planar,¹⁹⁰ but there is significant bond alternation.



¹⁸⁵ H. J. Tobler, A. Bauder, and H. H. Günthard, *J. Mol. Spectrosc.*, **18**, 239 (1965); G. W. Wheland and D. E. Mann, *J. Chem. Phys.*, **17**, 264 (1949).

¹⁸⁶ K. Hafner, R. Donges, E. Goedecke, and R. Kaiser, *Angew. Chem. Int. Ed. Engl.*, **12**, 337 (1973); S. You and M. Neuenschwander, *Chimia*, **50**, 24 (1996).

¹⁸⁷ T. Bally, S. Chai, M. Neuenschwander, and Z. Zhu, *J. Am. Chem. Soc.*, **119**, 1869 (1997).

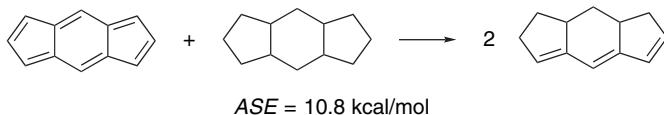
¹⁸⁸ T. K. Zywietsz, H. Jiao, P. v. R. Schleyer, and A. de Meijere, *J. Org. Chem.*, **63**, 3417 (1998).

¹⁸⁹ H. J. Dauben, Jr., and D. J. Bertelli, *J. Am. Chem. Soc.*, **83**, 4657, 4659 (1961).

¹⁹⁰ C. Kabuto and M. Oda, *Tetrahedron Lett.*, 103 (1980).

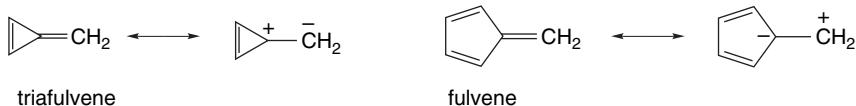
The bond at the ring fusion is quite long. A molecular mechanics calculation on this molecule, which includes an SCF-MO treatment of the planar conjugated system, concluded that the molecule is slightly destabilized (4 kcal/mol) relative to a polyene reference.¹⁹¹ HF/STO-3G calculations found a small stabilization.¹⁹² An experimental determination of ΔH_{H_2} also suggests a small (3.7 kcal/mol) stabilization.¹⁹³

The tricyclic fused systems known as *s*-indacene and *as*-indacene have also been of interest in assessing the range of aromaticity. *s*-Indacene derivatives have bond lengths varying from 1.39 to 1.44 Å in the crystal structure.¹⁹⁴ MO and DFT calculations vary in predicting the relative energy of localized and delocalized structures.¹⁹⁵ B3LYP/6-31G* calculations place the structures within 0.1 kcal/mol of one another.¹⁹⁶ An aromatic stabilization of 10.8 kcal/mol is calculated based on the following isodesmic reaction, which is much less than for anthracene.¹⁹⁷ The NICS values for both rings are positive and indicate a paramagnetic ring current.



The possibility of extra stabilization in systems that have conjugated components exocyclic to the ring has also been examined. Such substituents complete conjugated rings but are not part of the cyclic system. Some representative structures are shown in Scheme 8.5.

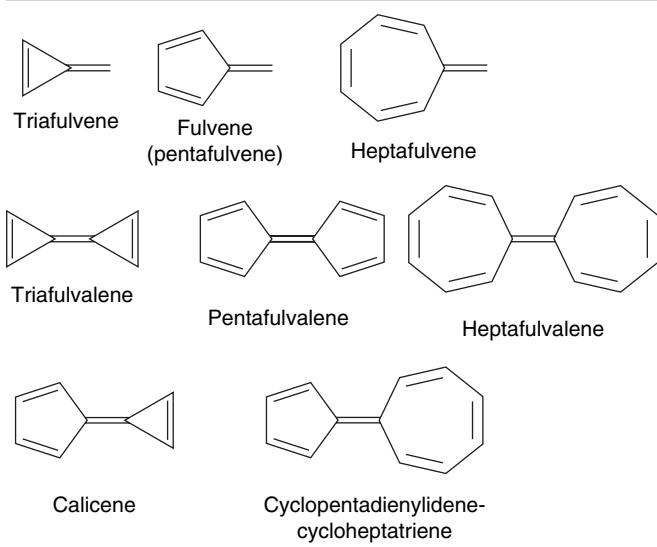
Cyclopropenes and cyclopentadienes with exocyclic double bonds provide the possibility of dipolar resonance structures that suggest aromatic character in the cyclic structure.



For methylenecyclopropene, a microwave structure determination has established bond lengths that show the strong alternation anticipated for a localized structure.¹⁹⁸ The molecule does have a significant (1.90 D) dipole moment, implying a contribution from the dipolar resonance structure. The net stabilization calculated at the MP/6-31G* level is small and comparable to the stabilization of 1,3-butadiene. The molecular geometry

- ^{191.} N. L. Allinger and Y. H. Yuh, *Pure Appl. Chem.*, **55**, 191 (1983).
- ^{192.} D. Cremer, T. Schmidt, and C. W. Bock, *J. Org. Chem.*, **50**, 2684 (1985).
- ^{193.} W. Roth, H.-W. Lennartz, E. Vogel, M. Leiendoeker, and M. Oda, *Chem. Ber.*, **119**, 837 (1986).
- ^{194.} K. Hafner, B. Stowasser, H.-P. Krimmer, S. Fischer, M. C. Böhm, and H. J. Lindner, *Angew. Chem. Int'l. Ed. Engl.*, **25**, 6201 (1986); J. D. Dunitz, C. Kruger, H. Imgartinger, E. F. Maverick, Y. Wang, and M. Nixdorf, *Angew. Chem. Int'l. Ed. Engl.*, **27**, 387 (1988).
- ^{195.} C. Gellini, G. Cardini, P. R. Salvi, G. Marconi, and K. Hafner, *J. Phys. Chem.*, **97**, 1286 (1993); R. H. Hertwig, M. C. Holthausen, W. Koch, and Z. B. Maksic, *Angew. Chem. Int'l. Ed. Engl.*, **33**, 1192 (1994); R. H. Hertwig, M. C. Holthausen, and W. Koch, *Intl. J. Quantum Chem.*, **54**, 147 (1995).
- ^{196.} M. Nendel, B. Goldfuss, B. Beno, K. N. Houk, K. Hafner, and H.-J. Lindner, *Pure Appl. Chem.*, **71**, 221 (1999).
- ^{197.} M. Nendel, B. Goldfuss, K. N. Houk, and K. Hafner, *Theochem*, **461-2**, 23 (1999).
- ^{198.} T. D. Norden, S. W. Staley, W. H. Taylor, and M. D. Harmony, *J. Am. Chem. Soc.*, **108**, 7912 (1986).

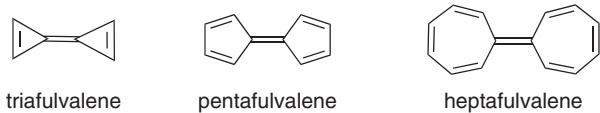
Scheme 8.5. Completely Conjugated Hydrocarbons Incorporating Exocyclic Double Bonds



of dimethylfulvene has been examined by electron diffraction methods. Strong bond length alternation indicative of a localized structure was found.¹⁹⁹



The fulvalene systems are not predicted to be aromatic by any of the theoretical estimates of stability. Even simple resonance considerations would suggest polyene behavior, since only dipolar resonance structures can be drawn in addition to the single nonpolar structure.



Triafulvalene (cyclopropenylidenecyclopropene) has not been isolated. A substantial number of pentafulvalene derivatives have been prepared.²⁰⁰ The chemical properties of these molecules are those of reactive polyenes. The NMR spectrum of pentafulvalene is characteristic of a localized system.²⁰¹ Heptafulvalene (cycloheptatrienylidene-cycloheptatriene) is a well-characterized compound with the properties expected for a polyene.²⁰²

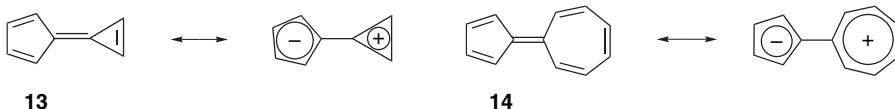
^{199.} J. F. Chiang and S. H. Bauer, *J. Am. Chem. Soc.*, **92**, 261 (1970).

^{200.} E. D. Bergmann, *Chem. Rev.*, **68**, 41 (1968).

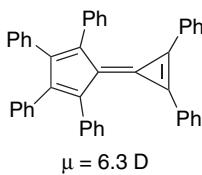
^{201.} E. Escher, P. Bönzli, A. Otter, and M. Neuenschwander, *Mag. Reson. Chem.*, **24**, 350 (1986).

^{202.} T. Nozoe and I. Murata, *Int. Rev. Sci., Org. Chem. Ser. Two*, **3**, 197 (1976).

Because the five-membered ring is a substituted cyclopentadienide anion in some dipolar resonance structures, it might be expected that exocyclic groups that could strongly stabilize a positive charge might lead to a larger contribution from dipolar structures and enhanced stability. Structures **13** and **14** are cases in which a large dipolar contribution would be feasible.

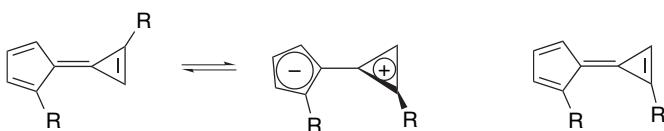


The stability of such dipolar systems depends on the balance between the increase in energy required to separate unlike charges and the aromaticity associated with Hückel $4n + 2$ systems. The parent compound, trientafulvalene, is unknown, but BLYP/6-31G* and MP2/6-31G* calculations suggest some delocalization and a substantial dipole moment.²⁰³ Phenyl-substituted analogs are known, and the large measured dipole moments suggest considerable charge separation.



Ref. 204

Some alkyl derivatives have been prepared. Their chemical behavior is that of highly reactive polyenes. One interesting property does appear in the NMR spectra, which reveal a reduced barrier to rotation about the double bond between the two rings.²⁰⁵ This property suggests that rotation about this bond takes place easily through a TS in which the two charged aromatic rings are twisted out of conjugation.



MO calculations (HF/STO-3G and HF/3-21G) indicate a rotational barrier that is substantially reduced relative to the corresponding barrier in ethene. The TS for the rotation is calculated to have a charge separation of the type suggested by the dipolar resonance structure.²⁰⁶

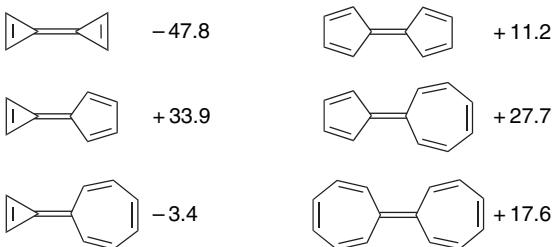
Agranat, Radom, and co-workers surveyed the fulvene and fulvalene combinations including three-, five-, and seven-membered rings. Structures and energies were calculated at the BLYP/6-31G* and MP2/6-31G* levels.²⁰³ A large destabilization was found for triafulvalene on the basis of homodesmotic reactions. The potentially

²⁰³. A. P. Scott, I. Agranat, P. U. Biedermann, N. V. Riggs, and L. Radom, *J. Org. Chem.*, **62**, 2026 (1997).

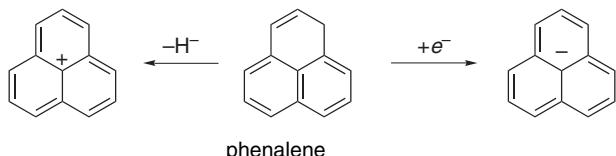
²⁰⁴. E. D. Bergmann and I. Agranat, *J. Chem. Soc. Chem. Commun.*, 512 (1965).

²⁰⁵. A. S. Kende, P. T. Izzo, and W. Fulmer, *Tetrahedron Lett.*, 3697 (1966); H. Prinzbach, *Pure Appl. Chem.*, **28**, 281 (1971).

²⁰⁶. B. A. Hess, Jr., L. J. Schaad, C. S. Ewig, and P. Carsky, *J. Comput. Chem.*, **4**, 53 (1982).



The hydrocarbon phenalene is the precursor of a highly stabilized anion and cation. The HMO diagram is shown in Figure 8.10. The single orbital at the nonbonding level is the LUMO in the cation and the HOMO in the anion. The stabilization energy calculated is the same for both and is 0.41β by the HMO' comparison.²⁰⁷ The pK for conversion of phenalene to its anion is 19.²⁰⁸ The cation is estimated to have a pK_{R+} of about 0–2.²⁰⁹ Several methods for generating the phenalenyl cation have been developed.²¹⁰ Since the center carbon is part of the conjugated system, the Hückel rule, which applies only to *monocyclic* conjugated systems, cannot be applied to just the peripheral conjugation. The nature of the phenalenyl system is considered further in Problem 8.12.



The general conclusion is that the HMO', RE, and SCF methods based on comparison with conjugated polyenes make reasonably accurate predictions about the stabilization in conjugated molecules. The stabilization is general for benzenoid compounds, but quite restricted in nonbenzenoid systems. Since the HMO', method of estimating stability is based on the ideas of HMO theory, its success vindicates the ability of this very simplified MO approach to provide insight into the structural nature of the annulenes and other conjugated polyenes. Of course, more sophisticated MO methods are now accessible and can be applied for more detailed analyses of the structures of these molecules.

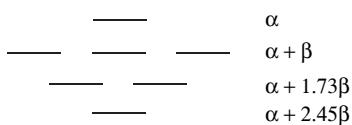


Fig. 8.10. Hückel molecular orbitals for phenalenyl.

²⁰⁷ J. Aihara, *Bull. Chem. Soc. Japan*, **51**, 3540 (1978); P. Ilic and N. Trinjastic, *J. Org. Chem.*, **45**, 1738 (1980).

²⁰⁸ A. Streitwieser, Jr., J. M. Word, F. Guibe, and J. S. Wright, *J. Org. Chem.*, **46**, 2588 (1981); R. A. Cox and R. Stewart, *J. Am. Chem. Soc.*, **98**, 488 (1976).

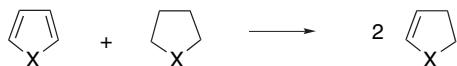
²⁰⁹ D. Menche, H. Strauss, and E. Heilbronner, *Helv. Chim. Acta*, **41**, 57 (1958).

²¹⁰ I. Murata, in *Topics in Nonbenzenoid Aromatic Chemistry*, T. Nozoe, R. Breslow, K. Hafner, S. Ito, and I. Murata, ed., Hirokawa, Tokyo, 1976, pp. 159–190.

8.6. Heteroaromatic Systems

Certain structural units containing heteroatoms can be inserted into aromatic systems in such a way that the system remains conjugated and isoelectronic with the original hydrocarbon. The most common examples are $-\text{CH}=\text{N}-$ and $-\text{N}=\text{N}-$ double bonds and divalent sp^2 $-\text{O}-$, $-\text{S}-$, and $-\text{NR}-$ units. Each of these structural fragments can replace $-\text{CH}=\text{CH}-$ in an aromatic ring and contribute two π electrons.²¹¹ These compounds are called *heteroaromatic* to recognize both their heterocyclic and aromatic nature. Scheme 8.6 gives some of the common structures that are isoelectronic with benzene and naphthalene.

Various approaches have been taken to estimate the aromaticity of these compounds. The Hess-Schaad HMO' values are available,²¹² as are SCF comparisons with polyene models.²¹³ Generally speaking, the various approaches suggest that the aromatic stabilization of pyridine is similar to that of benzene. This is in agreement with thermochemical estimates of the pyridine stabilization energy.²¹⁴ Typically, the five-membered compounds are found to be somewhat less stabilized than benzene with resonance energies in the range of 0.5 to 0.75 of that for benzene.²¹⁵ Theoretical calculations at the MP2/6-31G* and B3LYP/6-31G** have provided aromatic stabilization energies (ASE; see p. 717).



The ASE values correlate with magnetic susceptibility for the five-membered heteroaromatic compounds.²¹⁶ Magnetic and polarizability criteria put the order of aromaticity as thiophene > pyrrole > furan.^{215a,c} The other criteria of aromaticity discussed in Section 8.2 are also applicable to heterocyclic compounds. HOMO-LUMO gaps²¹⁷ and Fukui functions²¹⁸ (see Topic 1.5) have been calculated for compounds such as indole, benzofuran, and benzothiophene and are in accord with the known reactivity patterns of these heterocycles.

Additional heteroaromatic structures can be built up by fusing benzene rings to the aromatic heterocyclic rings or by fusing heterocyclic rings together. Examples of the former type are included in Scheme 8.6. When benzene rings are fused to the heterocyclic five-membered rings, the structures from fusion at the 2,3-positions are much more stable than those from fusion at the 3,4-positions. The π -electron system in the 3,4-fused compounds is more similar to a peripheral 10 π -electron system than

- ²¹¹ B. Ya. Simkin, V. I. Minkin, and M. N. Glukhovtsev, *Adv. Heterocycl. Chem.*, **56**, 303 (1993).
- ²¹² B. A. Hess, L. S. Schaad, and C. W. Holyoke, *Tetrahedron*, **31**, 295 (1975); B. A. Hess and L. S. Schaad, *J. Am. Chem. Soc.*, **95**, 3907 (1973).
- ²¹³ M. J. S. Dewar, A. J. Harget, N. Trinastic, and S. D. Worley, *Tetrahedron*, **28**, 4505 (1970).
- ²¹⁴ K. B. Wiberg, D. Nakaji, and K. M. Morgan, *J. Am. Chem. Soc.*, **115**, 3527 (1993).
- ²¹⁵ (a) M. Stolze and D. H. Sutter, *Z. Naturforsch. A*, **42**, 49 (1987); (b) L. Nyulaszi, P. Varnai, and T. Veszpremi, *Theochem*, **358**, 55 (1995); (c) A. Hincliffe and H. J. Soscul, *Theochem*, **331**, 109 (1995); (d) P. Friedman and K. F. Ferris, *Int. J. Quantum Chem., Symposium* **24**, 843 (1990); (e) G. P. Bean, *J. Org. Chem.*, **63**, 2497 (1998).
- ²¹⁶ P. v. R. Schleyer, P. K. Freeman, H. Jiao, and B. Goldfuss, *Angew. Chem. Int. Ed. Engl.*, **34**, 337 (1995); M. K. Cyranski, P. v. R. Schleyer, T. M. Krygowski, H. Jiao, and G. Hohlneicher, *Tetrahedron*, **59**, 1657 (2003).
- ²¹⁷ B. S. Jursic, *J. Heterocycl. Chem.*, **33**, 1079 (1996); B. S. Jursic, *Theochem*, **468**, 171 (1999).
- ²¹⁸ R. Salcedo, A. Martinez, and L. E. Sansores, *Tetrahedron*, **57**, 8759 (2001); A. Martinewz, M.-V. Vazquez, J. L. Carreon-Macedo, L. E. Sansores, and R. Salcedo, *Tetrahedron*, **59**, 6415 (2003).

Scheme 8.6. Stabilization Energy and Index of Aromaticity for Heteroaromatic Compounds Isoelectronic with Benzene and Naphthalene

A. Structures isoelectronic with benzene

	Pyridine	Pyrimidine	Pyrazine	Pyridazine	s-Triazine
SE	43.3	40.6	40.9	32.7	44.9
HMO'	0.35	0.30	0.29		
SCF-MO	20.9	20.2	14.6		
AM1	25.6	25.0	24.6	22.6	
IA	86	84	89	79	100
	Furan	Pyrrole	Thiophene	Imidazole	Thiazole
SE	27.2	40.4	43.0 0.19	48.3 15.4	42.0
HMO'					
SCF-MO	1.6	8.5			
AM1	12.1	22.5	16.5		
IA	53	90	81.5	79	79

B. Structures isolelectronic with naphthalene

	Quinoline	Isoquinoline	Indole	Benzimidazole
SE	81.0	81.0	73.8	78.9
HMO'	0.51	0.52		30.9
SCF-MO	32.9			
IA	134	133	146	148
	Benzofuran	Isobenzofuran	Isoindole	Benzothiophene
SE	55.4			0.44
HMO'				
SCF-MO	20.3			
IA	94			

SE: Thermochemical stabilization in kcal/mol based on the difference between ΔH_f and summation of standard bond energies. Benzene = 45.8 kcal/mol. C. W. Bird, *Tetrahedron*, **48**, 335 (1992); *Tetrahedron*, **52**, 9945 (1996).

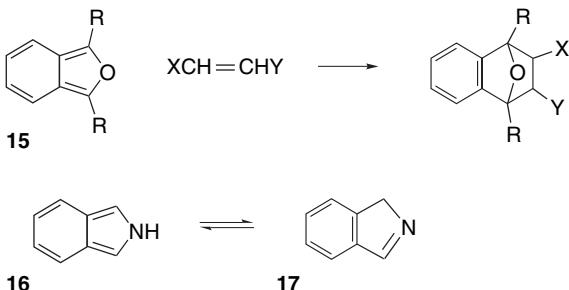
HMO': HMO stabilization in β relative to localized bond model. Benzene = 0.39; B. A. Hess, Jr., L.J. Schaad, and C. W. Holyoke, *J. Org. Chem.*, **31**, 295 (1975); B. A. Hess, Jr., and L. J. Schaad, *J. Am. Chem. Soc.*, **95**, 3907 (1973).

SCF-MO: Difference in total energy in kcal/mol relative to polyene model; Benzene = 20 kcal/mol. M. J. S. Dewar, A. J. Harget, and N. Trinajstic, *J. Am. Chem. Soc.*, **91**, 6321 (1969).

AM1: Stabilization in kcal/mol relative to localized model using AM1 semiempirical calculations; M. J. S. Dewar and A. J. Holder, *Heterocycles*, **28**, 1135 (1989).

IA: Index of aromaticity based on bond length variation. Benzene = 100.

to the 10 electron system for naphthalene. As a result these compounds have a strong tendency to undergo reactions that restore benzene conjugation in the carbocyclic ring. The isobenzofuran structure **15** is known to be an exceptionally reactive diene, for example. Isoindole, **16**, readily tautomerizes to the benzenoid imine **17**.



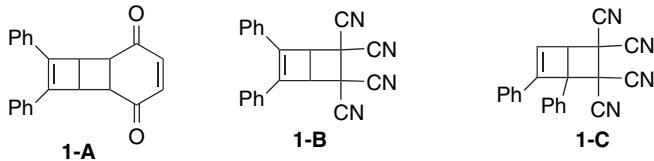
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- I. Gutman and S. J. Cyvin, *Introduction to the Theory of Benzenoid Hydrocarbons*, Springer-Verlag, Berlin, 1989.
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- V. I. Minkin, M. N. Glukhovtsev and B. Y. Simkin, *Aromaticity and Anti-aromaticity*, Wiley, New York, 1994.
- M. Sainsbury, *Aromatic Chemistry*, Oxford University Press, Oxford, 1992.

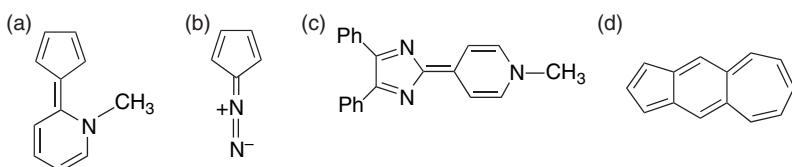
Problems

(References for these problems will be found on page 1163.)

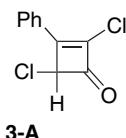
- 8.1. The reaction of 1,2-diphenylcyclobutadiene (generated *in situ* by oxidation of its iron tricarbonyl complex) with *p*-benzoquinone yields adduct **1-A** as the exclusive product. A completely analogous structure is obtained using maleimide as the dienophile. However, with the more reactive dienophiles tetracyanoethylene and dicyanomaleimide, two isomeric adducts of type **1-B** and **1-C** are found in a 1:7 ratio in each case. Discuss these results and explain how they relate to the issue of a square versus a rectangular structure for the cyclobutadiene ring.



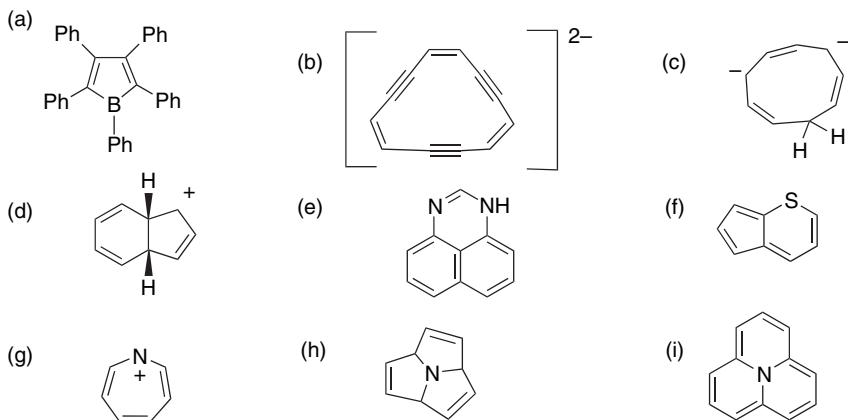
- 8.2. A single resonance structures is shown below for each of several molecules. Consider other resonance structures and identify those that would be expected to make a major stabilizing contribution to the molecule in question.



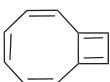
- 8.3. a. A synthesis of tropone (cycloheptatrienone) entails treating 1-methoxy-1,3,5-cycloheptatriene with bromine. A salt is produced that yields tropone on treatment with aqueous NaHCO_3 . What is a likely structure for the salt? Write a mechanism for its formation and for the formation of tropone on hydrolysis.
- b. The optically active dichlorophenylcyclobutene **3-A** undergoes racemization in acetic acid at 100°C . Suggest an experiment to determine if the enol (a hydroxycyclobutadiene) is an intermediate.



- 8.4. Predict whether or not the following structures would show strong delocalization and stabilization (aromatic), weak stabilization by conjugation (nonaromatic), or strong destabilization (antiaromatic) relative to acyclic model structures. Explain the basis for your prediction.



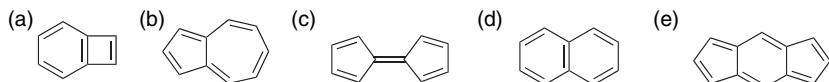
- 8.5. Bicyclo[6.2.0]deca-2,4,6,8,10-pentaene has been synthesized, and a number of MO and MM calculations have been performed to assess its aromaticity or antiaromaticity. Consider the structure and discuss the points below.



- a. What aspects of the structure suggest that antiaromaticity might be observed?
- b. What aspects of the structure suggest that aromaticity might be observed?

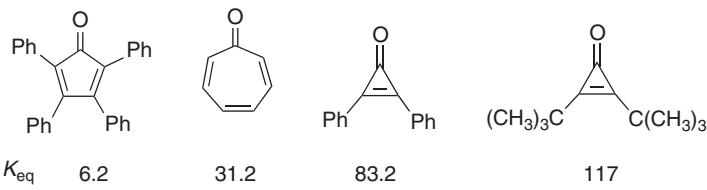
c. What are some of the experimental and computational criteria that could be applied to assess aromaticity or antiaromaticity? Cite at least three such probes and indicate the nature of the observation and interpretation.

8.6. Using the empirically chosen energy equivalents for bond types given on p. 748 and a standard compilation of HMO calculations, determine the resonance energies of the following molecules by the Hess-Schaad procedure (p. 747). Do you find any discrepancies between the predicted and observed properties, as described in Section 8.5?



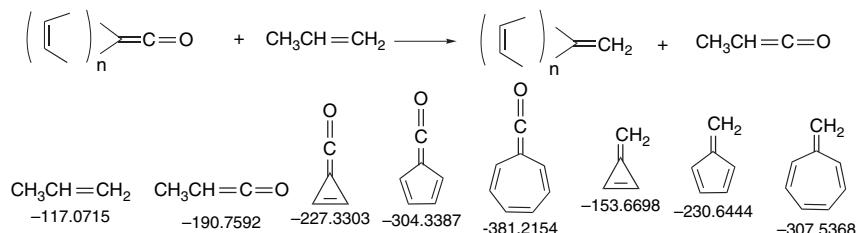
8.7. The completely conjugated cyclic polyenones have attracted considerable interest. Consider the following aspects of their properties:

a. The relative basicity of carbonyl oxygens can be measured by studying the strength of hydrogen bonding with a hydrogen donor such as phenol. The K_{eq} for 1:1 complexation of the following substituted cyclenones was determined. What conclusions do you draw from these data?

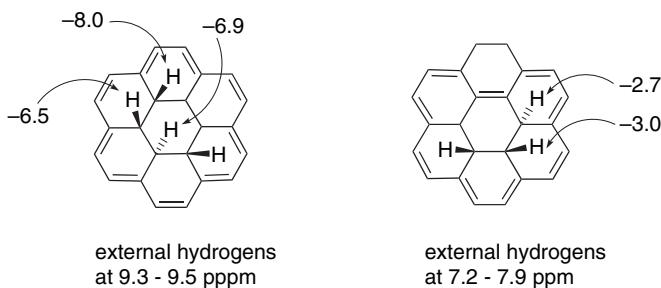


b. There have been extensive physical and chemical studies on cyclopropenone, cyclopentadienone, and cycloheptatrienone (tropone). The results of these studies can be briefly summarized as follows: (a) cyclopropenone appears to be stabilized by 20 ± 5 kcal/mol, relative to localized model structures; (b) cyclopentadienone is a kinetically unstable molecule; (c) tropone is estimated to be stabilized by less than 10 kcal/mol, relative to localized models. It is nonplanar and rather reactive. Rationalize these results in terms of MO concepts.

8.8. The isodesmic reaction series shown below has been used to compare the stabilities of the cyclopolyene ketenes. The total energies (HF/6-31G*) are given in hartrees. Calculate the stabilization found for each cyclopolyene ketene for $n = 1-3$. Account for the differences in stabilization and compare the results of these exocyclic ketenes to the corresponding cyclopolyenones (Problem 8.7).

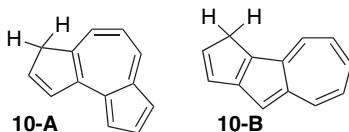


8.9. One criterion of aromaticity is the diamagnetic ring current, which is indicated by a substantial chemical shift difference between hydrogens in the plane of a conjugated system and those above or below the plane. The chemical shifts of two isomeric hydrocarbons are given below. In qualitative terms, which compound appears to be more aromatic? (Because the chemical shift owing to ring current depends on the detailed geometry, a quantitative calculation would be necessary to confirm the correctness of the qualitative assessment.) Does HMO theory predict a difference in the aromaticity of these two compounds?

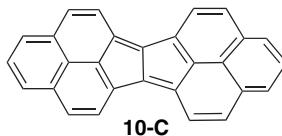


8.10. Offer an explanation for the following observations:

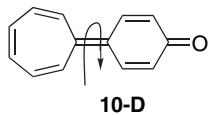
- a. Hydrocarbon **10-A** ($pK \approx 14$) is considerably more acidic than **10-B** ($pK \approx 22$).



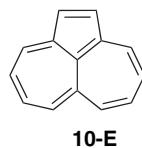
- b. Hydrocarbon **10-C** has an unusually small separation of its oxidation and reduction potentials, as established by electrochemical measurements. It is both easily reduced and easily oxidized. Both mono- and dicitations and mono- and dianions can be readily formed.



- c. The barrier for rotation about the marked bond in **10-D** is only about 14 kcal/mol.



- d. The hydrocarbon **10-E** is easily reduced to a dianion. The ^1H NMR spectrum of the dianion shows an average downfield shift relative to the hydrocarbon. The central carbon shows a large upfield shift in the ^{13}C -NMR spectrum.

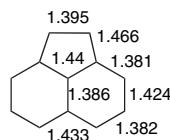


- 8.11. The HMOs for acenaphthene are shown below. The atomic coefficients for the orbital that is the LUMO in the neutral compound and the HOMO in the dianion are given at the right.

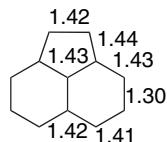
—	-2.36		
—	-1.92	+0.322	-0.322
—	-1.43	+0.230	-0.230
—	-1.31	-0.388	+0.388
—	-1.00	-0.120	+0.120
—	-0.28	+0.422	-0.422
—	+0.63		
—	+0.83		
—	+1.00		
—	+1.69		
—	+2.47		

Comment on the aromaticity, antiaromaticity, or nonaromaticity of acenaphthene and its dianion on the basis of the following physical measurements:

- a. The bond lengths of acenaphthene are given below. Compare them with the bond lengths for naphthalene given on p. 18. What conclusions can you draw about the aromaticity of acenaphthene?



- b. Both X-ray crystallography and NMR data indicate that the C(1)–C(2) bond lengthens significantly in the dianion, as indicated below (X-ray data). There is also a different pattern of bond length alternation. What conclusions can you draw about the aromaticity of the acenaphthene dianion?



- c. The ^1H - and ^{13}C -NMR shifts for acenaphthene and its dianion (Na^+ counterion) are given below. What conclusions about charge density and aromaticity can be drawn from these data?

		1,2	3,8	4,7	5,6	2a,8a	5a	8b
^1H	Neutral	7.04	7.65	7.50	7.78			
	Dianion	4.49	4.46	5.04	3.34			
^{13}C	Neutral	129.9	124.7	128.3	127.8	140.7	129.1	129.3
	Dianion	86.1	97.0	126.8	82.6	123.4	149.3	137.7

- 8.12. The ^1H -NMR and ^{13}C -NMR spectra of both the anion and cation derived from phenalene have been observed. The HMO pattern for phenalene is given below.

HMO coefficients							
		atom	Energy(β)				
2		1	2.44949	1.73205	1.73205	1.00000	1.0000
1		2	0.22361	0.35355	0.20412	-0.00473	-0.35355
9		9a	0.18257	0.	0.00000	-0.00947	-0.00000
8		9b	0.36515	0.20412	0.35355	-0.00473	-0.35355
		4	0.44721	0.00000	0.00000	-0.40811	0.00000
		3a	0.22361	-0.00000	0.40825	0.41134	0.00000
		5	0.18257	-0.20412	0.035355	0.040661	0.35355
		7	0.22361	-0.35355	0.20412	-0.00473	0.35355
		6a	0.36515	-0.40825	0.00000	-0.41434	0.00000
		6					
		3					
		2a					

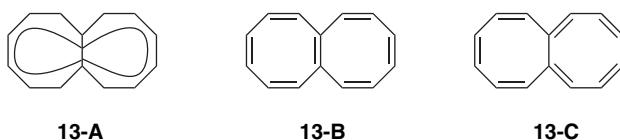
The chemical shifts observed for the cation and anion are given below.

	^1H -NMR			^{13}C -NMR		
	C(1)	C(2)	C(1)	C(2)	C(9b)	C(3a)
[Cation]	9.38	8.55	155.5	133.7	123.7	133.7
[Anion]	5.36	6.10	103.4	128.0	139.6	145.0

What conclusions can be drawn about electron distribution in the cation and anion from the NMR data and how does it relate to the HMO pattern?

- 8.13. The ^{13}C -NMR spectrum of octalene (**13-A**, **13-B**, or **13-C**) is temperature dependent. At -150°C , there are signals for 14 different carbons. At -100°C , these collapse to seven different signals. Above 80°C , all but one of the remaining signals become broad. Although not attained experimentally, because of decomposition, it would be expected that only four different signals would be obtained at still higher temperature. (1) Show that these data rule out structures **13-A** and **13-B** for the room temperature structure of octalene, and favor structure **13-C**. (2) What is the nature of the dynamic process that converts the 14-line spectrum

to a 7-line spectrum? (3) What would be the nature of the process that converts the 7-line spectrum to a 4-line spectrum?



8.14. When alcohol **14-A** is dissolved in FSO_3H at -136°C and then brought to -110°C , it gives rise to a ^{13}C -NMR spectrum having five lines in the intensity ratio 2:1:2:2:2.

- a. Suggest several possible structures for this cation and discuss stabilizing features that might favor a particular structure.

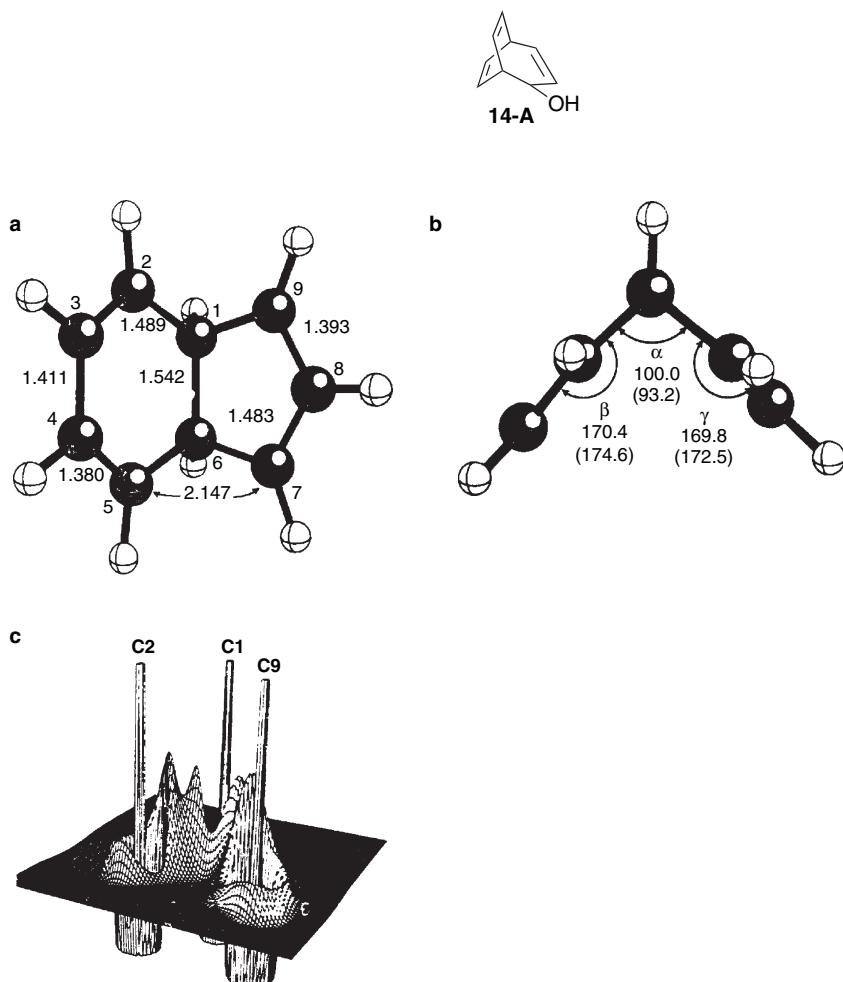


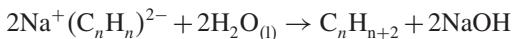
Fig. 8.P14. (a) Bond lengths and (b) inter-ring angles for minimum-energy cation; (c) $-\nabla^2\rho(\mathbf{r})$ in the $\text{C}(1)-\text{C}(2)-\text{C}(9)$ plane. Reproduced by permission of the American Chemical Society
Bond Orders: 1,2: 1.04; 2,3: 1.59; 3,4: 1.57; 1,6: 0.94; 1,9: 1.04; 8,9: 1.56; 2,9: 0.34.

b. Figure 8.P14(a, b) gives the computed minimum-energy structure at the MP4(SDQ)/6-31G(*d*) level. Diagram (c) is the $-\nabla^2\rho(\mathbf{r})$ in the C(1)–C(2)–C(9) plane. Does this structure correspond to any of those you have suggested in Part (a)? What structural representation would be most consistent with the calculated minimum-energy structure?

- 8.15. a. The heats of combustion (ΔH_c) and heats of hydrogenation (ΔH_{H_2}) for addition of 1 mol of H_2 and the estimated stabilization energy (SE) for benzene and cyclooctatetraene (in kcal/mol) are given below. The ΔH_c and ΔH_{H_2} are also given for [16]annulene. Compare the stabilization energy of [16]annulene with benzene and cyclooctatetraene on a per CH basis.

	Benzene	Cyclooctatetraene	[16]Annulene
ΔH_c	781	1086	2182
ΔH_{H_2}	-5.16	25.6	28.0
SE	36	4	?

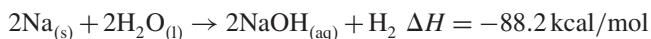
- b. The enthalpies of the reaction of the cyclooctatetraene and [16]annulene dianions with water have been measured.



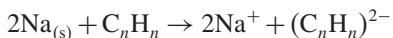
$$\Delta H = -33.33 \text{ kcal/mol for cyclooctatetraene}$$

$$\Delta H = -10.9 \text{ kcal/mol for [16]annulene.}$$

Using these data and the enthalpy of the reaction of sodium with water:

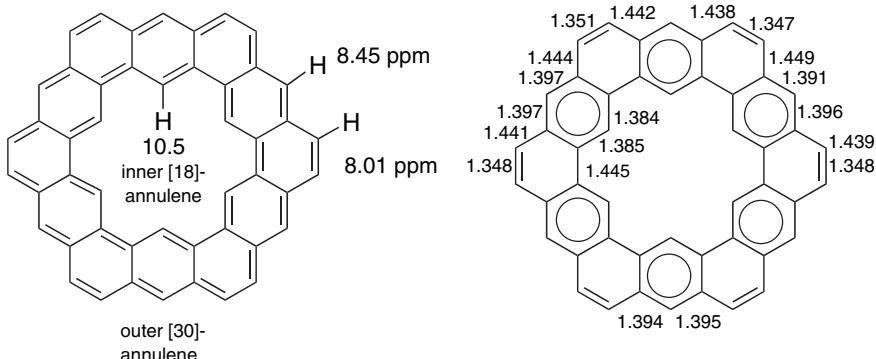


calculate ΔH for the reaction:

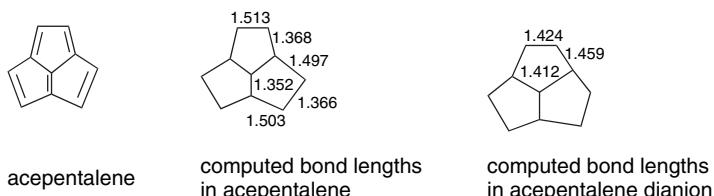


Why might the reaction of $[\text{C}_{16}\text{H}_{16}]^{2-}$ with water be less exothermic than for $[\text{C}_8\text{H}_8]^{2-}$? How do you interpret the difference in the heat of reaction of the two hydrocarbons to form the respective dianions?

- 8.16. Consider the two structures shown for kekulene, one suggesting inner and outer annulenes and the other a series of phenanthrene-like units. $^1\text{H-NMR}$ and bond length data are given. The NICS values are calculated as -4.3 for the angularly fused rings and -10.8 for the linearly fused rings. Indicate properties that you would expect to be associated with each structure. Do you consider the properties to be more consistent with the double-annulene or the phenanthrene-like structures?



8.17. Acepentalene is a rather unstable molecule, but its dianion can be formed quite readily. The structure and properties of acepentalene and its dianion and dication have been calculated (B3LYP/6-31G*) and are given below. The computed lowest-energy structure is slightly pyramidal, with an inversion barrier of 7.1 kcal/mol. The structure of the lithium salt of the dianion is given in the Figure 8.P17. The calculated inversion barrier for the dianion is 5.4 kcal/mol. The chemical shift of the ^1H signal in the dianion is at -8.2 .



- a. What evidence in terms of aromaticity/antiaromaticity can you offer for the apparently greater stability of the 12π -electron dianion as compared with the 10π -electron neutral? What accounts for the pyramidal as opposed to planar structures for the neutral and dianion?

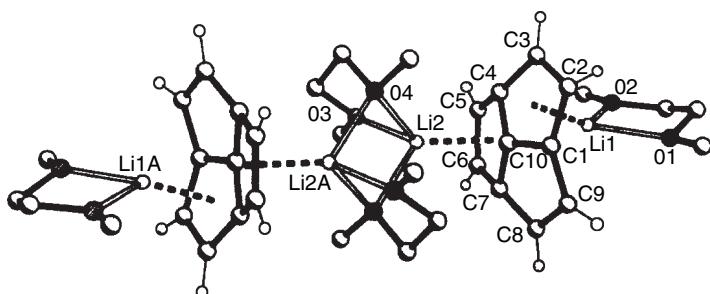


Fig. 8.P17. Crystal structure of $\text{Li}_2(\text{DME})_2$ acepentalenediide. Reproduced from *Angew. Chem. Int. Ed. Engl.*, **34**, 1492 (1995), by permission of Wiley-VCH.

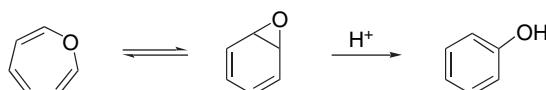
	NICS*	NICS _(in) ^a	NICS _(out) ^a	χ	Λ
Acepentalene	+42.3	50.0	31.0	-62.4	23.1
Dianion	-32.7	-42.3	-27.9	-141.0	-43.1
Dication	+10.2	-24.9	2.4	-72.9	-18.8

a. The NICS values are relative to positions 0.5 Å inside and outside the pyramidal structure. NICS* is the sum for all rings.

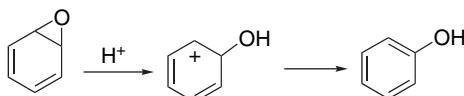
- b. The HMO orbitals of acepentalene are given below. How do the predictions of HMO theory accord with the experimental and B3LYP results?

—	-2.086
—	-1.879
—	-1.000
—	+0.347
—	+0.572
—	+1.532
—	+2.514

- 8.18. Arene oxides are important intermediates in the metabolism of aromatic compounds. Although they are highly reactive, both valence tautomerism to oxepins and acid-catalyzed ring opening to phenols can be observed and studied.

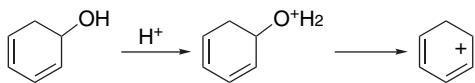


Surprisingly, the rate of acid-catalyzed ring opening is less than that for dehydration of “2,4-cyclohexadienol” even though they lead to similar cations. Normally, epoxide ring opening is much faster than alcohol dehydration. For example, the epoxide of cyclohexadiene is about 10^7 more reactive than cyclohexenol.



$$k [H^+][\text{oxide}] = 32 \text{ } M^{-1}\text{s}^{-1}$$

$$\Delta H_r = -57 \text{ kcal/mol}$$



$$k [H^+][\text{dien-ol}] = 190 \text{ } M^{-1}\text{s}^{-1}$$

$$\Delta H_r = -39 \text{ kcal/mol}$$



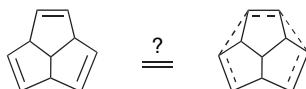
$$k [H^+][\text{oxide}] = 1.1 \times 10^4 \text{ } M^{-1}\text{s}^{-1} \quad k [H^+][\text{en-ol}] = 10^{-3} M^{-1}\text{s}^{-1}$$

What might account for the apparent kinetic stability of the arene oxide toward acid-catalyzed ring opening?

- 8.19. Using isodesmic reactions and the G2(MP2) energies given below, determine if 1,2,3-trichlorocyclopropenium ion is more or less stable than the *tert*-butyl carbocation. Are the chlorine substituents stabilizing or destabilizing with respect to cyclopropenium ion?

Substance	G2(MP2) energy (hartrees)
Trichlorocyclopropenium	-1492.916633
Cyclopropenium ion	-115.492839
<i>tert</i> -Butyl carbocation	-157.169332
1,2,3,3-tetrachlorocyclopropene	-1952.950661
3-Chlorocyclopropene	-575.525577
<i>tert</i> -Butyl chloride	-617.226718

- 8.20. Triquinacene is a hydrocarbon that might be stabilized by homoaromaticity.



The calculated (B3LYP/6-3111+G*) ΔH_{H_2} for the successive double bond are -27.6, -27.3, and -26.8 kcal/mol. The ΔH_{H_2} for cyclopentene is -26.9 kcal/mol. The existence of homoaromatic stabilization of triquinacene might be assessed by the following homodesmotic reaction, where $\Delta E = -0.8 \text{ kcal/mol}$:



$$\Delta E = -0.8 \text{ kcal/mol}$$

Do these data indicate homoaromatic stabilization of triquinacene? Why or why not?

Aromatic Substitution

Introduction

The introduction or replacement of substituents on aromatic rings by substitution reactions is one of the most fundamental transformations in organic chemistry. On the basis of the reaction mechanism, these substitution reactions can be divided into (a) electrophilic, (b) nucleophilic, (c) radical, and (d) transition metal catalyzed. In this chapter we consider the electrophilic and nucleophilic substitution mechanisms. Radical substitutions are dealt with in Chapter 11 and transition metal-catalyzed reactions are discussed in Chapter 9 of Part B.

9.1. Electrophilic Aromatic Substitution Reactions

Electrophilic aromatic substitution (abbreviated EAS in this chapter) reactions are important for synthetic purposes and are also among the most thoroughly studied classes of organic reactions from a mechanistic point of view. The synthetic aspects of these reactions are considered in Chapter 9 of Part B. This section focuses on the mechanisms of several of the most completely studied reactions. These mechanistic ideas are the foundation for the structure-reactivity relationships in aromatic electrophilic substitution that are discussed in Section 9.2.

A wide variety of electrophiles can effect aromatic substitution. Usually, it is a substitution of some other group for hydrogen that is of interest, but this is not always the case. For example, both silicon and mercury substituents can be replaced by electrophiles. Scheme 9.1 lists some of the specific electrophiles that are capable of carrying out substitution of hydrogen. Some indication of the relative reactivity of the electrophiles is given as well. Many of these electrophiles are not treated in detail until Part B. Nevertheless, it is important to recognize the very broad scope of electrophilic aromatic substitution.

The reactivity of a particular electrophile determines which aromatic compounds can be successfully substituted. The electrophiles grouped in the first category are sufficiently reactive to attack almost all aromatic compounds, even those having strongly

EWG substituents. Those in the second group react readily with benzene and derivatives having ERG substituents but are not generally reactive toward aromatic rings with EWG substituents. Those classified in the third group are reactive only toward aromatic compounds that are much more reactive than benzene. These groupings can provide a general guide to the feasibility of a given EAS reaction.

Despite the wide range of electrophilic species and aromatic ring systems that can undergo substitution, a single broad mechanistic picture encompasses most EAS reactions. The identity of the rate-determining step and the shape of the reaction energy profile are specific to individual reactions, but the sequence of steps and the nature of the intermediates are very similar across a wide range of reactivity. This permits discussion of EAS reactions in terms of the general mechanism that is outlined in Scheme 9.2.

A complexation of the electrophile with the π electron system of the aromatic ring is the first step. This species, called the π complex, may or may not be involved

Scheme 9.1. Electrophiles Active in Aromatic Substitution

	Electrophile	Typical means of generation
A. Electrophiles capable of substituting both activated and deactivated aromatic rings		
1 ^a	$O=N^+=O$	$2 H_2SO_4 + HNO_3 \rightleftharpoons NO_2^+ + 2 HSO_4^- + H_3O^+$
2 ^b	Br_2 or Br_2-MX_n	$Br_2 + MX_n \rightleftharpoons Br_2-MX_n$
3 ^b	BrO^+H_2	$BrOH + H_3O^+ \rightleftharpoons BrO^+H_2$
4 ^b	Cl_2 or Cl_2-MX_n	$Cl_2 + MX_n \rightleftharpoons Cl_2-MX_n$
5 ^b	CIO^+H_2	$CIOH + H_3O^+ \rightleftharpoons CIO^+H_2$
6 ^c	SO_3 or SO_2O^+H	$H_2S_2O_7 \rightleftharpoons HSO_4^- + SO_2O^+H$
7 ^d	RSO_2^+	$RSO_2Cl + AlCl_3 \rightleftharpoons RSO_2^+ + AlCl_4^-$
B. Electrophiles capable of substituting activated but not deactivated aromatic rings		
8 ^e	R_3C^+	$R_3CX + MX_n \rightleftharpoons R_3C^+ + [MX_{n+1}]^-$
9 ^f	R_3C^+	$R_3COH + H^+ \rightleftharpoons R_3C^+ + H_2O$
10 ^g	$R_2C=CHR'_2$	$R_2C=CR'_2 + H^+ \rightleftharpoons R_2C=CHR'_2$
11 ^e	RCH_2X-MX_n	$RCH_2X + MX_n \rightleftharpoons RCH_2X-MX_n$
12 ^h	$RC\equiv O^+$	$RCOX + MX_n \rightleftharpoons RC\equiv O^+ + [MX_{n+1}]^-$
13 ^h	$RCOX-MX_n$	$RCOX + MX_n \rightleftharpoons RCOX - MX_n$
14 ⁱ	$RC^+=O^+H$	$RCOX + MX_n + H^+ \rightleftharpoons RC^+=O^+H + [MX_{n+1}]^-$
15 ^j	H^+	$HX \rightleftharpoons H^+ + X^-$
16 ^k	$R_2C=O^+H$	$R_2C=O + H^+ \rightleftharpoons R_2C=O^+H$
17 ^k	$R_2C=O^+-M^-X_n$	$R_2C=O + MX_n \rightleftharpoons R_2C=O^+-M^-X_n$
18 ⁱ	$HC^+=N^+H_2$	$HC\equiv N + 2H^+ \rightleftharpoons HC^+=N^+H_2$

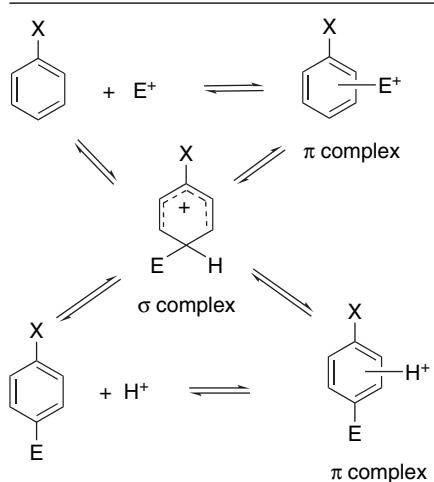
C. Electrophiles capable of substitution only strongly activated aromatic rings

19 ^l	$\text{HC}\equiv\text{N}^+\text{H}$	$\text{HC}\equiv\text{N} + \text{HX} \rightleftharpoons \text{HC}\equiv\text{N}^+\text{H} + \text{X}^-$	SECTION 9.1 <i>Electrophilic Aromatic Substitution Reactions</i>
20 ^m	$\text{N}\equiv\text{O}^+$	$\text{HONO} + \text{H}^+ \rightleftharpoons \text{N}\equiv\text{O}^+ + \text{H}_2\text{O}$	
21 ⁿ	$\text{ArN}^+\equiv\text{N}$	$\text{ArNH}_2 + \text{HONO} + \text{H}^+ \rightleftharpoons \text{ArN}^+\equiv\text{N} + 2\text{H}_2\text{O}$	

- a. G. A. Olah and S. J. Kuhn, in *Friedel-Crafts and Related Reactions*, Vol. III, G. A. Olah, ed., Interscience, New York, 1964, Chapter XLIII.
 b. H. P. Braendlin and E. T. McBee, in *Friedel-Crafts and Related Reactions*, Vol. III, G. A. Olah, ed., Interscience, New York, 1964, Chapter XLVI.
 c. K. L. Nelson, in *Friedel-Crafts and Related Reactions*, Vol. III, G. A. Olah, ed., Interscience, New York, 1964, Chapter, XLVII.
 d. F. R. Jensen and G. Goldman, in *Friedel-Crafts and Related Reactions*, Vol. III, G. A. Olah, ed., Interscience, New York, 1964, Chapter XL.
 e. F. A. Drahowzal, in *Friedel-Crafts and Related Reactions*, Vol. II, G. A. Olah, ed., Interscience, New York, 1964, Chapter XVII.
 f. A. Schreisheim, in *Friedel-Crafts and Related Reactions*, Vol. II, G. A. Olah, ed., Interscience, New York, 1964, Chapter XVIII.
 g. S. H. Patinkin and B. S. Friedman, in *Friedel-Crafts and Related Reactions*, Vol. II, G. A. Olah, ed., Interscience, New York, 1964, Chapter XIV.
 h. P. H. Gore, in *Friedel-Crafts and Related Reactions*, Vol III, G. A. Olah, ed., Interscience, New York, 1964, Chapter XXXI.
 i. Y. Sato, M. Yato, T. Ohwada, S. Saito, and K. Shudo, *J. Am. Chem. Soc.*, **117**, 3037 (1995).
 j. R. O. C. Norman and R. Taylor, *Electrophilic Substitution in Benzenoid Compounds*, Elsevier, New York, 1965, Chapter 8.
 k. J. E. Hofmann and A. Schreisheim, in *Friedel-Crafts and Related Reactions*, Vol. II, G. A. Olah, ed., Interscience, New York, 1964, Chapter XIX.
 l. W. Ruske, in *Friedel-Crafts and Related Reactions*, Vol. III, G. A. Olah, ed., Interscience, New York, 1964, Chapter XXXII.
 m. B. C. Challis, R. J. Higgins, and A. J. Lawson, *J. Chem. Soc., Perkin Trans.*, **2**, 1831 (1972).
 n. H. Zollinger, *Azo and Diazo Chemistry*, transl. H. E. Nursten, Interscience, New York, 1961, Chapter 10.

directly in the substitution mechanism. π Complex formation is, in general, rapidly reversible and in many cases the equilibrium constant is small. The π complex is a donor-acceptor type of complex with the π electrons of the aromatic ring donating electron density to the electrophile. Although these complexes are readily observed by spectroscopic measurements, they generally are of only modest stability. Only recently

Scheme 9.2. Generalized Mechanism for Electrophilic Aromatic Substitution



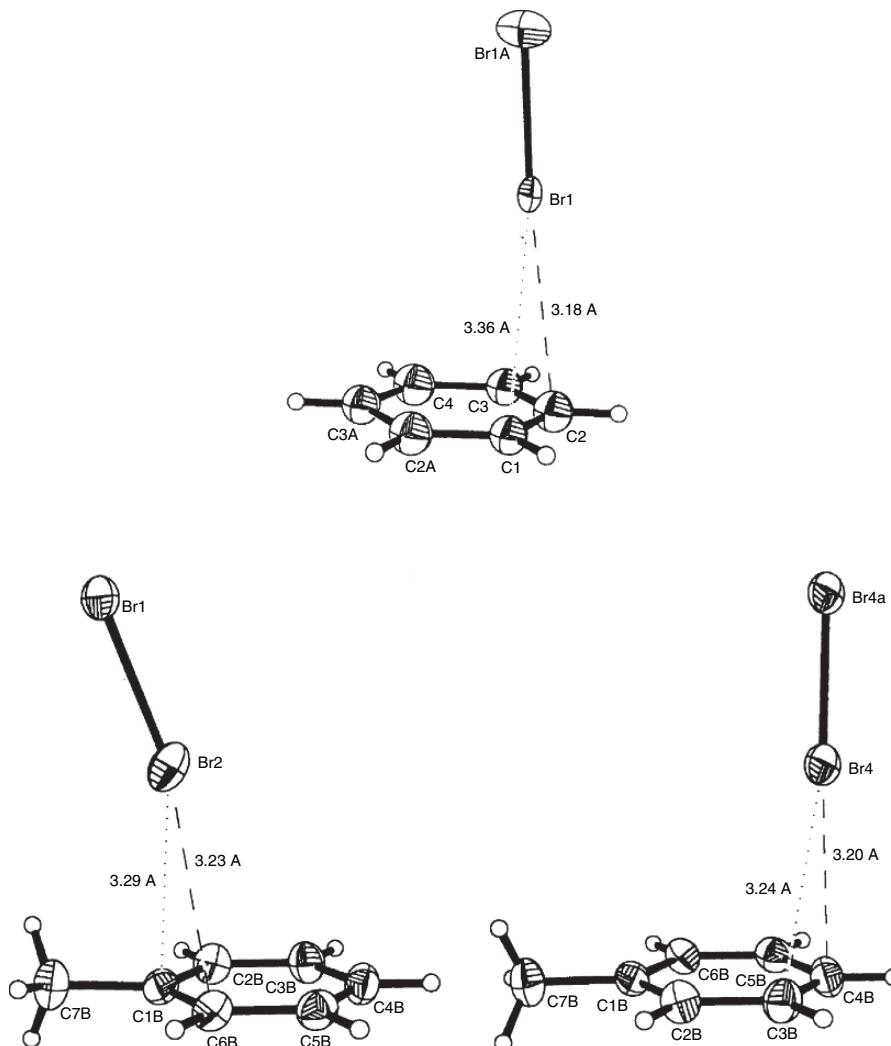


Fig. 9.1. Structures of benzene- Br_2 (top) and toluene- Br_2 (bottom) complexes. Reproduced from *Chem. Commun.*, 909 (2001), by permission of the Royal Society of Chemistry.

has structural data become available. The structures of the Br_2 complexes with benzene and toluene have been examined by X-ray crystallography at low temperature. The Br_2 molecule is nearly perpendicular to the ring and located between two specific carbons, as opposed to being associated with the delocalized π electron density. For toluene, there are two complexes with the Br_2 being associated with the *ortho* and *para* carbons.¹ This is significant because these are also the preferred sites for substitution, and the structures indicate that an aspect of position selectivity is present at the π complex stage. These structures are shown in Figure 9.1.

Structural information is also available on the complex between mesitylene and the nitrosonium ion, NO^+ .² In this case there appears to be a high degree of charge transfer and the complex is essentially between the aromatic radical cation and the NO

¹ A. V. Vasilyev, S. V. Lindeman, and J. K. Kochi, *Chem. Commun.*, 909 (2001); S. V. Rosokha and J. K. Kochi, *J. Org. Chem.*, **67**, 1727 (2002).

² E. K. Kim and J. K. Kochi, *J. Am. Chem. Soc.*, **113**, 4962 (1991).

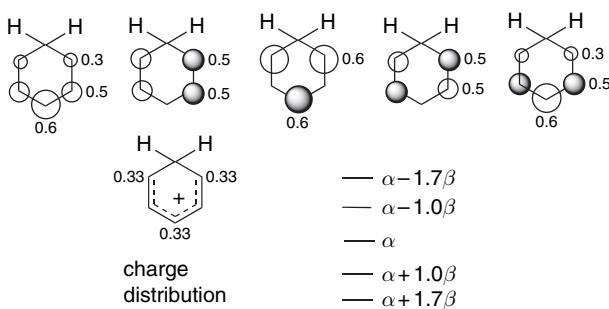
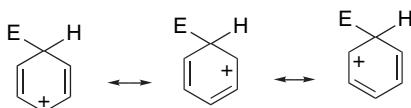


Fig. 9.2. π Molecular orbitals and energy levels for the cyclohexadienylum ion.

molecule, which is located centrally with respect to the aromatic ring. The N–O bond distance is 1.07 Å and the C–C bond distances are similar to those observed for the radical cation.³ There are probably similar complexes in other EAS reactions. Recent computational studies of the nitration of benzene describe the earliest energy minimum as NO_2^+ approaches benzene (in the gas phase) as being directed at the midpoint of a particular C–C bond, as opposed to the center of the ring.⁴

In order for a substitution to occur, a “ σ complex” must be formed. The term σ complex is used to describe a *cationic intermediate* in which the carbon at the site of substitution is bonded to both the electrophile and the hydrogen that is being displaced. As the term implies, a σ bond is formed at the site of substitution. The intermediate is a *cyclohexadienylum cation*. Its fundamental electronic characteristics can be described in simple MO terms, as shown in Figure 9.2. The intermediate is a 4π electron delocalized system that is electronically equivalent to a pentadienyl cation. There is no longer cyclic conjugation. The LUMO has nodes at C(2) and C(4) of the pentadienyl structure and these correspond to the positions *meta* to the site of substitution on the aromatic ring. As a result, the positive charge of the cation is located at the positions *ortho* and *para* to the site of substitution. These electronic features of the σ -complex intermediate are also shown by resonance structures.

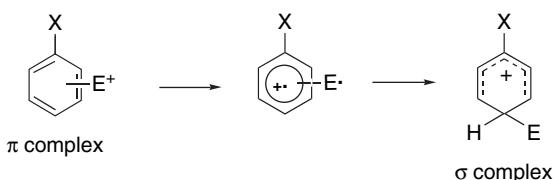


As we will see in Section 9.2, this pattern of charge distribution leads to the *o,p*- or *m*-directing characteristics of various ring substituents.

There is considerable interest in the mechanism for conversion of the π complex into the σ complex. In particular, the question arises as to whether an electron transfer occurs to yield a discrete cation–radical pair.

³ S. V. Rosokha and J. K. Kochi, *J. Am. Chem. Soc.*, **123**, 8985 (2001).

⁴ H. Xiao, L. Chen, X. Ju, and G. Li, *Science in China B*, **46**, 453 (2003); P. M. Esteves, J. W. de Carneiro, S. P. Cardoso, A. G. H. Barbosa, K. K. Laali, G. Rasul, G. K. S. Prakash, and G. A. Olah, *J. Am. Chem. Soc.*, **125**, 4836 (2003).



This mechanism implies that a considerable change in the structure of the electrophile occurs prior to σ -bond formation. These structural changes could account in large part for the energy barrier to formation of the σ complex.⁵ Moreover, this mechanism implies that the cation radical–radical pair might play a key role in determining the isomeric (*ortho*, *meta*, *para*) product composition. These issues have been investigated most closely for nitration and bromination and are considered further when those reactions are discussed.

Formation of the σ complex can be reversible. The partitioning of the σ complex forward to product or back to reactants depends on the ease with which the electrophile can be eliminated, relative to a proton. For most electrophiles, it is easier to eliminate the proton, in which case the formation of the σ complex is essentially irreversible. The electrophiles in group A of Scheme 9.1 are the least likely to be reversible, whereas those in group C are most likely to undergo reversible σ -complex formation. Formation of the σ complex is usually, but not always, the rate-determining step in EAS. There may also be a π complex involving the aromatic ring and the departing electrophile. This would be expected on the basis of the principle of microscopic reversibility, but there is little direct evidence on this point.⁶

Let us now consider some of the evidence for this general mechanism. Such evidence has, of course, been gathered by study of specific reaction mechanisms. Only some of the most clear-cut cases are cited here. Additional evidence is mentioned when individual mechanisms are discussed in Section 9.4. A good example of studies that have focused on the identity and mode of generation of the electrophile is aromatic nitration. Primarily on the basis of kinetic studies, it has been shown that the active electrophile in nitration is often the nitronium ion, NO_2^+ , which is formed by the reaction of nitric acid with concentrated sulfuric. Several other lines of evidence support the role of the nitronium ion. It can be detected spectroscopically and the freezing-point depression of the solution is consistent with the following equation:



Solid salts in which the nitronium ion is the cation can be prepared with unreactive anion such as for $\text{NO}_2^+\text{BF}_4^-$ and $\text{NO}_2^+\text{PF}_6^-$. These salts act as nitrating reagents.

Two types of rate expressions have been found to describe the kinetics of many aromatic nitration reactions. With relatively unreactive substrates, second-order kinetics, first order in the nitrating reagent and first order in the aromatic, are observed. This second-order relationship corresponds to rate-limiting attack of the electrophile on the aromatic reactant. With more reactive aromatics, this step can be faster than formation of the active electrophile. In these cases, the generation of the electrophile

⁵ S. V. Rosokha and J. K. Kochi, *J. Org. Chem.*, **67**, 1727 (2002).

⁶ For additional discussion of the role of σ and π complexes in aromatic substitution, see G. A. Olah, *Acc. Chem. Res.*, **4**, 240 (1971); J. H. Ridd, *Acc. Chem. Res.*, **4**, 248 (1971).

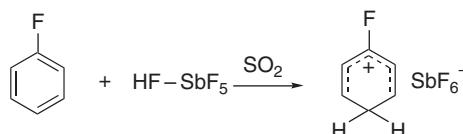
is the rate-determining step. When formation of the active electrophile is the rate-determining step, the concentration of the aromatic reactant no longer appears in the observed rate expression. Under these conditions, different aromatic substrates undergo nitration at the same rate, corresponding to the rate of formation of the active electrophile.

An important general point to be drawn from the specific case of nitration is that the active electrophile is usually some species that is more reactive than the added reagents. The active electrophile is formed from the reagents by a subsequent reaction, often involving a Brønsted or Lewis acid. One goal of mechanistic study is to determine the identity of the active electrophile, the formation of which may or may not be the rate-determining step. Scheme 9.1 indicates the structure of some of the electrophilic species that are involved in EAS processes and the reactions involved in their formation.

There are several lines of evidence pointing to formation of σ complexes as intermediates in EAS. One approach involves measurement of isotope effects on the rate of substitution. If removal of the proton at the site of substitution is concerted with the introduction of the electrophile, a primary isotope effect is expected when electrophilic attack on the ring is rate determining. This is not the case for nitration. Nitration of aromatic substrates partially labeled by tritium shows no selectivity between protium- and tritium-substituted sites.⁷ Similarly, the rate of nitration of nitrobenzene is identical to that of penta-deutero-nitrobenzene.⁸

The lack of a primary isotope effect indicates that the proton is lost in a fast step following the rate-determining step, which means that proton loss must occur from some intermediate that is formed before the cleavage of the C–H bond begins. The σ -complex intermediate fits this requirement. There are some electrophilic aromatic substitution reactions that show k_H/k_D values between 1 and 2 and there are a few others that are in the range indicating a primary isotope effect.⁹ The existence of these isotope effects is compatible with the general mechanism if the proton removal is rate limiting (or partially rate limiting). Many of the modest kinetic isotope effects ($k_H/k_D \sim 1.2 - 2.0$) have been interpreted in terms of comparable rates for formation and deprotonation of the σ -complex intermediate.

The case for the cyclohexadienylium ion intermediates is further strengthened by numerous studies showing that such cations can exist as stable entities under suitable conditions. Substituted cyclohexadienylium ions can be observed by NMR under stable ion conditions. They are formed by protonation of the aromatic reactant.¹⁰



Ref. 11

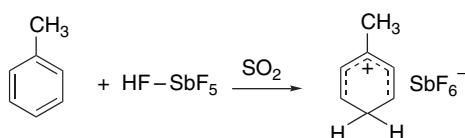
⁷. L. Melander, *Acta Chem. Scand.*, **3**, 95 (1949); *Arkiv Kemi.*, **2**, 211 (1950).

⁸. T. G. Bonner, F. Bower, and G. Williams, *J. Chem. Soc.*, 2650 (1953).

⁹. H. Zollinger, *Adv. Phys. Org. Chem.*, **2**, 163 (1964).

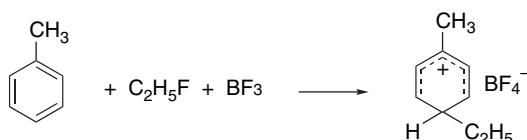
¹⁰. G. A. Olah, R. H. Schlosberg, R. D. Porter, Y. K. Mo, D. P. Kelly, and G. Mateescu, *J. Am. Chem. Soc.*, **94**, 2034 (1972).

¹¹. G. A. Olah and T. E. Kiovsky, *J. Am. Chem. Soc.*, **89**, 5692 (1967).



Ref. 12

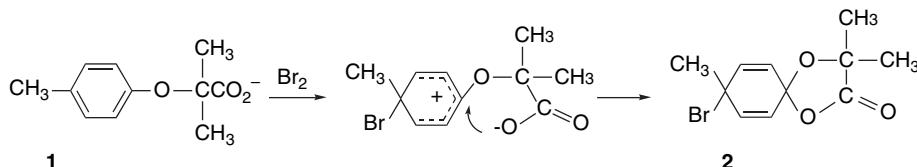
Cations formed by alkylation of benzene derivatives have also been characterized.



Ref. 13

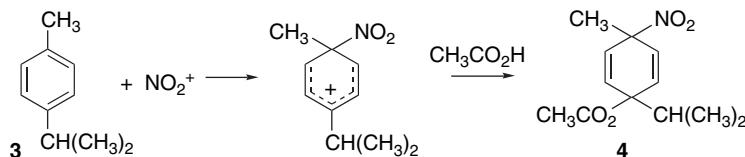
Under normal conditions of electrophilic substitution, these cyclohexadienyl cations are short-lived intermediates. The fact that the structures are stable in nonnucleophilic media clearly demonstrates the feasibility of such intermediates.

The existence of σ -complex intermediates can be inferred from experiments in which they are trapped by nucleophiles in special circumstances. For example, treatment of the acid **1** with bromine gives the cyclohexadienyl lactone **2**. This product results from intramolecular nucleophilic capture of the σ complex by the carboxylate group.



Ref. 14

A number of examples of intramolecular nucleophilic capture of cyclohexadienyl intermediates have also been uncovered in the study of nitration of alkylated benzenes in acetic acid. For example, nitration of **3** at 0°C leads to formation of **4** with acetate serving as the nucleophile.¹⁵



This type of addition process is particularly likely to be observed when the electrophile attacks a position that is already substituted, since facile rearomatization by deprotonation is then blocked. Attack at a substituted position is called *ipso* attack. Addition

^{12.} G. A. Olah, *J. Am. Chem. Soc.*, **87**, 1103 (1965).

^{13.} G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **80**, 6541 (1958).

^{14.} E. J. Corey, S. Barcza, and G. Klotmann, *J. Am. Chem. Soc.*, **91**, 4782 (1969).

^{15.} R. C. Hahn and D. L. Strack, *J. Am. Chem. Soc.*, **96**, 4335 (1974).

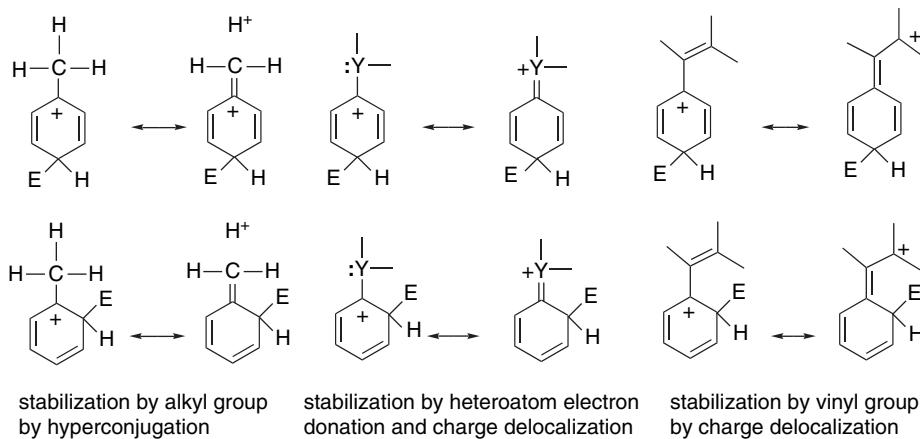
products have also been isolated when initial electrophilic attack has occurred at an unsubstituted position. The extent of addition in competition with substitution increases on going to naphthalene and the larger polycyclic aromatic ring systems.¹⁶

The general mechanistic framework outlined in this section can be elaborated by other details to more fully describe the mechanisms of the individual electrophilic substitutions. The question of the identity of the active electrophile in each reaction is important. We have discussed the case of nitration in which, under many circumstances, the electrophile is the nitronium ion. Similar questions about the structure of the active electrophile arise in most of the other substitution processes. Another issue that is important is the ability of the electrophile to select among the alternative positions on a substituted aromatic ring (*position selectivity*). The relative reactivity and selectivity of substituted benzenes toward various electrophiles is important in developing a firm understanding of EAS. The next section considers some of the structure-reactivity relationships that have proven to be informative.

9.2. Structure-Reactivity Relationships for Substituted Benzenes

9.2.1. Substituent Effects on Reactivity

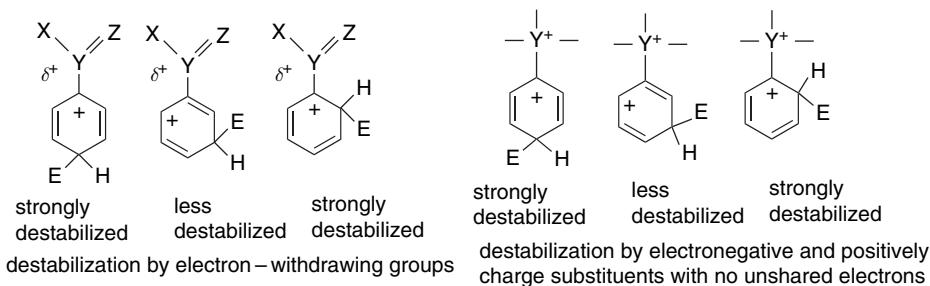
The effect that existing substituents have on EAS reactions has been studied since about 1870. The classification of substituents as *activating* and *ortho-para* directing or *deactivating* and *meta* directing became clear from these early studies. An understanding of the origin of these substituent effects became possible when ideas about electronic interactions and resonance theory were developed. Activating, *ortho-para*-directing substituents are those that can serve as electron donors and stabilize the TS leading to σ -complex formation. Saturated and unsaturated hydrocarbon groups and substituents having an unshared electron pair on the atom adjacent to the ring fall into this group. The stabilizing effects of these types of substituents can be expressed in terms of resonance and hyperconjugation. Direct resonance stabilization is only possible when the substituent is *ortho* or *para* to the incoming electrophile. As a result the TSs for *ortho* and *para* substitution are favored over that for *meta* substitution.



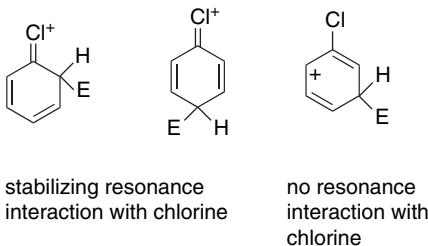
¹⁶. P. B. de la Mare, *Acc. Chem. Res.*, **7**, 361 (1974).

As the substituent groups have a direct resonance interaction with the charge that develops in the σ complex, quantitative substituent effects exhibit a high-resonance component. Hammett equations usually correlate best with the σ^+ -substituent constants (see Section 3.5).¹⁷

EWGs retard electrophilic substitution. The classification of specific substituents given in Scheme 3.1 (p. 299) indicates the ones that are electron attracting. Substituents in this group include those in which a carbonyl group is directly attached to the ring and substituents containing electronegative elements that do not have an unshared pair on an atom adjacent to the ring. Owing to the greater destabilization at the *ortho* and *para* positions, electrophilic attack occurs primarily at the *meta* position, which is *less deactivated* than the *ortho* and *para* positions.



A few substituents, most notably the halogens, decrease the rate of reaction, but nevertheless direct incoming electrophiles to the *ortho* and *para* positions. This is the result of the opposing influence of polar and resonance effects for these substituents. The halogens are more electronegative than carbon, and the carbon-halogen bond dipole opposes the development of positive charge in the ring. Overall reactivity toward electrophiles is therefore reduced. However, the unshared electron pairs on the halogen can preferentially stabilize the *ortho* and *para* TSs by resonance. As a result the substituents are deactivating but nevertheless *ortho*-*para* directing.

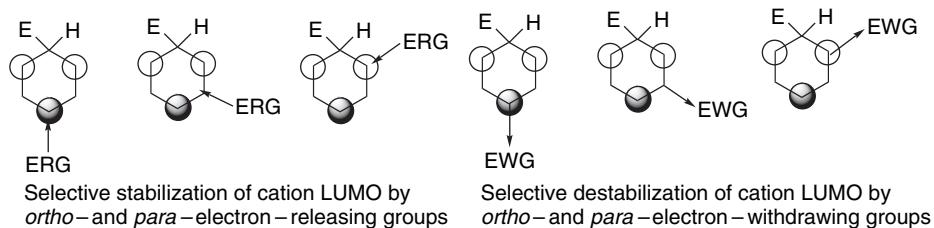


The *o,p*-directing and activating versus *m*-directing and deactivating effect of substituents can also be described in MO terminology. The discussion can focus either on the σ complex or on the aromatic reactant. According to the Hammond postulate, it would be most appropriate to focus on the intermediate in the case of reactions that have relatively high E_a and a late TS. In such cases, the TS should closely resemble the cyclohexadienylum intermediate. For highly reactive electrophiles, where the E_a is low, it may be more appropriate to regard the TS as closely resembling the

¹⁷ H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).

reactant aromatic. Let us examine the MO description of substituent effects from both these perspectives.

The TS resembles the intermediate, a substituted cyclohexadienylium ion. The electrophile has localized one pair of electrons to form the new σ bond. The Hückel orbitals are the same as for the pentadienyl system, as shown in Figure 9.2. A substituent can stabilize the cation by electron donation. The LUMO is ψ_3 . This orbital has its highest coefficients at carbons 1, 3, and 5 of the pentadienyl system, which are the positions that are *ortho* and *para* to the position occupied by the electrophile. EWG substituents at the 2 and 4 (*meta*) positions stabilize the system much less, because of the nodes at these carbons in the LUMO. If we consider a π -acceptor substituent, we see that such a substituent strongly destabilizes the system when it occupies the 1, 3, or 5 position on the pentadienyl cation. The destabilizing effect is less at the 2 or 4 position. The conclusions drawn by this MO interpretation are the same as from resonance arguments. ERG substituents will be *most stabilizing* in the TS leading to *ortho*-*para* substitution. EWG substituents will be *least destabilizing* in the TS leading to *meta* substitution.



The effect of the bond dipole associated with EWG groups can also be expressed in terms of its interaction with the cationic σ complex. The atoms with the highest coefficient of the LUMO ψ_3 are the most positive. The unfavorable interaction of the bond dipole will therefore be greatest at these positions. This effect operates with substituents such as carbonyl, cyano, and nitro. With alkoxy and amino substituents, the unfavorable dipole interaction is outweighed by the stabilizing delocalization effect of the electron pair donation.

The effect of substituents was probed by MO calculations at the HF/STO-3G level.¹⁸ An isodesmic reaction corresponding to transfer of a proton from a substituted σ complex to an unsubstituted one indicates the stabilizing or destabilizing effect of the substituent. The results are given in Table 9.1.



The calculated energy differences give a good correlation with Hammett σ^+ values. The ρ parameter ($\rho = -17$) is considerably larger than that observed experimentally for proton exchange ($\rho \sim -8$). A physical interpretation of this difference is that the computational results pertain to the gas phase, where substituents are at a maximum because of the absence of any leveling effect owing to solvation. Note that the numerical results parallel the conclusions from qualitative application of resonance

¹⁸ J. M. McKelvey, S. Alexandratos, A. Streitwieser, Jr., J.-L. M. Abboud, and W. J. Hehre, *J. Am. Chem. Soc.*, **98**, 244 (1976).

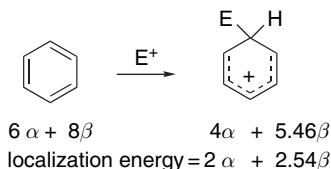
Table 9.1. Energy Changes for Isodesmic Proton-Transfer Reactions of Substituted Benzenes^a

Substituent	ΔE (kcal/mol)	
	<i>meta</i>	<i>para</i>
NO ₂	-17.9	-22.1
CN	-14.0	-13.8
CF ₃	-7.5	-8.4
F	-7.5	3.7
CH ₃	2.0	8.5
OCH ₃		15.7
OH	-5.3	16.0
NH ₂	0.6	27.2

a. From HF/STO-3G calculations reported by J. M. McKelvey, S. Alexandratos, A. Streitwieser, Jr., J.-L. M. Abboud, and W. H. Hehre, *J. Am. Chem. Soc.*, **98**, 244 (1976).

and MO arguments. Strong EWGs are more destabilizing at the *ortho* and *para* position than at the *meta* position. Methyl is stabilizing at both positions, but more so at *para*. Methoxy and amino are very stabilizing at the *para* position. Fluoro is slightly stabilizing at the *para* position, but strongly destabilizing at the *meta* position, in agreement with its competing resonance and polar effects.

Both HMO calculations and more elaborate MO methods can be applied to the issue of the position selectivity in EAS. The most direct approach is to calculate the *localization energy*, which is the energy difference between the aromatic molecule and the cyclohexadienylum intermediate. In simple HMO calculations, the localization energy is just the difference between the energy calculated for the initial π system and that remaining after two electrons and the carbon atom at the site of substitution are removed from the conjugated system.



Comparison of localization energies has been applied to prediction of the relative positional reactivity in polycyclic aromatic hydrocarbons. Simple HMO calculations are only marginally success; CNDO/2 and SCF calculations give results that show good correlation with experimental data on the rate of proton exchange.¹⁹

Now let us turn to the case of a highly reactive electrophile, where we expect an early TS. In this case the charge density distribution and coefficients of the HOMO characteristic of the aromatic reactant are expected to be major factors governing the orientation of electrophilic attack. The TS should resemble the reactants and, according to frontier orbital theory, the electrophile will attack the position with the largest coefficient of the HOMO. The case of methoxybenzene (anisole) can be taken as an example of a reactive molecule. MO calculations place the lone-pair oxygen orbital lower in energy than the ψ_2 and ψ_3 orbitals, leading to the MO diagram in Figure 9.3.

¹⁹ A. Streitwieser, Jr., P. C. Mowery, R. G. Jesaitis, and A. Lewis, *J. Am. Chem. Soc.*, **92**, 6529 (1970).

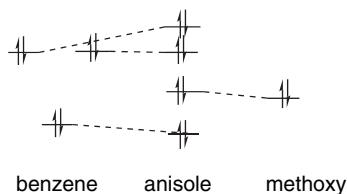


Fig. 9.3. MO diagram for anisole (methoxybenzene) showing effects of methoxy substituent.

The degeneracy of the two highest-lying occupied π orbitals is broken because the methoxy group interacts preferentially with one of them. The other has a node at the site of methoxy substitution.

Figure 9.4 gives the coefficients for the two highest-occupied π orbitals, as calculated by the CNDO method. We see that the HOMO has its highest coefficients at the *ipso*, *ortho*, and *para* positions. As indicated in Figure 9.3, the energy of this orbital is raised by its interaction with the electron donor substituent. Figure 9.5 shows the distribution of π electrons from all the orbitals, based on HF/STO-3G calculations.²⁰ The ERG substituents show increased electron density at the *ortho* and *para* positions. Both the HOMO coefficients and the total charge distribution predict preferential attack by the electrophile *ortho* and *para* to donor substituents.

Figures 9.4 and 9.5 also show some examples of EWG substituents, which, as expected, lower the energies of the π orbitals, but the HOMO distribution remains highest at the *para* position. The total charge distribution shows greater depletion at the *ortho* and *para* position than at the *meta* position. The lower energy of the HOMO is consistent with decreased reactivity for rings with an EWG substituent. However, if frontier orbital theory is used, the distribution of the HOMO in Figure 9.4

HOMO	0.20 0.52 0.31 0.53 0.24 0.53	0.56 0.38 0.58 0.47 0.31 0.18	0.46 0.27 0.53 0.45 0.28 0.20	0.51 0.26 0.23 0.50 0.26 0.28
energy	-0.48	-0.46	-0.50	-0.57
NHOMO	0.0 0.50 0.50 0.0 0.50 0.0	0.0 0.50 0.50 0.0 0.50 0.0	0.0 0.50 0.50 0.0 0.50 0.0	0.0 0.50 0.50 0.0 0.50 0.0
energy	-0.51	-0.52	-0.54	-0.60

Fig. 9.4. Orbital coefficients for HOMO and next highest π MO for some substituted benzenes (from CNDO/2 calculations). The individual *ortho* and *meta* coefficients have been averaged in the case of the unsymmetrical methoxy and formyl substituents. Orbital energies are in atomic units.

²⁰ W. J. Hehre, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.*, **94**, 1496 (1972).

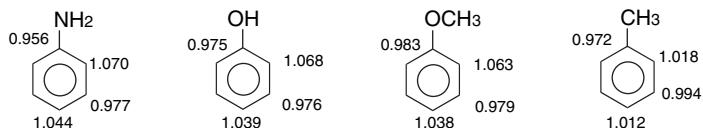
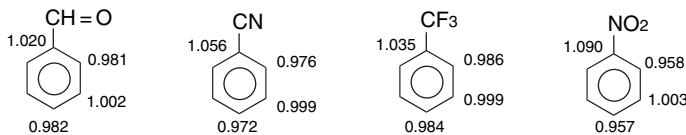
Electron-releasing substituents*Electron-attracting substituents*

Fig. 9.5. Total π -electron density for some substituted benzenes. From HF/STO-3G calculations.

erroneously predicts *para* substitution.. Aromatic rings with EWG substituents are relatively unreactive and therefore will not have early TSs. For such compounds, considerations of the stability of the cyclohexadienylum intermediate, which correctly predict *meta* substitution, are more appropriate.

Prediction of reactivity toward EAS on the basis of MO computations can be improved by considering hybrid MOs rather than the conventional aromatic MOs. Orbitals called *reactive hybrid orbitals* can be defined to combine the contributions of all MOs to the reactivity at each site. The properties of these orbitals can be computed on the basis of the extent of electron transfer to a proton located 1.5 Å above each ring position.²¹ The properties of these orbitals correlate well not only with the position selectivity of the substituents, but also with relative reactivity. Figure 9.6 shows a correlation between the energy of interaction and the partial rate factors (a measure of relative reactivity; see p. 786–787) for several reactions.

Substituents that are not directly bound to the aromatic ring also influence the course of EAS. Several alkyl groups bearing EWG substituents are *meta* directing and deactivating. Some examples are given in Table 9.2. In these molecules, stabilization of the *ortho* and *para* σ complex by electron release from the alkyl group is opposed by the polar effect of the electronegative substituent. Both the reduced electron density at the alkyl substituent and the bond dipoles in the substituent reduce electron donation by the methylene group. From the examples in Table 9.2 we see that $\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$, CHCl_2 , and CH_2CCl_3 remain *o-p* directing, but with reduced selectivity. The stronger EWGs, CH_2NO_2 , CCl_3 , and $\text{CH}_2\text{N}^+(\text{CH}_3)_3$, lead to predominantly *meta* substitution.

The relationships between substituents and the typical electrophilic substitution reactions, such as those listed in Scheme 9.1, can be summarized as follows:

1. The hydroxy and amino groups are highly activating *ortho-para* directing. Such compounds are attacked by all the electrophilic reagents tabulated in Scheme 9.1 (p. 772). With some electrophilic reagents, all available *ortho* and *para* positions are rapidly substituted.
2. The alkyl, amido, and alkoxy groups are activating and *ortho-para* directing, but not as strongly so as hydroxy or amino groups. Synthetically useful conditions for selective substitution are available for essentially all the electrophiles in Scheme 9.1 except for very weak electrophiles such as NO^+ or PhN_2^+ .

²¹. H. Hirao and T. Ohwada, *J. Phys. Chem. A*, **107**, 2875 (2003).

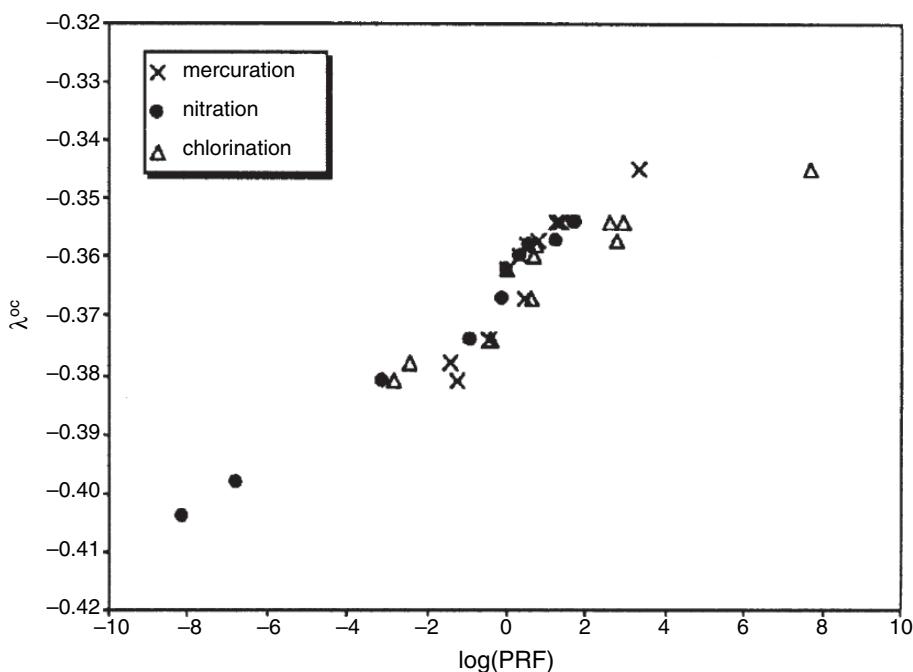


Fig. 9.6. Correlation between the interaction energy $\lambda^{\circ c}$ and the log of partial rate factors for mercuration, nitration, and chlorination. Reproduced from *J. Phys. Chem. A*, **107**, 2875 (2003), by permission of the American Chemical Society.

3. The halobenzenes, are unusual substituents, being deactivating but *ortho*-*para* directing. In general, halogenated aromatics react successfully with electrophiles listed in categories A and B.
4. The carbonyl group in aldehydes, ketones, acids, esters, and carboxamides is deactivating and *meta* directing. There are limitations on the type of substitution reactions that are satisfactory for these deactivating substituents. In general, only those electrophiles in category A in Scheme 9.1 react readily.
5. The cyano, nitro, and quaternary ammonium groups are strongly deactivating and *meta* directing. Electrophilic substitutions of compounds with these substituents require vigorous conditions, and fail completely with the less reactive electrophiles.

Nitration has been studied over a wide variety of aromatic compounds, which makes it a useful reaction for illustrating the directing effect of substituent groups. Table 9.3 presents some of the data. A range of reaction conditions is represented, so direct comparison is not always valid, but the trends are nevertheless clear. It is important to remember that other electrophiles, while following the same qualitative trends, show large quantitative differences in position selectivity.

The groups in the top half of the table are *meta* directing. Note that the carbonyl and cyano groups give rise to relatively high ratios of *ortho* product. This may be due to intramolecular process in which the nitronium ion initially bonds at the functional group.²² The halogens show *o,p*-directing effects with fluorine being much less favorable to *ortho* substitution, because of the stronger C–F dipole, which results

²² G. S. Hammond, F. J. Modic, and R. M. Hedges, *J. Am. Chem. Soc.*, **75**, 1388 (1953); P. Kovacic and J. J. Hillier, Jr., *J. Org. Chem.*, **30**, 2871 (1985).

Table 9.2. Percent *meta* Nitration for Some Alkyl Groups with Electron-Withdrawing Substituents^a

<chem>c1ccccc1C(C(=O)OC2CC2)C</chem>	<chem>c1ccccc1CClCl</chem>	<chem>c1ccccc1CClCCl</chem>	<chem>c1ccccc1CC(=O)N=O</chem>	<chem>c1ccccc1CClC(F)(F)</chem>	<chem>c1ccccc1CC[N+]((CH3)3)C</chem>
11%	34%	37%	55 %	64%	85 %

a. From C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, 2nd Edition, Cornell University Press, Ithaca, 1969, pp. 275, 281; F. De Sarlo, A. Ricci, and J. H. Ridd, *J. Chem. Soc. B*, 719 (1971).

in both electrostatic and polarization effects that destabilize the *ortho* TS.²³ The trichloromethyl and trifluoromethyl groups are *meta* directing. Similarly to some of the groups in Scheme 9.2, the CH₂CN and CH₂NO₂ groups are also *meta* directing. The alkyl and methoxy groups are strongly *o-p* directing.

The effect of substituents on electrophilic substitution can be placed on a quantitative basis by use of *partial rate factors*. The reactivity of each position in a substituted aromatic compound can be compared with benzene by measuring the overall

Table 9.3. Isomer Proportions in the Nitration of Some Substituted Benzenes^a

Substituent	Product (%)		
	<i>ortho</i>	<i>meta</i>	<i>para</i>
N ⁺ H ₃	3–5	35–50	50–60
N ⁺ (CH ₃) ₃	0	89	11
CH ₂ N ⁺ (CH ₃) ₃	0	85	15
S ⁺ (CH ₃) ₂	4	90	6
NO ₂	5–8	91–93	0–2
CO ₂ H	15–20	75–85	~1
CN	15–17	81–83	~2
CO ₂ C ₂ H ₅	24–28	66–73	1–6
COCH ₃	26	72	0–2
F	9–13	0–1	86–91
Cl	30–35	~1	64–70
Br	36–43	1	56–62
I	38–45	1–2	54–60
CCl ₃	7	64	29
CF ₃	6	91	3
CH ₂ CN	24	20	56
CH ₂ NO ₂	22	55	23
CH ₂ OCH ₃	51	7	42
CH ₃	56–63	2–4	34–41
CH ₂ CH ₃	46–59	2–4	46–51
OCH ₃	30–40	0–2	60–70

a. Data are from Tables 9.1, 9.2, 9.3, 9.4, 9.5, and 9.6 in J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, 1971.

²³ P. Laszlo and P. Pennetreau, *J. Org. Chem.*, **52**, 2407 (1987); J. Rosenthal and D. I. Schuster, *J. Chem. Educ.*, **80**, 679 (2003).

rate relative to benzene and dividing the total rate among the *ortho*, *meta*, and *para* products. Correction for the statistical factor arising from the relative number of available positions permits the partial rate factors to provide comparisons at positions on a substituted ring with a single position on benzene.

$$\text{Partial rate factor} = f = \frac{6(k_{\text{subs}})(\text{Fraction of product})}{y(k_{\text{benz}})} \quad (9.1)$$

where y is the number of equivalent positions. A partial rate factor calculation for nitration of toluene is given in Example 9.1.

Example 9.1. The nitration of toluene is 23 times as fast as for benzene in nitric acid–acetic anhydride. The product ratio is 63% *ortho*, 34% *para*, and 3% *meta*. Calculate the partial rate factor at each position.

$$f_o = \frac{6}{2} \times \frac{23}{1} \times 0.63 = 43.5$$

$$f_m = \frac{6}{2} \times \frac{23}{1} \times 0.03 = 2.1$$

$$f_p = \frac{6}{1} \times \frac{23}{1} \times 0.34 = 46.9$$

Partial rate factors give insight into two related aspects of reactivity and reveal the selectivity of a given electrophile for different *reactants*. Some electrophiles exhibit high *reactant selectivity*; that is, there are large differences in the rate of reaction depending on the identity of the ring substituent. In general, low reactant selectivity is correlated with high electrophile reactivity and vice versa. Clearly, when reactant selectivity is high, the partial rate factors for the substituted aromatic compound will be very different from unity. The partial rate factors also reveal *positional selectivity* within the substituted aromatic, which also varies for different electrophiles and provides some insight into the mechanism. In general, there is a correlation between position and reactant selectivity. High reactant selectivity is accompanied by high position selectivity. Electrophiles that show high reactant selectivity generally exhibit low *ortho:para* ratios and negligible amounts of *meta* substitution. Very reactive electrophiles tend to show low position and reactant selectivity. Table 9.4 gives some data on the selectivity of some EAS reactions. The most informative data in terms of reactant is f_p , since the partial rate factors for *ortho* substitution contain variable steric components. With f_p as the criterion, halogenation and Friedel-Crafts acylation exhibit high selectivity, protonation and nitration are intermediate, and Friedel-Crafts alkylation shows low selectivity.

9.2.2. Mechanistic Interpretation of the Relationship between Reactivity and Selectivity

Reactivity and selectivity are largely determined by the position of the TS on the reaction coordinate. With highly reactive electrophiles, the TS will come early on the reaction coordinate as in Figure 9.7a. The TS then resembles the reactants more closely than the intermediate. The positive charge on the ring is small, and, as a result, the interaction with the substituent group is relatively weak. However, the substituent also effects electron distribution in the reactant, which can cause position selectivity.

Table 9.4. Selectivity in Some Electrophilic Aromatic Substitution Reactions^a

Reaction	Partial rate factors for toluene		
	f_o	f_m	f_p
Nitration			
HNO ₃ (CH ₃ NO ₂)	38.9	1.3	45.7
Halogenation			
Cl ₂ (CH ₃ CO ₂ H)	617	5	820
Br ₂ (CH ₃ CO ₂ H, H ₂ O)	600	5.5	2420
Protonation			
H ₂ SO ₄ -H ₂ O	83	1.9	83
H ₂ SO ₄ , CF ₃ CO ₂ H, H ₂ O	350	7.2	313
Acylation			
PhCOCl (AlCl ₃ , PhNO ₂)	32.6	5.0	831
CH ₃ COCl (AlCl ₃ , ClCH ₂ CH ₂ Cl)	4.5	4.8	749
Alkylation			
CH ₃ Br (GaBr ₃)	9.5	1.7	11.8
(CH ₃) ₂ CHBr (GaBr ₃)	1.5	1.4	5.0
PhCH ₂ Cl (AlCl ₃)	4.2	0.4	10.0

a. From L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, **1**, 35 (1963).

With a less reactive electrophile, the TS is reached later, as in Figure 9.7b. The bond to the electrophile is more completely formed and a substantial positive charge is present on the ring. This situation results in stronger substituent effects. These arguments follow the general lines of Hammond's postulate (Section 3.3.2.2). MO calculations at the HF/STO-3G level reproduce these qualitative expectations by revealing greater stabilization of the *ortho* and *para* positions in toluene with a closer approach of an electrophile.²⁴

Hammett correlations also permit some insight into the reactivity and selectivity of electrophiles in EAS reactions. In general, the standard Hammett σ substituent constants lead to poor correlations with EAS reactions. The σ^+ values, which reflect an increased importance of direct resonance interaction (see Section 3.6) give better correlations and, indeed, were developed as a result of the poor correlations observed with σ in EAS. It has been suggested that the position of a TS on the reaction coordinate can be judged from the slope, ρ , of the correlation line between the rate of substitution and σ^+ .²⁵ The rationale is the following: A numerically large value for ρ suggests a strong substituent effect, that is, a late TS that resembles the intermediate. A small value indicates a weak substituent effect and implies an early TS. Table 9.5 gives some of the ρ values for typical EAS reactions. The data indicate that the halogenation reactions show the characteristics of a highly selective electrophile, nitration and Friedel-Crafts acylation represent reactions of intermediate selectivity, and Friedel-Crafts alkylation is an example of low selectivity. This is in general agreement with the selectivity trend as measured by f_p , indicated in Table 9.4.

Isotope effects provide insight into other aspects of the mechanisms of individual electrophilic aromatic substitution reactions. In particular, since primary isotope effects are expected only when the deprotonation of the σ complex to product is rate determining, the observation of a substantial k_H/k_D points to a rate-determining

²⁴ C. Santiago, K. N. Houk, and C. L. Perrin, *J. Am. Chem. Soc.*, **101**, 1337 (1979).

²⁵ P. Rys, P. Skrabal, and H. Zollinger, *Angew. Chem. Int. Ed. Engl.*, **11**, 874 (1972).

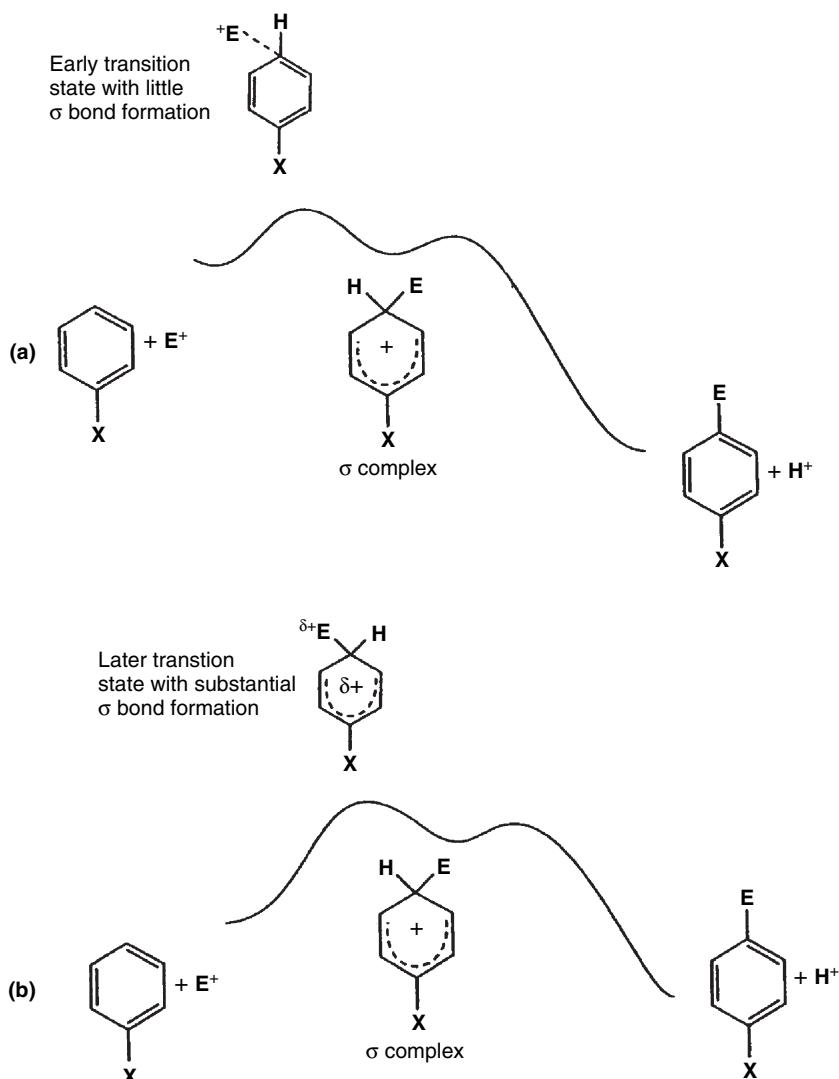


Fig. 9.7. Relation between transition state character and reaction energy profiles for highly reactive (a) and less reactive (b) electrophiles.

deprotonation. Some typical isotope effects are summarized in Table 9.6. Although isotope effects are seldom observed for nitration and halogenation, Friedel-Crafts acylation, sulfonation, nitrosation, and diazo coupling provide examples in which the rate of proton loss can affect the rate of substitution. Only in the case of the reactions involving weak electrophiles, namely nitrosation and diazo coupling, are isotope effects in the range expected for a fully rate-controlling deprotonation. Even for weak electrophiles, some factor that retards deprotonation is required for deprotonation to become rate determining. For example, in the two diazotizations cited, the steric hindrance associated with the C(8)-sulfonic acid group leads to the observation of a primary isotope effect, whereas in the unhindered four-isomer there is no isotope effect.

Table 9.5. Values of ρ for some Electrophilic Aromatic Substitution Reactions^a

Reaction	ρ
Bromination ($\text{CH}_3\text{CO}_2\text{H}$)	-13.3
Chlorination (CH_3NO_2)	-13.0
Chlorination ($\text{CH}_3\text{CO}_2\text{H}, \text{H}_2\text{O}$)	-8.8
Protonation ($\text{H}_2\text{SO}_4, \text{CF}_3\text{CO}_2\text{H}, \text{H}_2\text{O}$)	-8.6
Acetylation ($\text{CH}_3\text{COCl}, \text{AlCl}_3, \text{C}_2\text{H}_4\text{Cl}_2$)	-8.6
Nitration ($\text{HNO}_3, \text{H}_2\text{SO}_4$)	-6.4
Chlorination (HOCl, H^+)	-6.1
Alkylation ($\text{C}_2\text{H}_5\text{Br}, \text{GaBr}_3$)	-2.4

a. From P. Rys, P. Skrabal, and H. Zollinger, *Angew. Chem. Int'l. Ed. Engl.*, **11**, 874 (1972).

Figure 9.8 summarizes the general ideas presented in this section. At least four types of energy profiles can exist for individual EAS reactions. Case A is the rate-determining generation of the electrophile and is most readily identified by kinetics. A rate law independent of the concentration of the aromatic is diagnostic of this case. Case B represents rate-determining σ complex formation, with an electrophile of low selectivity. The rate law in such a case should have terms in both the electrophile and the aromatic. Furthermore, low selectivity, as indicated by low ρ values and low partial rate factors, is expected when this energy profile is applicable. Case C is rate-determining σ complex formation with a more selective electrophile having a

Table 9.6. Kinetic Isotope Effects for some Electrophilic Aromatic Substitution Reactions

Reaction and reactants	Reagent	$k_{\text{H}}/k_{\text{D}}$ or $k_{\text{H}}/k_{\text{T}}$
Nitration		
Benzene- <i>t</i> ^a	$\text{HNO}_3\text{-H}_2\text{SO}_4$	<1.2
Toluene- <i>t</i> ^a	$\text{HNO}_3\text{-H}_2\text{SO}_4$	<1.2
Nitrobenzene- <i>d</i> ₅ ^a	$\text{HNO}_3\text{-H}_2\text{SO}_4$	1
Halogenation		
Benzene- <i>d</i> ₆ ^a	$\text{HOBr}, \text{HClO}_4$	1
Methoxybenzene- <i>d</i> ^a	Br_2	1.05
Acylation		
Benzene- <i>d</i> ₆ ^b	$\text{CH}_3\text{CO}^+, \text{SbF}_6^-$, CH_3NO_2	2.25
Benzene- <i>d</i> ₆ ^b	$\text{PhCO}^+, \text{SbF}_6^-, \text{CH}_3\text{NO}_2$	1.58
Sulfonation		
Benzene- <i>d</i> ₆ ^c	$\text{ClSO}_3\text{H}, \text{CH}_3\text{NO}_2$	1.7
Benzene- <i>d</i> ₆ ^c	$\text{ClSO}_3\text{H}, \text{CH}_2\text{Cl}_2$	1.6
Nitrobenzene- <i>d</i> ₅ ^a	$\text{H}_2\text{SO}_4, \text{SO}_3$	1.6–1.7
Nitrosation		
Benzene- <i>d</i> ₆ ^d	$\text{HNO}_2, \text{D}_2\text{SO}_4$	8.5
Diazo coupling		
1-Naphthol-4-sulfonic acid ^a	PhN_2^+	1.0
2-Naphthol-8-sulfonic acid ^a	PhN_2^+	6.2

a. From a more extensive compilation by H. Zollinger, *Adv. Phys. Org. Chem.*, **2**, 163 (1964).

b. G. A. Olah, J. Lukas, and E. Lukas, *J. Am. Chem. Soc.*, **91**, 5319 (1969).

c. M. P. van Albada, and H. Cerfontain, *Rec. Trav. Chim.*, **91**, 499 (1972).

d. B. C. Challis, R. J. Higgins, and A. J. Lawson, *J. Chem. Soc., Perkin Trans. 2*, 1831 (1972).

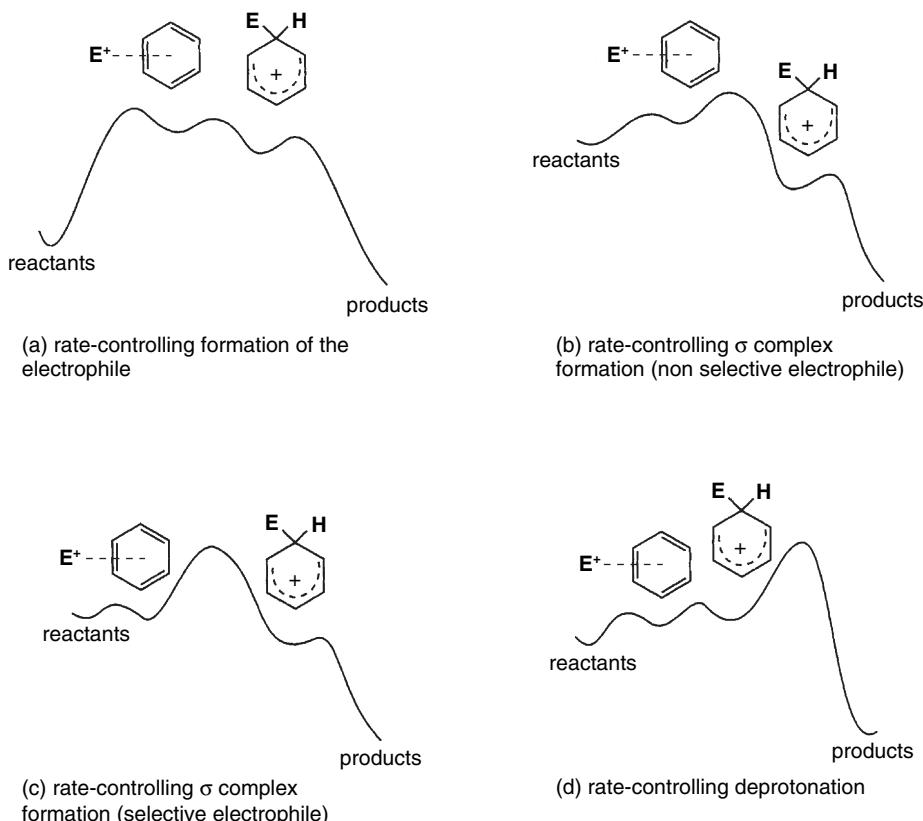
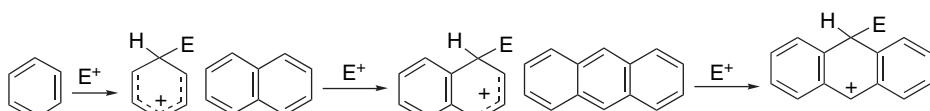


Fig. 9.8. Reaction energy profiles for electrophilic aromatic substitution showing variation in rate-determining step and electrophile selectivity.

later TS. Finally, there is case D, in which the proton removal and rearomatization are rate limiting. This case can be recognized by the observation of a primary kinetic isotope effect at the site of substitution.

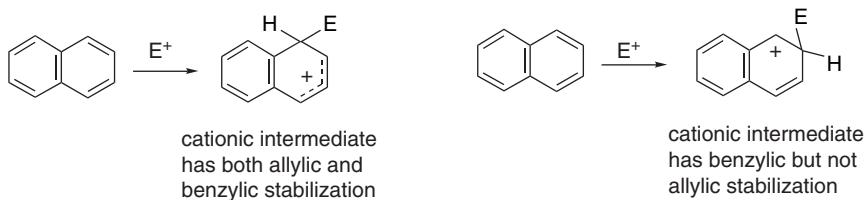
9.3. Reactivity of Polycyclic and Heteroaromatic Compounds

The polycyclic aromatic hydrocarbons such as naphthalene, anthracene, and phenanthrene undergo the various types of EAS and are generally more reactive than benzene. One reason for this is that the localization energy for formation of the cationic intermediate is lower than for benzene because more of the initial resonance stabilization is retained in intermediates that have a fused benzene ring. CNDO calculations provide estimates of the localization energies. For benzene, naphthalene, and anthracene, these are, respectively, 36.3, 15.4, and 8.3 kcal/mol.²⁶



²⁶. A. Streitwieser, Jr., P. C. Mowery, R. G. Jesaitis, and A. Lewis, *J. Am. Chem. Soc.*, **92**, 6529 (1970).

The relative stability of the TSs determines the position of substitution under kinetically controlled conditions. For naphthalene, the preferred site for electrophilic attack is the 1-position, which is the result of the greater stability of the cationic intermediate for 1-substitution.



The more rapid substitution at C(1) of naphthalene can be demonstrated by following the incorporation of deuterium under acidic conditions. Figure 9.9 shows that the $^1\text{H}(\text{C}1)$ signal disappears more rapidly than the $^1\text{H}(\text{C}2)$ signal. As reaction continues to equilibrium, the extent of deuteration becomes the same at both positions (about 80% in this example), because there is no difference in the thermodynamic stability of the two deuterated products.²⁷

Two factors can result in substitution at the 2-position. If the electrophile is very bulky, the hydrogen on the adjacent ring may cause a steric preference for attack at C(2). Under conditions of reversible substitution, where relative thermodynamic stability is the controlling factor, 2-substitution is frequently preferred. An example of this behavior is in sulfonation, where low-temperature reaction gives the 1-isomer, but at elevated temperatures the 2-isomer is formed.²⁸

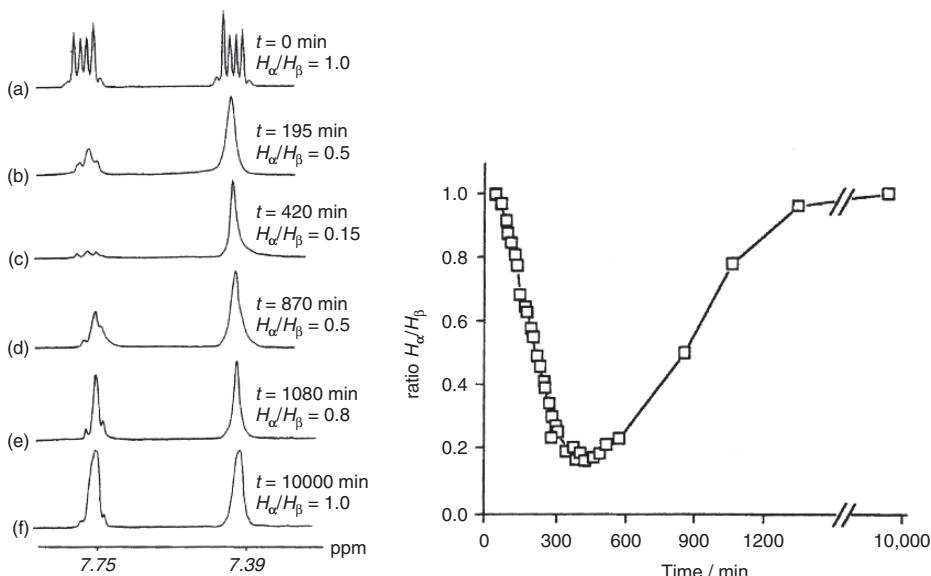
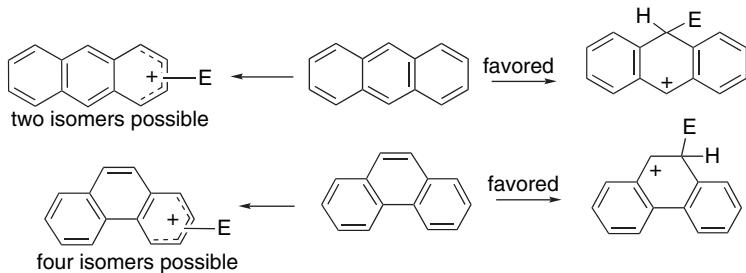


Fig. 9.9. Changes in ^1H -NMR spectrum of naphthalene heated with $\text{CF}_3\text{CO}_2\text{D}$ in the presence of $(\text{CF}_3\text{CO})_2\text{O}$ and $\text{Al}(\text{O}_2\text{CCF}_3)_3$ (left). Ratio of ^1H level at C(1)/C(2) (right). Reproduced from *J. Chem. Educ.*, **76**, 1246 (1999), by permission of the journal.

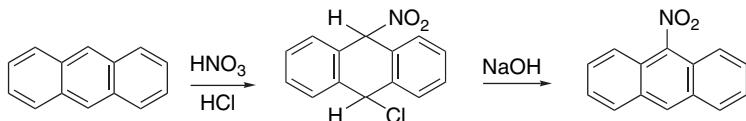
²⁷ L. D. Field, S. Sternhell, and H. V. Wilton, *J. Chem. Educ.*, **76**, 1246 (1999).

²⁸ H. Cernfontain, *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Interscience, New York, 1968, pp. 68–69.

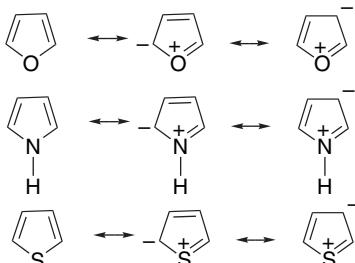
Phenanthrene and anthracene both react preferentially in the center ring. This behavior is consistent with resonance considerations. The σ complexes that result from substitution in the center ring have two intact benzene rings. The total resonance stabilization of these intermediates is larger than that of a naphthalene system that results if substitution occurs at one of the terminal rings.²⁹



Both phenanthrene and anthracene have a tendency to undergo addition reactions under the conditions involved in certain electrophilic substitutions.³⁰ For example, an addition product can be isolated in the nitration of anthracene in the presence of hydrochloric acid.³¹ This is a result of the relatively close balance in resonance stabilization to be regained by elimination (giving an anthracene ring) or addition (resulting in two benzene rings).



The heteroaromatic compounds can be divided into two broad groups, called π excessive and π deficient, depending on whether the heteroatom acts as an electron donor or electron acceptor. Furan, pyrrole, and thiophene, as well as other heterocyclics incorporating an oxygen, nitrogen, or sulfur atom that contributes two π electrons are in the π -excessive group. This classification is indicated by resonance structures and has been confirmed by various MO methods.³²



²⁹. D. Z. Wang and A. Streitwieser, *Theor. Chim. Acta*, **102**, 78 (1999).

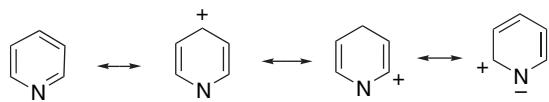
³⁰. P. B. D. de la Mare and J. H. Ridd, *Aromatic Substitution*, Academic Press, New York, 1959, p. 174.

³¹. C. E. Braun, C. D. Cook, C. Merritt, Jr., and J. E. Rousseau, *Org. Synth.*, **IV**, 711 (1965).

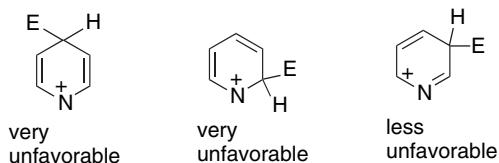
³². N. D. Epotis, W. P. Cherry, F. Bernardi, and W. J. Hehre, *J. Am. Chem. Soc.*, **98**, 4361 (1976); W. Adam and A. Grimison, *Theor. Chem. Acta*, **7**, 342 (1967); D. W. Genson and R. E. Christoffersen, *J. Am. Chem. Soc.*, **94**, 6904 (1972); N. Bodor, M. J. S. Dewar, and A. J. Harget, *J. Am. Chem. Soc.*, **92**, 2929 (1970).

The reactivity order is pyrrole > furan > thiophene, which indicates the order N > O > S in electron-donating capacity.³³ The N > O order is as expected on the basis of electronegativity, and O > S probably reflects the better overlap of the oxygen 2p orbital with the carbon 2p orbitals of the ring.

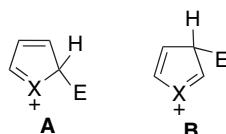
Structures such as pyridine that incorporate the $-\text{N}=\text{CH}-$ unit are called π deficient and are deactivated to electrophilic attack. Again a resonance interpretation is evident. The nitrogen, being more electronegative than carbon, is a net acceptor of π -electron density, especially at C(2) and C(4).



There is another important factor in the low reactivity of pyridine derivatives toward EAS. The $-\text{N}=\text{CH}-$ unit is basic because the electron pair on nitrogen is not part of the aromatic π system. The nitrogen is protonated or complexed with a Lewis acid under many of the conditions typical of EAS reactions. The formal positive charge present at nitrogen in such species further reduces the reactivity toward electrophiles. For pyridine, the reactivity toward electrophilic substitution is 3 > 4, 2. The ring nitrogen acts as a strongly destabilizing “internal” electron-withdrawing substituent in the 2- and 4- intermediates. The nitrogen also deactivates the 3-position, but less so than the 2- and 4-positions. These unfavorable effects are enhanced if the nitrogen is protonated or complexed with a Lewis acid.

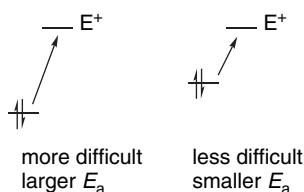


The position selectivity for electrophilic substitution in the five-membered heteroaromatic rings is usually 2 > 3, which reflects the more favorable conjugation in intermediate **A** than in intermediate **B**. In structure **A** the remaining C=C bond can delocalize the positive charge more effectively than in **B**, but substituents on the ring can override this directive influence.



Reactivity and orientation in EAS can also be related to the concept of hardness (see Section 8.1.3). Ionization potential is a major factor in determining hardness and is also intimately related to EAS. In MO terms, hardness is related to the gap between

³³ S. Clementi, F. Genel, and G. Marino, *Chem. Commun.*, 498 (1967).



This idea can be quantitatively expressed by defining *activation hardness* as the difference in the LUMO-HOMO gap for the reactant and the cationic intermediate³⁵:

$$\Delta\eta^* = \beta[(\chi_{\text{LUMO}}^{\text{R}} - \chi_{\text{HOMO}}^{\text{R}}) - (\chi_{\text{LUMO}}^{\sigma} - \chi_{\text{HOMO}}^{\sigma})]/2$$

where χ^{R} and χ^{σ} are the orbitals of the reactant and cationic intermediate.

Simple HMO theory has been used to calculate $\Delta\eta^*$ for several benzenoid hydrocarbons, substituted benzenes, and heterocycles. The resulting values are in qualitative agreement with reactivity trends. Scheme 9.3 gives some of the data. The less positive the number, the more reactive the position. Although there are some discrepancies between structural groups, within groups the $\Delta\eta^*$ values correlate well with position selectivity. The most glaring discrepancy is the smaller activation hardness for deactivated compared with activated benzenes. In particular, benzaldehyde and benzoic acid have $\Delta\eta^*$ values that are lower than that of benzene, which is counter to their relative reactivity. However, the preference for *meta* substitution of the deactivated benzenes is predicted correctly. The deactivation of pyridine, relative to benzene, is also not indicated by the $\Delta\eta^*$ value.

Scheme 9.3. Activation Hardness for Aromatic and Heteroaromatic Compounds^a

Hydrocarbons		Heteroaromatics	
	0.50		0.118
	0.255		-0.86 0.090
			0.139
Activated substituted benzenes		Deactivated substituted benzenes	
	0.492		0.411
	0.462		0.310
	0.486		0.279
	0.363		0.440
	0.391		0.203
	0.307		0.147
	0.435		0.322
	0.492		0.222
			0.325
			0.276
			0.269
			0.139

a. Z. Zhou and R. G. Parr, *J. Am. Chem. Soc.*, **112**, 5720 (1990).

³⁴. R. G. Pearson, *Proc. Natl. Acad. Sci. USA*, **83**, 8440 (1986).

³⁵. Z. Zhou and R. G. Parr, *J. Am. Chem. Soc.*, **112**, 5720 (1990).

9.4. Specific Electrophilic Substitution Reactions

At this point, we focus on specific electrophilic substitution reactions. The kinds of data that have been especially pertinent in elucidating mechanistic detail include linear free-energy relationships, kinetic studies, isotope effects, and selectivity patterns. In general, the basic questions to be asked about each mechanism are: (1) What is the active electrophile? (2) Which step in the general mechanism for EAS is rate determining? (3) What are the orientation and selectivity patterns?

9.4.1. Nitration

A substantial body of data including reaction kinetics, isotope effects, and structure-reactivity relationships is available for aromatic nitration.³⁶ As anticipated from the general mechanism for electrophilic substitution, there are three distinct steps. Conditions under which each of the first two steps is rate determining have been recognized. The third step is usually very fast.

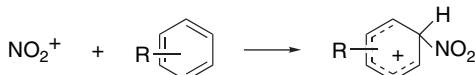
1. Generation of the electrophile



or



2. Attack on the aromatic ring forming the cationic intermediate



3. Deprotonation



The existence of the nitronium ion in sulfuric-nitric acid mixtures can be demonstrated by both cryoscopic measurements and spectroscopy. An increase in the strong acid concentration increases the rate of reaction by shifting the equilibrium of Step 1 to the right. Addition of a nitrate salt has the opposite effect by suppressing the preequilibrium dissociation of nitric acid. It is possible to prepare crystalline salts of nitronium ions such as nitronium tetrafluoroborate. Solutions of these salts in organic solvents nitrate aromatic compounds rapidly.³⁷

There are three general types of kinetic situations that have been observed for aromatic nitration. Aromatics of modest reactivity exhibit second-order kinetics in mixtures of nitric acid with the stronger sulfuric or perchloric acid.³⁸ Under these

- ³⁶. J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, 1971; L. M. Stock, *Prog. Phys. Org. Chem.*, **12**, 21 (1976); G. A. Olah, R. Malhotra, and S. C. Narang, *Nitration*, VCH Publishers, New York, 1989.
- ³⁷. S. J. Kuhn and G. A. Olah, *J. Am. Chem. Soc.*, **83**, 4564 (1961); G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **84**, 3684 (1962); C. M. Adams, C. M. Sharts, and S. A. Shackelford, *Tetrahedron Lett.*, **34**, 6669 (1993); C. L. Dwyer and C. W. Holzapfel, *Tetrahedron*, **54**, 7843 (1998).
- ³⁸. J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, 1971, Chap. 02.

conditions, the formation of the nitronium ion is a fast preequilibrium and Step 2 of the nitration mechanism is rate controlling. If nitration is conducted in inert organic solvents, such as nitromethane or carbon tetrachloride in the absence of a strong acid, the rate of formation of nitronium ion is slower and becomes rate limiting.³⁹ Finally, some very reactive aromatics, including alkylbenzenes, can react so rapidly under conditions where nitronium ion concentration is high that the rate of nitration becomes governed by encounter rates. Under these circumstances mixing and diffusion control the rate of reaction and no differences are observed between the reactants.⁴⁰

With very few exceptions, the final step in the nitration mechanism, the deprotonation of the σ complex, is fast and has no effect on the observed kinetics. The fast deprotonation can be confirmed by the absence of an isotope effect when deuterium or tritium is introduced at the substitution site. Several compounds such as benzene, toluene, bromobenzene, and fluorobenzene were subjected to this test and did not exhibit isotope effects during nitration.⁴¹ The only case where a primary isotope effect has been seen is with 1,3,5-tri-*t*-butylbenzene, where steric hindrance evidently makes deprotonation the slow step.⁴²

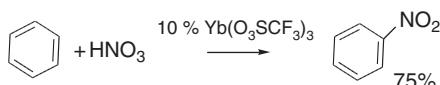
There are several other synthetic methods for aromatic nitration. Nitric acid in acetic anhydride is a potent nitrating agent and effects nitration at higher rates than nitric acid in inert organic solvents. Acetyl nitrate is formed and it is the nitrating agent.



A very convenient synthetic procedure for nitration involves the mixing of a nitrate salt with trifluoroacetic anhydride.⁴³ This generates trifluoroacetyl nitrate, which is even more reactive than acetyl nitrate.



Benzene, toluene, and aromatics of similar reactivity can be nitrated using $\text{Yb}(\text{O}_3\text{SCF}_3)_3$ and 69% nitric acid in an inert solvent.⁴⁴ The catalyst remains active and can be reused. The active nitrating agent under these conditions is uncertain but must be some complex of nitrate with the oxyphilic lanthanide.



³⁹ E. D. Hughes, C. K. Ingold, and R. I. Reed, *J. Chem. Soc.*, 2400 (1950); R. G. Coombes, *J. Chem. Soc. B*, 1256 (1969).

⁴⁰ R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 800 (1968); H. W. Gibbs, L. Main, R. B. Moodie, and K. Schofield, *J. Chem. Soc., Perkin Trans. 2*, 848 (1981).

⁴¹ G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Am. Chem. Soc.*, **83**, 4571, 4581 (1961); H. Suhr and H. Zollinger, *Helv. Chim. Acta*, **44**, 1011 (1961); L. Melander, *Acta Chem. Scand.*, **3**, 95 (1949); *Arkiv Kemi.*, **2**, 211 (1950).

⁴² P. C. Myhre, M. Beug, and L. L. James, *J. Am. Chem. Soc.*, **90**, 2105 (1968).

⁴³ J. V. Crivello, *J. Org. Chem.*, **46**, 3056 (1981).

⁴⁴ F. J. Waller, A. G. M. Barrett, D. C. Braddock, and D. Ramprasad, *Chem. Commun.*, 613 (1997).

The identification of a specific nitrating species can be approached by comparing selectivity with that of nitration under conditions known to involve the nitronium ion. Examination of Part B of Table 9.7 shows that the position selectivity exhibited by acetyl nitrate toward toluene and ethylbenzene is not very different from that observed with nitronium ion. The data for *i*-propylbenzene suggest a lower *ortho:para* ratio for acetyl nitrate nitrations, which could indicate a larger steric factor for nitration by acetyl nitrate.

Relative reactivity data for nitration must be treated with special caution because of the possibility of encounter control. An example of this can be seen in Part A of Table 9.7, where no difference in reactivity between mesitylene and xylene is found in $\text{H}_2\text{SO}_4\text{-HNO}_3\text{-H}_2\text{O}$ nitration, whereas in $\text{HNO}_3\text{-CH}_3\text{NO}_2$ the rates differ by a factor of more than 2. Encounter-control prevails in the former case. In general, nitration is a relatively unselective reaction with toluene f_p being about 50–60, as shown in

Table 9.7. Relative Reactivity and Position Selectivity for Nitration of Some Aromatic Compounds

A. Relative Reactivity of Some Hydrocarbons									
Reactant	$\text{H}_2\text{SO}_4\text{-HNO}_3\text{-H}_2\text{O}^a$			$\text{HNO}_3\text{-CH}_3\text{NO}_2^b$			$\text{HNO}_3\text{-}(\text{CH}_3\text{CO})_2\text{O}^c$		
Benzene	1			1			1		
Toluene	17			25			27		
<i>p</i> -Xylene	38			139			92		
<i>m</i> -Xylene	38			146			—		
<i>o</i> -Xylene	38			139			—		
Mesitylene	36			400			1750		

B. Partial Rate Factors for Some Monoalkylbenzenes									
Reactant	$\text{HNO}_3\text{-H}_2\text{SO}_4$ (sulfolane) ^d			$\text{HNO}_3\text{-CH}_3\text{NO}_2^e,f$			$\text{HNO}_3(\text{CH}_3\text{CO})_2\text{O}^g$		
	f_o	f_m	f_p	f_o	f_m	f_p	f_o	f_m	f_p
Toluene	52.1	2.8	58.1	49	2.5	56	49.7	1.3	60.0
Ethylbenzene	36.2	2.6	66.4	32.7	1.6	67.1	31.4	2.3	69.5
<i>i</i> -Propylbenzene	17.9	1.9	43.3	—	—	—	14.8	2.4	71.6
<i>t</i> -Butylbenzene				5.5	3.7	71.4	4.5	3.0	75.5

C. Relative Reactivity and Isomer Distribution for Nitrobenzene and the Nitrotoluenes ^h										
Product composition (%)										
Reactant	Relative reactivity			<i>ortho</i>			<i>meta</i>			<i>para</i>
Nitrobenzene	1			7			92			1
<i>o</i> -Nitrotoluene	545			29			1			70
<i>m</i> -Nitrotoluene	138			38			1			60
<i>p</i> -Nitrotoluene	217			100			0			—

a. R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 800 (1968).

b. J. G. Hoggett, R. B. Moodie, and K. Scholfield, *J. Chem. Soc. B*, 1 (1969).

c. A. R. Cooksey, K. J. Morgan, and D. P. Morrey, *Tetrahedron*, **26**, 5101 (1970).

d. G. A. Olah, S. J. Kuhn, S. H. Flood, and J. C. Evans, *J. Am. Chem. Soc.*, **84**, 3687 (1962).

e. L. M. Stock, *J. Org. Chem.*, **26**, 4120 (1961).

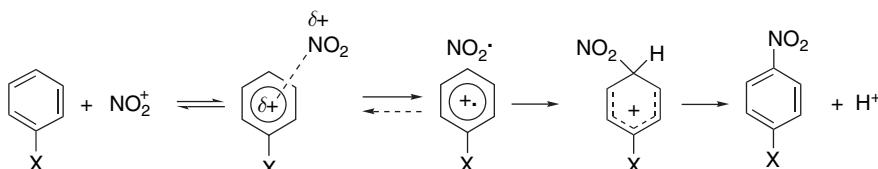
f. G. A. Olah and H. C. Lin, *J. Am. Chem. Soc.*, **96**, 549 (1974).

g. J. R. Knowles, R. O. C. Norman, and G. K. Radda, *J. Chem. Soc.*, 4885 (1960).

h. G. A. Olah and H. C. Lin, *J. Am. Chem. Soc.*, **96**, 549 (1974); *o,m*, and *p* designations for the toluenes are in relation to the methyl group.

Table 9.7. When the aromatic reactant carries an EWG, the selectivity increases, since the TS occurs later. For example, while toluene is about 20 times more reactive than benzene, *p*-nitrotoluene is about 200 times more reactive than nitrobenzene. The effect of the methyl substituent is magnified as a result of the later TS.

An aspect of aromatic nitration that has received attention is the role of charge transfer complexes and electron transfer intermediates on the path to the σ -complex intermediate. For some $\text{NO}_2\text{-X}$ nitrating reagents, the mechanism may involve formation of a distinct electron transfer intermediate prior to the formation of the σ complex.⁴⁵



The existence of charge transfer complexes can be demonstrated for several reaction combinations that eventually lead to nitration, but the crucial question is whether a complete electron transfer to a cation radical–radical pair occurs as a distinct step in the mechanism. This has been a matter of continuing discussion, both pro⁴⁶ and con.⁴⁷ One interesting fact that has emerged about nitration is that the product composition from toluene is virtually invariant at $4 \pm 2\%$ *meta*, $33 \pm 3\%$ *para*, and $65 \pm 5\%$ *ortho*, that is, close to a statistical *o:p* ratio over a wide range of nitrating species.⁴⁸ This argues for a common product-forming step, and one interpretation is that this step is a collapse of a $\text{NO}_2\cdot$ –cation radical pair, as in the electron transfer mechanism. If the σ -complex were formed in a single step from different $\text{NO}_2\text{-X}$ reagents, some variation of the product composition for different X would be expected.

The mechanism of aromatic nitration has been studied by computational methods. Various structures resulting from interaction of benzene with NO_2^+ were found by B3LYP/6-311++G** computations.⁴⁹ Three of the key intermediates are shown in Fig. 9.10. In structure **A** the NO_2 unit is associated with a single carbon atom with a C–N bond distance is 1.997 Å. This structure is only slightly more stable than **B**, in which the NO_2 group is located equidistant between two carbon atoms. The NO_2 group in both structures is significantly bent and resembles the neutral NO_2 molecule, suggesting that a substantial degree of electron transfer has occurred. CHELPG charge analysis is consistent with this conclusion. Various complexes with the linear NO_2^+ ion associated more generally with the ring are at considerably higher energies. Note that these structures are similar to the Br_2 -benzene and Br_2 -toluene complexes described on p. 774. The nitrocyclohexadienylum ion intermediate **C** is about 1 kcal/mol more stable than these oriented complexes. These results pertain to the gas phase.

- ^{45.} C. L. Perrin, *J. Am. Chem. Soc.*, **99**, 5516 (1977).
- ^{46.} J. K. Kochi, *Acc. Chem. Res.*, **25**, 39 (1992); T. M. Bockman and J. K. Kochi, *J. Phys. Org. Chem.*, **7**, 325 (1994); A. Peluso and G. Del Re, *J. Phys. Chem.*, **100**, 5303 (1996); S. V. Rosokha and J. K. Kochi, *J. Org. Chem.*, **67**, 1727 (2002).
- ^{47.} L. Eberson and F. Radner, *Acc. Chem. Res.*, **20**, 53 (1987); L. Eberson, M. P. Hartshorn, and F. Radner, *Acta Chem. Scand.*, **48**, 937 (1994); M. Lehnig, *J. Chem. Soc., Perkin Trans. 2*, 1943 (1996).
- ^{48.} E. K. Kim, K. Y. Lee, and J. K. Kochi, *J. Am. Chem. Soc.*, **114**, 1756 (1992).
- ^{49.} P. M. Esteves, J. W. de Carneiro, S. P. Cardoso, A. G. H. Barbosa, K. K. Laali, G. Rasul, G. K. S. Prakash, and G. A. Olah, *J. Am. Chem. Soc.*, **125**, 4836 (2003).

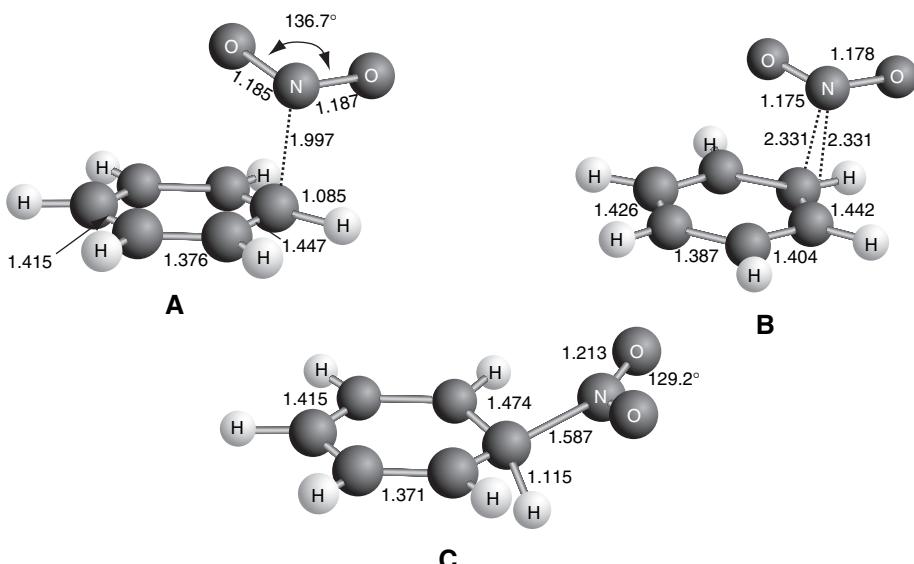


Fig. 9.10. Oriented complexes and nitrocyclohexadienylum intermediate in the nitration of benzene.
Adapted from *J. Am. Chem. Soc.*, **125**, 4836 (2003), by permission of the American Chemical Society.

The nitration mechanism also has been modeled by B3LYP/6-311G** computations using a continuum solvent model.⁵⁰ Structures corresponding to an oriented π complex and the TS and σ complex intermediate were identified. Computations were done at several solvent dielectrics, ϵ , ranging from 0 (vacuum) to 78.5 (water). The barrier for σ complex formation is small and decreases as ϵ increases. The reaction is calculated to occur without a barrier at $\epsilon > 50$. These computational results are consistent with an electron transfer mechanism for nitration of benzene. The reaction occurs through a complex that allows charge transfer to form a radical cation– NO_2^\cdot pair, which is followed by collapse to the nitrocyclohexadienylum intermediate. The product distribution is determined at this latter stage. This feature of the mechanism explains the relatively constant position selectivity of nitration because only the NO_2 group is in intimate contact with the substrate at that point.

Visual models, additional information and exercises on Nitration of Benzene can be found in the Digital Resource available at: Springer.com/carey-sundberg.

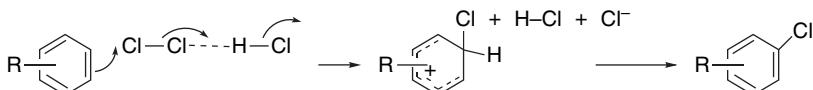
9.4.2. Halogenation

Substitution for hydrogen by halogen is a synthetically important electrophilic aromatic substitution reaction. The reactivity of the halogens increases in the order $\text{I}_2 < \text{Br}_2 < \text{Cl}_2 < \text{F}_2$. Halogenation reactions are normally run in the presence of Lewis acids, in which case a complex of the halogen with the Lewis acid is probably the active electrophile. The molecular halogens are reactive enough to halogenate activated aromatics. Bromine and iodine form stable complexes with the corresponding halide

⁵⁰ H. Xiao, L. Chen, X. Ju, and G. Ji, *Science in China B*, **46**, 453 (2003).

ions. These anionic trihalide ions are less reactive than the free halogen, but are capable of substituting highly reactive rings. This factor can complicate kinetic studies, since the concentration of halide ion increases during the course of halogenation and successively more of the halogen is present as the trihalide ion.

Molecular chlorine is believed to be the active electrophile in uncatalyzed chlorination of reactive aromatic compounds. Second-order kinetics are observed in acetic acid.⁵¹ The reaction is much slower in nonpolar solvents such as dichloromethane and carbon tetrachloride, and chlorination in nonpolar solvents is catalyzed by added acid. The catalysis by acids is probably the result of assistance by proton transfer in the cleavage of the Cl–Cl bond.⁵²

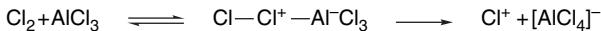


Chlorination in acetic acid is characterized by a large ρ value (~ -9 to -10) and a high partial rate factor for toluene, $f_p = 820$. Both values indicate a late TS that resembles the σ complex intermediate.

For preparative purposes, a Lewis acid such as AlCl₃ or FeCl₃ is often used to catalyze chlorination. Chlorination of benzene using AlCl₃ is overall third order.⁵³

$$\text{Rate} = k[\text{ArH}][\text{Cl}_2][\text{AlCl}_3]$$

This rate law is consistent with formation of a Cl₂-AlCl₃ complex that acts as the active halogenating agent but is also consistent with a rapid equilibrium involving formation of Cl⁺.

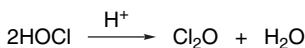


There is, however, no direct evidence for the formation of Cl⁺, and it is much more likely that the complex is the active electrophile. The substrate selectivity under catalyzed conditions ($k_{\text{tol}} = 160k_{\text{benz}}$) is lower than in uncatalyzed chlorinations, as would be expected for a more reactive electrophile. The effect of the Lewis acid is to weaken the Cl–Cl bond and lower the activation energy for σ complex formation.

Hypochlorous acid is a weak chlorinating agent. In acidic solution, it is converted to a much more active chlorinating agent. Although early mechanistic studies suggested that Cl⁺ might be formed under these conditions, it was shown that this is not the case. Detailed kinetic analysis of the chlorination of methoxybenzene revealed a rather complex rate law.⁵⁴

$$\text{Rate} = k_1[\text{HOCl}]^2 + k_2[\text{H}_3\text{O}^+][\text{HOCl}]^2 + k_3[\text{ArH}][\text{H}_3\text{O}^+][\text{HOCl}]$$

Some of the terms are independent of the concentration of the aromatic reactant. This rate law can be explained in terms of the formation of Cl₂O, the anhydride of hypochlorous acid.



⁵¹. L. M. Stock and F. W. Baker, *J. Am. Chem. Soc.*, **84**, 1661 (1962).

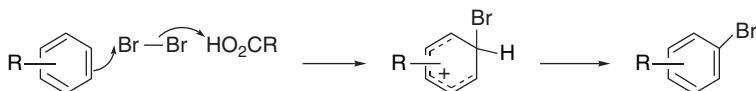
⁵². L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **81**, 1063 (1959); R. M. Keefer and L. J. Andrews, *J. Am. Chem. Soc.*, **82**, 4547 (1960).

⁵³. S. Y. Caille and R. J. P. Corriu, *Tetrahedron*, **25**, 2005 (1969).

⁵⁴. C. G. Swain and D. R. Crist, *J. Am. Chem. Soc.*, **94**, 3195 (1972).

Both Cl_2O and $[\text{H}_2\text{OCl}]^+$ apparently are active electrophiles under these conditions. The terms involving Cl_2O are zero order in the aromatic reactant because formation of Cl_2O is the rate-limiting step. Thermodynamic considerations argue strongly against rate-determining cleavage of $[\text{H}_2\text{OCl}]^+$ to H_2O and Cl^+ . The estimated equilibrium constant for this dissociation is so small that the concentration of Cl^+ would be far too low to account for the observed reaction rate.⁵⁵

Molecular bromine is thought to be the reactive brominating agent in uncatalyzed brominations. The bromination of benzene and toluene are first order in both bromine and the aromatic reactant in trifluoroacetic acid solution,⁵⁶ but becomes more complicated in the presence of water.⁵⁷ The bromination of benzene in aqueous acetic acid exhibits a first-order dependence on bromine concentration when bromide ion is present. The observed rate is dependent on bromide ion concentration, decreasing with increasing concentration. The acids presumably assist in the rate-determining step, as in the case of chlorination. The detailed kinetics are consistent with a rate-determining formation of the σ complex when bromide ion concentration is low, but with a shift to reversible formation of the σ complex with rate-determining deprotonation at high bromide ion concentration.⁵⁸



The issue of involvement of an electron-transfer step in the formation of the intermediate has been investigated both experimentally and computationally. As noted in Section 9.1, discrete complexes of bromine with aromatic hydrocarbons have been characterized structurally for benzene and toluene.⁵⁹ Kinetic studies show that the rate of disappearance of the complexes is identical to the rate of formation of the bromination product, but this alone does not prove that the complex is an intermediate.⁶⁰ Computational studies are consistent with formation of a benzene radical cation- $[\text{Br}_2 \cdot]^-$ radical pair as an intermediate. The calculated ΔH^\ddagger is about 10 kcal/mol less than for a mechanism leading directly to a cyclohexadienylum ion intermediate.⁶¹

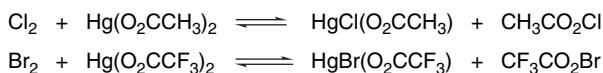
Bromination is characterized by high reactant selectivity.⁶² The data in Table 9.4 showed that for toluene f_p is around 2500, as compared to about 50 for nitration. The very large stabilizing effect of ERG substituents is also evident in the large negative ρ value (-12).⁶³ The fact that substituents can strongly influence both the rate and the orientation implies that the TS comes late in the reaction and resembles the intermediate cyclohexadienylum ion.

- ⁵⁵. E. Berliner, *J. Chem. Ed.*, **43**, 124 (1966).
- ⁵⁶. H. C. Brown and R. A. Wirkkala, *J. Am. Chem. Soc.*, **88**, 1447 (1966).
- ⁵⁷. W. M. Schubert and D. F. Gurka, *J. Am. Chem. Soc.*, **91**, 1443 (1969).
- ⁵⁸. E. Berliner and J. C. Powers, *J. Am. Chem. Soc.*, **83**, 905 (1961); W. M. Schubert and J. L. Dial, *J. Am. Chem. Soc.*, **97**, 3877 (1975).
- ⁵⁹. A. V. Vasilyev, S. V. Lindeman, and J. K. Kochi, *Chem. Commun.*, 909 (2001); S. V. Rosokha and J. K. Kochi, *J. Org. Chem.*, **67**, 1727 (2002).
- ⁶⁰. S. Fukuzumi and J. K. Kochi, *J. Org. Chem.*, **46**, 4116 (1981); S. Fukuzumi and J. K. Kochi, *J. Am. Chem. Soc.*, **103**, 7240 (1981).
- ⁶¹. W. B. Smith, *J. Phys. Org. Chem.*, **16**, 34 (2003).
- ⁶². L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, **1**, 35 (1963).
- ⁶³. H. C. Brown and L. M. Stock, *J. Am. Chem. Soc.*, **79**, 1421 (1957).

Bromination has been shown not to exhibit a primary kinetic isotope effect in the case of benzene,⁶⁴ bromobenzene,⁶⁵ toluene,⁶⁶ or methoxybenzene.⁶⁷ There are several examples of reactants that do show significant isotope effects, including substituted anisoles,⁴⁶ *N,N*-dimethylanilines,⁶⁸ and 1,3,5-trialkylbenzenes.⁶⁹ The observation of isotope effects in highly substituted systems seems to be the result of steric factors that can operate in two ways. There may be resistance to the bromine taking up a position coplanar with adjacent substituents in the aromatization step, which would favor return of the σ complex to reactants. In addition, the steric bulk of several substituents may hinder solvent or other base from assisting in proton removal. Either factor could allow deprotonation to become rate controlling.

Bromination is catalyzed by Lewis acids, and a study of the kinetics of bromination of benzene and toluene in the presence of aluminum chloride has been reported.⁷⁰ Toluene is found to be about 35 times more reactive than benzene under these conditions. The catalyzed reaction thus shows a good deal less substrate selectivity than the uncatalyzed reaction, as would be expected on the basis of the greater reactivity of the aluminum chloride-bromine complex.

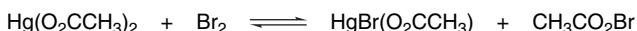
Halogenation is also effected by acyl hypohalites, such as acetyl hypochlorite and trifluoroacetyl hypobromite.⁷¹



The latter is an extremely reactive species. Trifluoroacetate is a good leaving group and facilitates cleavage of the O–Br bond. The acyl hypohalites are also the active halogenating species in solutions of the hypohalous acids in carboxylic acids, where they exist in equilibrium. Acetyl hypobromite is considered to be the active halogenating species in solutions of hypobromous acid in acetic acid:



This reagent can also be formed by reaction of bromine with mercuric acetate:



Both of the above equilibria lie to the left, but acetyl hypobromite is sufficiently reactive that it is the principal halogenating species in both solutions. The reactivity of the acyl hypohalites as halogenating agents increases with the ability of the carboxylate to function as a leaving group. This is, of course, correlated with the acidity of the carboxylic acid. The estimated order of reactivity of Br_2 , $\text{CH}_3\text{CO}_2\text{Br}$, and $\text{CF}_3\text{CO}_2\text{Br}$ is

- ⁶⁴ P. B. D. de la Mare, T. M. Dunn, and J. T. Harvey, *J. Chem. Soc.*, 923 (1957).
- ⁶⁵ L. Melander, *Acta Chem. Scand.*, **3**, 95 (1949); *Arkiv Kemi.*, **2**, 211 (1950).
- ⁶⁶ R. Josephson, R. M. Keefer, and L. J. Andrews, *J. Am. Chem. Soc.*, **83**, 3562 (1961).
- ⁶⁷ J.-J. Aaron and J.-E. Dubois, *Bull. Soc. Chim. Fr.*, 603 (1971).
- ⁶⁸ J.-E. Dubois and R. Uzan, *Bull. Soc. Chim. Fr.*, 3534 (1968); A. Nilsson, *Acta Chem. Scand.*, **21**, 2423 (1967); A. Nilsson and K. Olsson, *Acta Chem. Scand.*, **23**, 2317 (1969).
- ⁶⁹ P. C. Myhre, *Acta Chem. Scand.*, **14**, 219 (1969).
- ⁷⁰ S. Y. Caille and R. J. P. Corriu, *Tetrahedron*, **25**, 2005 (1969).
- ⁷¹ (a) A. L. Henne and W. F. Zimmer, *J. Am. Chem. Soc.*, **73**, 1362 (1951); (b) P. B. D. de la Mare, I. C. Hilton, and S. Varma, *J. Chem. Soc.*, 4044 (1960); (c) P. B. D. de la Mare and J. L. Maxwell, *J. Chem. Soc.*, 4829 (1962); (d) Y. Hatanaka, R. M. Keefer, and L. J. Andrews, *J. Am. Chem. Soc.*, **87**, 4280 (1965); (e) J. R. Bennett, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **94**, 6129 (1972).

$1:10^6:10^{10}$.^{71b,e} It is this exceptionally high reactivity of the hypobromites that permits them to be the reactive halogenating species in solutions where they are present in relatively low equilibrium concentration.

Molecular iodine is not a very powerful halogenating agent. Only very reactive aromatics such as anilines or phenolate anions are reactive toward iodine. Iodine monochloride can be used as an iodinating agent. The greater electronegativity of the chlorine makes the iodine the electrophilic entity in the substitution reaction. Iodination by iodine monochloride is catalyzed by Lewis acids, such as ZnCl_2 .⁷² Iodination can also be carried out with acetyl hypoiodite and trifluoroacetyl hypoiodite. The methods of formation of these reagents are similar to those for the hypobromites.⁷³

Direct fluorination of aromatics is not a preparatively important laboratory reaction because it can occur with explosive violence. Mechanistic studies have been done at very low temperatures and with low fluorine concentrations. For toluene, the f_p and f_m values are 8.2 and 1.55, respectively, indicating that fluorine is a very unselective electrophile. The ρ value in a Hammett correlation with σ^+ is -2.45 . Thus, fluorination exhibits the characteristics that would be expected for a very reactive electrophile.⁷⁴ A number of reagents in which fluorine is bound to a very electronegative group also serve as fluorinating agents, including CF_3OF , $\text{CF}_3\text{CO}_2\text{F}$, $\text{CH}_3\text{CO}_2\text{F}$, and HOSO_2OF .⁷⁵ The synthetic applications of these reagents are discussed in Section 11.1.2 of Part B.

9.4.3. Protonation and Hydrogen Exchange

Hydrogen exchange resulting from reversible protonation of an aromatic ring can be followed by the use of isotopic labels. Either deuterium or tritium can be used and the experiment can be designed to follow either the incorporation or the release of the isotope. The study of the mechanism of electrophilic hydrogen exchange is somewhat simplified by the fact that the proton is the active electrophile. The principle of microscopic reversibility implies that the TS occurs on a symmetrical potential energy surface, since the attacking electrophile is chemically identical to the displaced proton. The TS involves partial transfer of a proton to (or from) a solvent molecule(s) to the aromatic ring. The intermediate σ complex is a cyclohexadienylum cation.

Partial rate factors for exchange for a number of substituted aromatic compounds have been measured. They reveal activation of *ortho* and *para* positions by ERGs. Some typical data are given in Table 9.8. The $k_{\text{tol}}/k_{\text{benz}}$ ratio of around 300 indicates considerable substrate selectivity. The f_p value for toluene varies somewhat, depending on the reaction medium, but is generally about 10^2 .⁷⁶ The ρ value for hydrogen exchange in $\text{H}_2\text{SO}_4\text{-CF}_3\text{CO}_2\text{H}\text{-H}_2\text{O}$ is -8.6 .⁷⁷ A similar ρ value of -7.5 has been observed in aqueous sulfuric acid.⁷⁸ As seen for other electrophilic aromatic substitution reactions, the best correlation is with σ^+ . These ρ values put protonation in the intermediate range of selectivity.

⁷². R. M. Keefer and L. J. Andrews, *J. Am. Chem. Soc.*, **78**, 5623 (1956).

⁷³. E. M. Chen, R. M. Keefer, and L. J. Andrews, *J. Am. Chem. Soc.*, **89**, 428 (1967).

⁷⁴. F. Cacace, P. Giacomello, and A. P. Wolff, *J. Am. Chem. Soc.*, **102**, 3511 (1980).

⁷⁵. A. Haas and M. Lieb, *Chimia*, **39**, 134 (1985).

⁷⁶. L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, **1**, 35 (1963).

⁷⁷. P. Rys, P. Skrabal, and H. Zollinger, *Angew. Chem. Int. Ed. Engl.*, **11**, 874 (1972).

⁷⁸. S. Clementi and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 2*, 1077 (1973).

**Table 9.8. Partial Rate Factors for Hydrogen Exchange
for Some Substituted Aromatic Compounds**

Substituent	f_o	f_m	f_p
CH ₃ ^a	330	7.2	313
F ^b	0.136	-	1.70
Cl ^b	0.035	-	0.161
OPh ^c	6900	~0.1	31,000
Ph ^d	133	< 1	143

- a. C. Eaborn and R. Taylor, *J. Chem. Soc.*, 247 (1961).
 b. C. Eaborn and R. Taylor, *J. Chem. Soc.*, 2388 (1961).
 c. R. Baker and C. Eaborn, *J. Chem. Soc.*, 5077 (1961).
 d. C. Eaborn and R. Taylor, *J. Chem. Soc.*, 1012 (1961).

Among the many experimental results pertaining to hydrogen exchange, a most important one is that general acid catalysis has been demonstrated,⁷⁹ a finding that is in accord with a rate-limiting proton transfer step. Since proton removal is partially rate determining, hydrogen exchange exhibits an isotope effect. A series of experiments using both deuterium and tritium labels arrived at $k_H/k_D = 9.0$ for the proton-loss step for 1,3,5-trimethoxybenzene.⁸⁰ A substantial isotope effect has also been observed for the exchange process with azulene.⁸¹

9.4.4. Friedel-Crafts Alkylation and Related Reactions

The Friedel-Crafts reaction is a very important method for introducing alkyl substituents on an aromatic ring by generation of a carbocation or related electrophilic species. The usual method of generating these electrophiles involves reaction between an alkyl halide and a Lewis acid. The most common Friedel-Crafts catalyst for preparative work is AlCl₃, but other Lewis acids such as SbF₅, TiCl₄, SnCl₄, and BF₃ can also promote reaction. Alternative routes to alkylating species include reaction of alcohols or alkenes with strong acids.

There are relatively few kinetic data on the Friedel-Crafts reaction. Alkylation of benzene or toluene with methyl bromide or ethyl bromide with gallium bromide as the catalyst is first order in each reactant and in the catalyst.⁸² With aluminum bromide as the catalyst, the rate of reaction changes with time, apparently because of heterogeneity of the reaction mixture.⁸³ The initial rate data fit the following kinetic expression:

$$\text{Rate} = k[\text{EtBr}][\text{benzene}][\text{AlBr}_3]^2$$

- ⁷⁹. A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **83**, 2877 (1961); A. J. Kresge, S. Slae, and D. W. Taylor, *J. Am. Chem. Soc.*, **92**, 6309 (1970).
⁸⁰. A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **89**, 4411 (1967).
⁸¹. L. C. Gruen and F. A. Long, *J. Am. Chem. Soc.*, **89**, 1287 (1967).
⁸². S. U. Choi and H. C. Brown, *J. Am. Chem. Soc.*, **85**, 2596 (1963).
⁸³. B. J. Carter, W. D. Covey, and F. P. DeHaan, *J. Am. Chem. Soc.*, **97**, 4783 (1975); cf. S. U. Choi and H. C. Brown, *J. Am. Chem. Soc.*, **81**, 3315 (1959); F. P. DeHaan and H. C. Brown, *J. Am. Chem. Soc.*, **91**, 4844 (1969); H. Jungk, C. R. Smoot, and H. C. Brown, *J. Am. Chem. Soc.*, **78**, 2185 (1956).

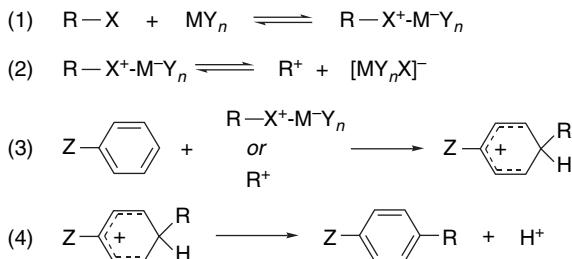
The reaction rates of toluene and benzene with *i*-propyl chloride⁸⁴ or *t*-butyl chloride⁸⁵ in nitromethane can be fit to a third-order rate law.

$$\text{Rate} = k[\text{AlCl}_3][i\text{-PrCl}][\text{ArH}]$$

Rates that are *independent* of aromatic substrate concentration have been found for reaction of benzyl chloride catalyzed by TiCl_4 or SbF_5 in nitromethane.⁸⁶ This can be interpreted as resulting from rate-determining formation of the electrophile, presumably a benzyl ion pair. The reaction of benzyl chloride and toluene shows a second-order dependence on the titanium chloride concentration under conditions where there is a large excess of hydrocarbon.⁸⁷ This is attributed to reaction through a 1:2 benzyl chloride- TiCl_4 complex, with the second TiCl_4 molecule assisting in the ionization reaction:

$$\text{Rate} = k[\text{PhCH}_2\text{Cl}][\text{TiCl}_4]^2$$

All these kinetic results can be accommodated by a general mechanistic scheme that incorporates the following fundamental components: (1) complexation of the alkylating agent and the Lewis acid; in some systems, there may be an ionization of the complex to yield a discrete carbocation; (2) electrophilic attack on the aromatic reactant to form the cyclohexadienylium ion intermediate; and (3) deprotonation. The formation of carbocations accounts for the fact that rearrangement of the alkyl group is observed frequently during Friedel-Crafts alkylation.



Absolute rate data for the Friedel-Craft reactions are difficult to obtain. The reaction is very sensitive to the effects of moisture and heterogeneity. For this reason, most of the structure-reactivity trends have been developed using competitive methods, rather than by direct measurements. Relative rates are established by allowing the electrophile to compete for an excess of the two reactants. The product ratio establishes

- ⁸⁴. F. P. DeHaan, G. L. Delker, W. D. Covey, J. Ahn, R. L. Cowan, C. H. Fong, G. Y. Kim, A. Kumar, M. P. Roberts, D. M. Schubert, E. M. Stoler, Y. J. Suh, and M. Tang, *J. Org. Chem.*, **51**, 1587 (1986).
- ⁸⁵. F. P. DeHaan, W. H. Chan, J. Chang, D. M. Ferrara, and L. A. Wamschel, *J. Org. Chem.*, **51**, 1591 (1986).
- ⁸⁶. F. P. DeHaan, G. L. Delker, W. D. Covey, J. Ahn, M. S. Anisman, E. C. Brehm, J. Chang, R. M. Chicz, R. L. Cowan, D. M. Ferrara, C. H. Fong, J. D. Harper, C. D. Irani, J. Y. Kim, R. W. Meinhold, K. D. Miller, M. P. Roberts, E. M. Stoler, Y. J. Suh, M. Tang, and E. L. Williams, *J. Am. Chem. Soc.*, **106**, 7038 (1984); F. P. DeHaan, W. H. Chan, J. Chang, T. B. Chang, D. A. Chiriboga, M. M. Irving, C. R. Kaufmann, G. Y. Kim, A. Kumar, J. Na, T. T. Nguyen, D. T. Nguyen, B. R. Patel, N. P. Sarin, and J. H. Tidwell, *J. Am. Chem. Soc.*, **112**, 356 (1990).
- ⁸⁷. F. P. DeHaan, W. D. Covey, R. L. Ezelle, J. E. Margetan, S. A. Pace, M. J. Sollenberger, and D. S. Wolfe, *J. Org. Chem.*, **49**, 3954 (1984).

SECTION 9.4

Specific Electrophilic
Substitution Reactions

the relative reactivity. These studies indicate low reactant and position selectivity for the Friedel-Crafts alkylation reaction.

A study of alkylations with a group of substituted benzyl halides and a range of Friedel-Crafts catalysts provided insight into the trends in selectivity and orientation that accompany changes in both the alkyl group and the catalysts.⁸⁸ There is a marked increase in selectivity on going from *p*-nitrobenzyl chloride to *p*-methoxybenzyl chloride. For example, with TiCl_4 as the catalyst, $k_{\text{tol}}/k_{\text{benz}}$ increases from 2.5 to 97. This increase in reactant selectivity is accompanied by an increasing preference for *para* substitution. With *p*-nitrobenzyl chloride, the *o:p* ratio is close to the statistically expected 2:1 ratio, whereas with the *p*-methoxy compound, the *para* product dominates by 2.5:1. There is a clear trend within the family of substituted benzyl chlorides of increasing selectivity with the increasing ERG capacity of the benzyl substituent. All of the reactions, however, remain in a region that constitutes rather low selectivity. Therefore it seems that the TS for substitution by a benzylic cation comes quite early. The substituents on the ring undergoing substitution have a relatively weak orienting effect on the attacking electrophile. With benzylic cations stabilized by donor substituents, the TS comes later and the selectivity is somewhat higher.

Toluene-benzene reactivity ratios under a number of Friedel-Crafts conditions are recorded in Table 9.9. As would be expected on the basis of the low substrate selectivity, position selectivity is also modest. The amount of *ortho* product is often comparable to the *para* product. Steric effects play a major role in determining the *o:p* ratio in Friedel-Crafts alkylations. The amount of *ortho* substitution of toluene

Table 9.9. Reactant and Position Selectivity in Friedel-Crafts Alkylation Reactions

	Electrophilic reagent	$k_{\text{tol}}/k_{\text{benz}}$	Toluene <i>o:p</i> ratio
1	$\text{CH}_3\text{Br}-\text{AlBr}_3^{\text{a}}$	2.5–4.1	1.9
2	$\text{C}_2\text{H}_5\text{Br}-\text{GaBr}_3^{\text{b}}$	6.5	—
3	$(\text{CH}_3)_2\text{CHBr}-\text{AlCl}_3^{\text{c}}$	1.9	1.2
4	$(\text{CH}_3)_2\text{CHCl}-\text{AlCl}_3^{\text{d}}$	2.0	1.5
5	$(\text{CH}_3)_3\text{CCl}-\text{AlCl}_3^{\text{e}}$	25	0
6	$(\text{CH}_3)_3\text{CBr}-\text{SnCl}_4^{\text{f}}$	16.6	0
7	$(\text{CH}_3)_3\text{CBr}-\text{AlCl}_3^{\text{f}}$	1.9	0
8	$\text{PhCH}_2\text{Cl}-\text{AlCl}_3^{\text{g}}$	3.2	0.82
9	$\text{PhCH}_2\text{Cl}-\text{AlCl}_3^{\text{h}}$	2–3	0.9
10	$\text{PhCH}_2\text{Cl}-\text{TiCl}_4^{\text{i}}$	6.3	0.74
11	$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{Cl}-\text{TiCl}_4^{\text{i}}$	97	0.40
12	$p\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{Cl}-\text{TiCl}_4^{\text{j}}$	2.5	1.7

a. H. C. Brown and H. Jungk, *J. Am. Chem. Soc.*, **77**, 5584 (1955).

b. S. U. Choi and H. C. Brown, *J. Am. Chem. Soc.*, **85**, 2596 (1963).

c. G. A. Olah, S. H. Flood, S. J. Kuhn, M. E. Moffatt, and N. A. Overchuck, *J. Am. Chem. Soc.*, **86**, 1046 (1964).

d. F. P. DeHaan, G. L. Delker, W. D. Covey, J. Ahn, R. L. Cowan, C. H. Fong, G. Y. Kim, A. Kumar, M. P. Roberts, D. M. Schubert, E. M. Stoler, Y. J. Suh, and M. Tang, *J. Org. Chem.*, **51**, 1587 (1986).

e. F. P. DeHaan, W. H. Chan, J. Chang, D. M. Ferrara, and L. A. Wainschel, *J. Org. Chem.*, **51**, 1591 (1986).

f. G. A. Olah, S. H. Flood, and M. E. Moffatt, *J. Am. Chem. Soc.*, **86**, 1060 (1964).

g. G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Am. Chem. Soc.*, **84**, 1688 (1962).

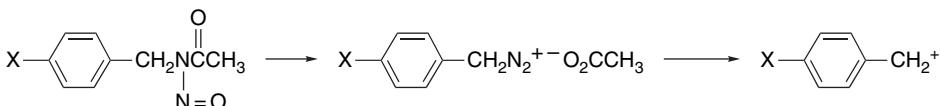
h. F. P. DeHaan, W. D. Covey, R. L. Ezelle, J. E. Margetan, S. A. Pace, M. J. Sollenberger, and D. S. Wolf, *J. Org. Chem.*, **49**, 3954 (1984).

i. G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.*, **94**, 7448 (1972).

⁸⁸. G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.*, **94**, 7448 (1972).

decreases as the size of the entering alkyl group increases along the series methyl, ethyl, *i*-propyl.⁸⁹ No *ortho* product is found when the entering group is *t*-butyl.⁹⁰

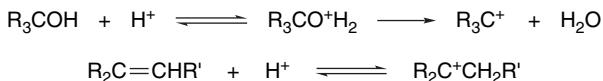
Selectivity by substituted benzyl cations has also been investigated using cations generated from benzyldiazonium ion intermediates.⁹¹ This system removes potential complications of direct involvement of the Lewis acid in the substitution.



Toluene/benzene selectivity decreases in the order $\text{X} = \text{CH}_3 > \text{H} \sim \text{Cl} > \text{NO}_2$, in agreement with the expectation that the least stable (and most reactive) carbocation would be the least selective. These reactions also show low position selectivity.

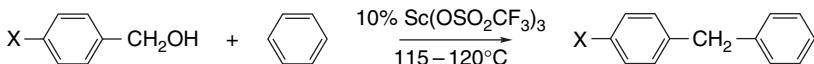
A good deal of experimental care is often required to ensure that the product mixture at the end of a Friedel-Crafts reaction is determined by *kinetic control*. The strong Lewis acid catalysts can catalyze the isomerization of alkylbenzenes and, if isomerization takes place, the product composition is not informative about the position selectivity of electrophilic attack. Isomerization increases the amount of the *meta* isomer in the case of dialkylbenzenes because this isomer is thermodynamically the most stable.⁹²

Alcohols and alkenes can also serve as sources of electrophiles in Friedel-Crafts reactions in the presence of strong acids.



The generation of carbocations from these sources is well documented (see Section 4.4). The reaction of aromatics with alkenes in the presence of Lewis acid catalysts is the basis for the industrial production of many alkylated aromatic compounds. Styrene, for example, is prepared by dehydrogenation of ethylbenzene, which is made from benzene and ethylene.

Benzyl and allyl alcohols that can generate stabilized carbocations give Friedel-Crafts alkylation products with mild Lewis acid catalysts such as $\text{Sc}(\text{O}_3\text{SCF}_3)_3$.⁹³



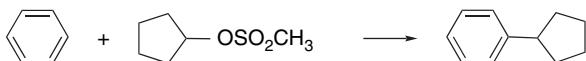
⁸⁹ R. H. Allen and L. D. Yats, *J. Am. Chem. Soc.*, **83**, 2799 (1961).

⁹⁰ G. A. Olah, S. H. Flood, and M. E. Moffatt, *J. Am. Chem. Soc.*, **86**, 1060 (1964).

⁹¹ E. H. White, R. W. Darbeau, Y. Chen, S. Chen, and D. Chen, *J. Org. Chem.*, **61**, 7986 (1996); E. H. White, *Tetrahedron Lett.*, **38**, 7649 (1997); R. W. Darbeau and E. H. White, *J. Org. Chem.*, **65**, 1121 (2000).

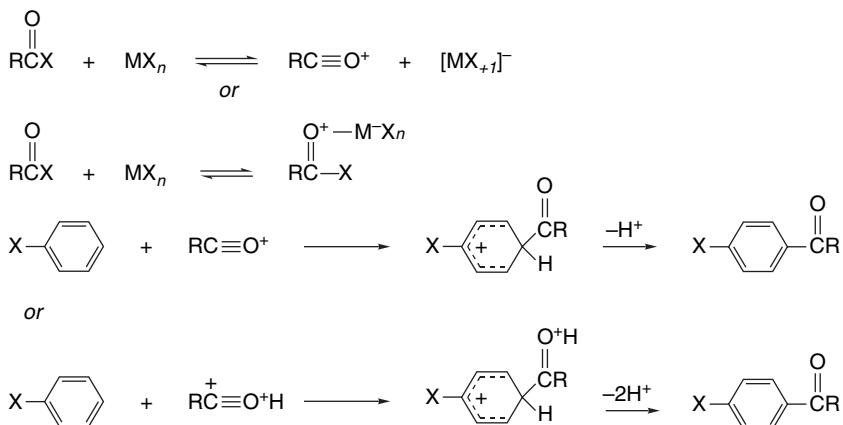
⁹² D. A. McCaulay and A. P. Lien, *J. Am. Chem. Soc.*, **74**, 6246 (1952).

⁹³ T. Tsuchimoto, K. Tobita, T. Hiyama, and S. Fukuzawa, *Synlett*, 557 (1996); T. Tsuchimoto, K. Tobita, T. Hiyama, and S. Fukuzawa, *J. Org. Chem.*, **62**, 6997 (1997).



9.4.5. Friedel-Crafts Acylation and Related Reactions

Friedel-Crafts acylation usually involves the reaction of an acyl halide, a Lewis acid catalyst, and the aromatic reactant. Several species may function as the active electrophile, depending on the reactivity of the aromatic compound. For activated aromatics, the active electrophile can be a discrete positively charged acylium ion or a complex formed between the acyl halide and the Lewis acid catalyst. For benzene and less reactive aromatics, it is believed that the active electrophile is a protonated acylium ion or an acylium ion complexed by a Lewis acid.⁹⁵ Reactions using acylium salts are slow with toluene or benzene as the reactant and do not proceed with chlorobenzene. The addition of triflic acid accelerates the reactions with benzene and toluene and permits reaction with chlorobenzene. These results suggest that a protonation step must be involved.



The formation of acyl halide–Lewis acid complexes can be demonstrated readily. Acetyl chloride, for example, forms both 1:1 and 1:2 complexes with AlCl_3 that can be observed by NMR.⁹⁶ Several Lewis acid complexes of acyl chlorides have been characterized by low-temperature X-ray crystallography.⁹⁷ For example, the crystal structures of PhCOCl-SbCl_5 and PhCOCl-GaCl_3 and $[\text{PhCOCl-TiCl}_4]_2$ have been determined. In all of these complexes, the *Lewis acid is bound to the carbonyl oxygen*. Figure 9.11 shows two examples.

Acylium salts are generated at slightly higher temperatures or with more reactive acyl halides. For example, both 4-methylbenzoyl chloride and 2,4,6-trimethylbenzoyl

⁹⁴ H. Kotsuki, T. Oshisi, and M. Inoue, *Synlett*, 2551 (1998); R. P. Singh, R. M. Kamble, K. L. Chandra, P. Saravanan, and V. K. Singh, *Tetrahedron*, **57**, 241 (2000).

⁹⁵ M. Vol'pin, I. Akhrem, and A. Orlinkov, *New J. Chem.*, **13**, 771 (1989); Y. Sato, M. Yato, T. Ohwada, S. Sato, and K. Shudo, *J. Am. Chem. Soc.*, **117**, 3037 (1995).

⁹⁶ B. Glavincevski and S. Brownstein, *J. Org. Chem.*, **47**, 1005 (1982).

⁹⁷ M. G. Davlieva, S. V. Lindeman, I. S. Neretin, and J. K. Kochi, *J. Org. Chem.*, **70**, 4013 (2005).

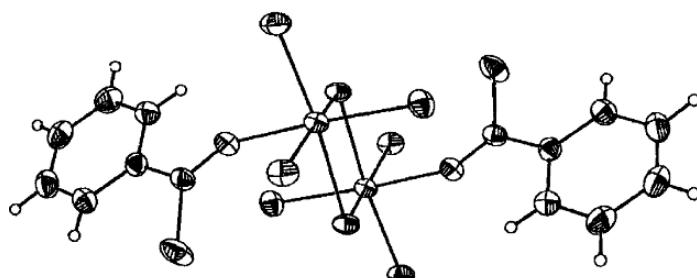
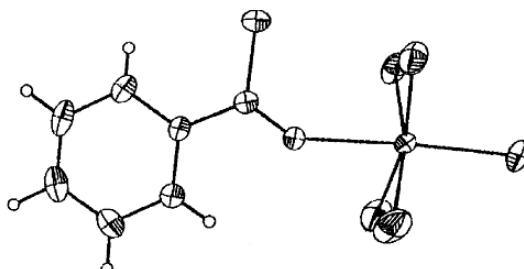
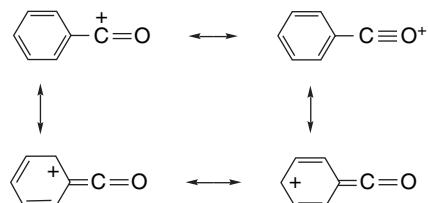


Fig. 9.11. X-Ray crystal structures of PhCOCl-SbCl_5 (top) and $[\text{PhCOCl-TiCl}_4]_2$ (bottom). Reproduced from *J. Org. Chem.*, **70**, 4013 (2005), by permission of the American Chemical Society.

chloride give acylium salts with SbCl_5^- . Acylium salts are also formed from benzoyl fluoride and SbF_5^- . The structure of other acylium ions has been demonstrated by X-ray diffraction. For example, crystal structure determinations have been reported for *p*-methylphenylacylium⁹⁸ and acetylum⁹⁹ ions as SbF_6^- salts. There is also evidence from NMR measurements that demonstrates that acylium ions can exist in nonnucleophilic solvents.¹⁰⁰ The positive charge on acylium ions is delocalized onto the oxygen atom.¹⁰¹ This delocalization is demonstrated by the short O–C bond length in acylium ions, which implies a major contribution from the structure having a triple bond.



Aryl acylium ions are also stabilized by charge delocalization into the aromatic ring.



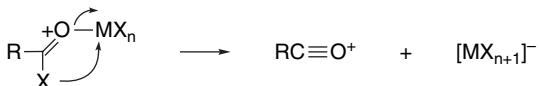
⁹⁸ B. Chevrier, J.-M. LeCarpentier, and R. Weiss, *J. Am. Chem. Soc.*, **94**, 5718 (1972).

⁹⁹ F. P. Boer, *J. Am. Chem. Soc.*, **90**, 6706 (1968).

¹⁰⁰ N. C. Deno, C. U. Pittman, Jr., and M. J. Wisotsky, *J. Am. Chem. Soc.*, **86**, 4370 (1964); G. A. Olah and M. B. Comisarow, *J. Am. Chem. Soc.*, **88**, 4442 (1966).

¹⁰¹ T. Xu, D. H. Barich, P. D. Torres, J. B. Nicholas, and J. F. Haw, *J. Am. Chem. Soc.*, **119**, 396 (1997).

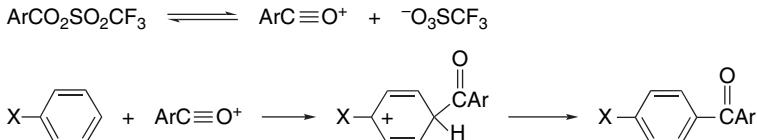
These acylium ions react rapidly with aromatic hydrocarbons such as pentamethylbenzene to give the Friedel-Crafts acylation products. Thus, the mechanisms consists of formation of the complex, ionization to an acylium ion, and substitution via a cyclohexadienylum ion intermediate.⁹⁷ The most likely mechanism for formation of the acylium ion is by an intramolecular transfer of the halide to the Lewis acid.



As is the case with Friedel-Crafts alkylations, direct kinetic measurements are difficult, and not many data are available. Rate equations of the form

$$\text{Rate} = k_1[\text{RCOCl-AlCl}_3][\text{ArH}] + k_2[\text{RCOCl-AlCl}_3]^2[\text{ArH}]$$

have been reported for the reaction of benzene and toluene with both acetyl and benzoyl chloride.¹⁰² The available kinetic data usually do not permit unambiguous conclusions about the identity of the active electrophile. Direct kinetic evidence for acylium ions acting as electrophiles has been obtained using aroyl triflates, which can ionize without assistance from a Lewis acid.¹⁰³ Either formation of the acylium ion or formation of the σ complex can be rate determining, depending on the reactivity of the substrate.



Selectivity in Friedel-Crafts acylation with regard to both reactant selectivity and position selectivity is moderate. Some representative data are collected in Table 9.10. It can be seen that the toluene:benzene reactivity ratio is generally between 100 and 200. A progression from low substrate selectivity (Entries 5 and 6) to higher substrate selectivity (Entries 8 and 9) has been demonstrated for a series of aroyl halides.¹⁰⁴ EWGs on the aroyl chloride lead to low selectivity, presumably because of the increased reactivity of such electrophiles. ERGs diminish reactivity and increase selectivity. For the more selective electrophiles, the selectivity for *para* substitution is unusually high. Friedel-Crafts acylation is generally a more selective reaction than Friedel-Crafts alkylation. The implication is that acylium ions are less reactive electrophiles than the cationic intermediates involved in the alkylation process.

Steric factors clearly enter into determining the *o:p* ratio. The hindered 2,4,6-trimethylbenzoyl group is introduced with a 50:1 preference for the *para* position.⁷⁷ Similarly, in the benzoylation of alkylbenzenes by benzoyl chloride–aluminum chloride, the amount of *ortho* product decreases (10.3, 6.0, 3.1, and 0.6%, respectively) as the branching of the alkyl group is increased along the series methyl, ethyl, *i*-propyl, *t*-butyl.¹⁰⁵

¹⁰². R. Corriu, M. Dore, and R. Thomassin, *Tetrahedron*, **27**, 5601, 5819 (1971).

¹⁰³. F. Effenberger, J. K. Ebehard, and A. H. Maier, *J. Am. Chem. Soc.*, **118**, 12572 (1996).

¹⁰⁴. G. A. Olah and S. Kobayashi, *J. Am. Chem. Soc.*, **93**, 6964 (1971).

¹⁰⁵. G. A. Olah, J. Lukas, and E. Lukas, *J. Am. Chem. Soc.*, **91**, 5319 (1969).

Table 9.10. Reactant and Position Selectivity in Friedel-Crafts Acylation Reactions

	Electrophilic reagents	$k_{\text{tol}}/k_{\text{benz}}$	Toluene <i>o</i> : <i>p</i> ratio
1	$\text{CH}_3\text{COCl-AlCl}_3^{\text{a}}$	134	0.012
2	$\text{CH}_3\text{CH}_2\text{COCl-AlCl}_3^{\text{b}}$	106	0.033
3	$\text{CH}_3\text{C}\equiv\text{O}^+ \text{SbF}_6^-{}^{\text{c}}$	125	0.014
4	$\text{HCOF-BF}_3^{\text{d}}$	35	0.82
5	2,4-Dinitrobenzoyl chloride- AlCl_3^{d}	29	0.78
6	Pentafluorobenzoyl chloride- AlCl_3^{d}	16	0.61
7	$\text{PhCOCl-AlCl}_3^{\text{d}}$	153	0.09
8	<i>p</i> -Toluoyl chloride- AlCl_3^{d}	164	0.08
9	<i>p</i> -Methoxybenzoyl chloride- AlCl_3^{d}	233	0.2

a. G. A. Olah, M. E. Moffatt, S. J. Kuhn, and B. A. Hardie, *J. Am. Chem. Soc.*, **86**, 2198 (1964).

b. G. A. Olah, J. Lukas, and E. Lukas, *J. Am. Chem. Soc.*, **91**, 5139 (1969).

c. G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardi, *J. Am. Chem. Soc.*, **86**, 2203 (1964).

d. G. A. Olah and S. Kobayashi, *J. Am. Chem. Soc.*, **93**, 6964 (1972).

One other feature of the data in Table 9.10 is worthy of further comment. Note that alkyl- (acetyl-, propionyl-)substituted acylium ions exhibit a smaller *o*:*p* ratio than the various aryl systems. If steric factors were dominating the position selectivity, one would expect the opposite result. A possible explanation for this feature of the data is that the aryl compounds are reacting via free acylium ions, whereas the alkyl systems may involve more bulky acid-chloride catalyst complexes.

Friedel-Crafts acylation sometimes shows a modest kinetic isotope effect.¹⁰⁶ This observation suggests that the proton removal is not much faster than the formation of the cyclohexadienylum ion and that its formation may be reversible under some conditions. It has been shown that the *o*:*p* ratio can depend on the rates of deprotonation of the σ complex. With toluene, for example, aryl triflates give higher ratios of *ortho* product when a base, (2,4,6-tri-*t*-butylpyridine) is present.¹⁰⁷ This is because in the absence of base, reversal of acylation leads to reaction through the more easily deprotonated *para* intermediate. Steric effects on deprotonation have also been surmised to be a factor in the 1- versus 2-acylation of naphthalene by acetyl chloride- AlCl_3 .¹⁰⁸ The two competing reactions show different concentration dependence, with 1-acylation being second order in acylating agent, whereas 2-acylation is first order:

$$\text{Rate (1-acylation)} = k_1[\text{naphth}][\text{CH}_3\text{COCl-AlCl}_3]^2$$

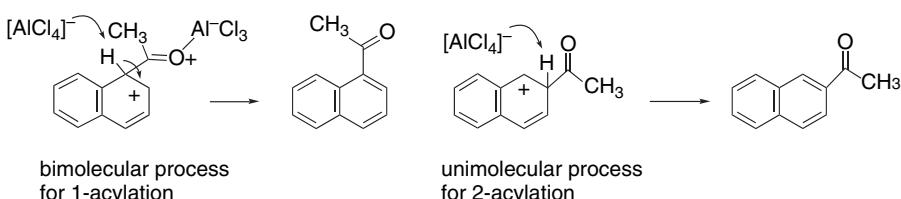
$$\text{Rate (2-acylation)} = k_2[\text{naphth}][\text{CH}_3\text{COCl-AlCl}_3]$$

The 2-acylation also showed a much larger H/D isotope effect (~ 5.4 versus 1.1). The postulated mechanism suggests that breakdown of the more hindered σ complex for 1-acylation is bimolecular, whereas a unimolecular deprotonation process occurs for 2-acylation.

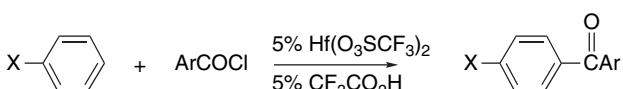
¹⁰⁶. G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, *J. Am. Chem. Soc.*, **86**, 2203 (1964); D. B. Denney and P. P. Klemchuk, *J. Am. Chem. Soc.*, **80**, 3285, 6014 (1958).

¹⁰⁷. F. Effenberger and A. H. Maier, *J. Am. Chem. Soc.*, **123**, 3429 (2001).

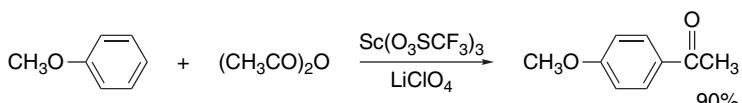
¹⁰⁸. D. Dowdy, P. H. Gore, and D. N. Walters, *J. Chem. Soc., Perkin Trans. I*, 1149 (1991).



Although the Lewis acids used as co-reagents in Friedel-Crafts acylations are often referred to as “catalysts,” they are in fact consumed in the reaction with the generation of strong acids. There has been interest in finding materials that could function as true catalysts.¹⁰⁹ Considerable success has been achieved using lanthanide triflates.¹¹⁰



These reactions are presumed to occur through aroyl triflate intermediates that dissociate to aryl acylium ions. Lithium perchlorate and scandium triflate also promote acylation.¹¹¹



A number of variations of the Friedel-Crafts reaction conditions are possible. Acid anhydrides can serve as the acylating agent in place of acyl chlorides, and the carboxylic acid can be used directly, particularly in combination with strong acids. For example, mixtures of carboxylic acids with polyphosphoric acid in which a mixed anhydride is presumably formed *in situ* are reactive acylating agents.¹¹² Similarly, carboxylic acids dissolved in trifluoromethanesulfonic acid can carry out Friedel-Crafts acylation. The reactive electrophile under these conditions is believed to be the protonated mixed anhydride.¹¹³ In these procedures, the leaving group from the acylating agent is different, but other aspects of the reaction are similar to those under the usual conditions. Synthetic applications of Friedel-Crafts acylation are discussed further in Chapter 11 of Part B.

9.4.6. Aromatic Substitution by Diazonium Ions

Among the reagents that are classified as weak electrophiles, the best studied are the aryl diazonium ions. These reagents react only with aromatic substrates having strong ERG substituents, and the products are azo compounds. The aryl diazonium

¹⁰⁹. K. Smith, *J. Chem. Tech. Biotech.*, **68**, 432 (1997).

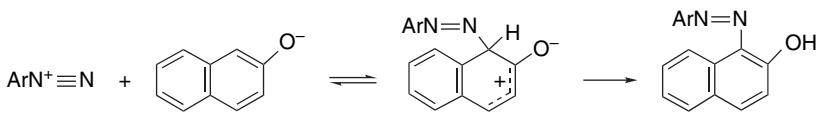
¹¹⁰. I. Hachiya, K. Morikawa, and S. Kobayashi, *Tetrahedron Lett.*, **36**, 409 (1995); S. Kobayashi and S. Iwamoto, *Tetrahedron Lett.*, **39**, 4697 (1998).

¹¹¹. A. Kawada, S. Mitamura, and S. Kobayashi, *Chem. Commun.*, 183 (1996).

¹¹². T. Katuri and K. M. Damodaran, *Can. J. Chem.*, **47**, 1529 (1969).

¹¹³. R. M. G. Roberts and A. R. Sardi, *Tetrahedron*, **39**, 137 (1983).

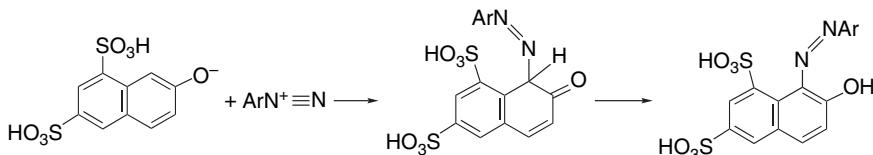
ions are usually generated by diazotization of aromatic amines. The mechanism of diazonium ion formation is discussed more completely in Section 11.2.1 of Part B.



Aryl diazonium ions are stable in solution only near or below room temperature, and this also limits the range of compounds that can be successfully substituted by diazonium ions.

Kinetic investigations revealed second-order kinetic behavior for substitution by diazonium ions in a number of instances. In the case of phenols, it is the *conjugate base* that undergoes substitution.¹¹⁴ This finding is entirely reasonable, since the deprotonated oxy group is a better electron donor than the neutral hydroxy substituent. The reactivity of the diazonium ion depends on the substituent groups that are present. Reactivity is increased by EWG and decreased by ERG.¹¹⁵

An unusual feature of the mechanism for diazonium coupling is that in some cases proton loss can be demonstrated to be the rate-determining step. This feature is revealed in two ways. First, diazonium couplings of several naphthalenesulfonate ions exhibit primary isotope effects in the range 4–6 when deuterium is present at the site of substitution, clearly indicating that cleavage of the C–H bond is rate determining. Second, these reactions can also be shown to be general base catalyzed. This, too, implies that proton removal is rate determining.¹¹⁶



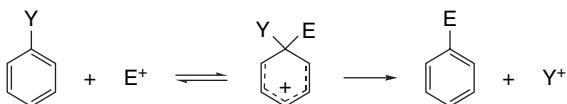
Because of the limited range of aromatic compounds that react with diazonium ions, selectivity data comparable to those discussed for other electrophilic substitutions are not available. Diazotization, since it involves a weak electrophile, would be expected to reveal high substrate and position selectivity.

9.4.7. Substitution of Groups Other than Hydrogen

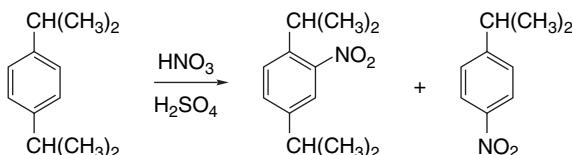
The general mechanism for EAS suggests that groups other than hydrogen could be displaced, provided that the electrophile attacked at the substituted carbon. Substitution at a site already having a substituent is called *ipso* substitution and has been observed in a number of circumstances. The ease of removal of a substituent depends on its ability to accommodate a positive charge. This factor determines whether the

- ¹¹⁴. R. Wistar and P. D. Bartlett, *J. Am. Chem. Soc.*, **63**, 413 (1941).
- ¹¹⁵. A. F. Hegarty, in *The Chemistry of the Diazonium and Diazo Groups*, S. Patai, ed., John Wiley & Sons, New York, 1978, Chap. 12; H. Mayr, M. Hartnagel, and K. Grimm, *Liebigs Ann.*, **55** (1997).
- ¹¹⁶. H. Zollinger, *Azo and Diazo Chemistry*, transl. H. E. Nursten, Interscience, New York, 1961, Chap. 10; H. Zollinger, *Adv. Phys. Org. Chem.*, **2**, 163 (1964); H. Zollinger, *Helv. Chim. Acta*, **38**, 1597 (1955).

newly attached electrophile or the substituent is eliminated from the intermediate on rearomatization.



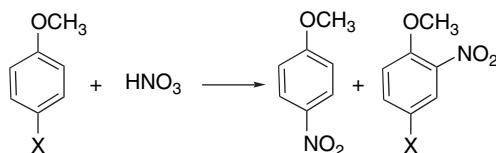
One type of substituent replacement involves cleavage of a highly branched alkyl substituent. The alkyl group is expelled as a carbocation, so substitution is most common for branched alkyl groups. The nitration 1,4-bis-(*i*-propyl)benzene provides an example.



Ref. 117

Cleavage of *t*-butyl groups has been observed in halogenation reactions. Minor amounts of dealkylated products are formed during chlorination and bromination of *t*-butyl-benzene.¹¹⁸ The amount of dealkylation increases greatly in the case of 1,3,5-tri-*t*-butylbenzene, and the principal product of bromination is 3,5-dibromo-*t*-butylbenzene.¹¹⁹

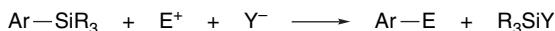
The replacement of bromine and iodine during aromatic nitration has also been observed. *p*-Bromoanisole and *p*-iodoanisole, for example, both give 30–40% of *p*-nitroanisole, a product resulting from displacement of halogen on nitration.



Ref. 120

Owing to the greater resistance to elimination of chlorine as a positively charged species, *p*-chloroanisole does not undergo dechlorination under similar conditions.

The most general type of aromatic substitution involving replacement of a substituent group in preference to a hydrogen is the electrophilic substitution of arylsilanes.



The silyl group directs electrophiles to the substituted position; that is, it is an *ipso*-directing group. Because of the polarity of the carbon-silicon bond, the substituted

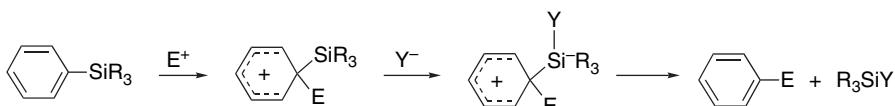
¹¹⁷ G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **86**, 1067 (1964).

¹¹⁸ P. B. D. de la Mare and J. T. Harvey, *J. Chem. Soc.*, 131 (1957); P. B. D. de la Mare, J. T. Harvey, M. Hassan, and S. Varma, *J. Chem. Soc.*, 2756 (1958).

¹¹⁹ P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Am. Chem. Soc.*, **76**, 2349 (1954).

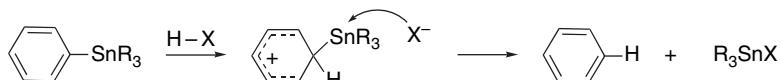
¹²⁰ C. L. Perrin and G. A. Skinner, *J. Am. Chem. Soc.*, **93**, 3389 (1971).

position is relatively electron rich. The ability of silicon substituents to stabilize carbocation character at β -carbon atoms (see Section 5.10.5, p. 564) also promotes *ipso* substitution. A silicon substituent is easily removed from the intermediate by reaction with a nucleophile. The desilylation step probably occurs through a pentavalent silicon species.



The reaction exhibits other characteristics typical of an electrophilic aromatic substitution.¹²¹ Examples of electrophiles that can effect substitution for silicon include protons and the halogens, as well as acyl, nitro, and sulfonyl groups.¹²² The fact that these reactions occur very rapidly has made them attractive for situations where substitution must be done under very mild conditions.¹²³ One example is the introduction of radioactive iodine for use in tracer studies.¹²⁴

Trialkyltin substituents are also powerful *ipso*-directing groups. The overall electronic effects are similar to those in silanes but the tin substituent is more metallic and less electronegative. The electron density at carbon is increased, as is the stabilization of β -carbocation character. Acidic cleavage of arylstannanes is an electrophilic aromatic substitution proceeding through an *ipso*-oriented σ -complex.¹²⁵



9.5. Nucleophilic Aromatic Substitution

Neither of the major mechanisms for nucleophilic substitution in saturated compounds is accessible for substitution on aromatic rings. A back-side S_N2 -type reaction is precluded by the geometry of the benzene ring. The back lobe of the sp^2 orbital is directed toward the center of the ring. An inversion mechanism is precluded by the geometry of the ring. An S_N1 mechanism is very costly in terms of energy because a cation directly on a benzene ring is very unstable. From the data in Figure 3.18 (p. 300) it is clear that a phenyl cation is less stable than even a primary carbocation, which is a consequence of the geometry and hybridization of the aromatic

¹²¹ F. B. Deans and C. Eaborn, *J. Chem. Soc.*, 2299 (1959).

¹²² F. B. Deans, C. Eaborn, and D. E. Webster, *J. Chem. Soc.*, 3031 (1959); C. Eaborn, Z. Lasocki, and D. E. Webster, *J. Chem. Soc.*, 3034 (1959); C. Eaborn, *J. Organomet. Chem.*, **100**, 43 (1975); J. D. Austin, C. Eaborn, and J. D. Smith, *J. Chem. Soc.*, 4744 (1963); F. B. Deans and C. Eaborn, *J. Chem. Soc.*, 498 (1957); R. W. Bott, C. Eaborn, and T. Hashimoto, *J. Chem. Soc.*, 3906 (1963).

¹²³ S. R. Wilson and L. A. Jacob, *J. Org. Chem.*, **51**, 4833 (1986).

¹²⁴ E. Orstad, P. Hoff, L. Skattebol, A. Skretting, and K. Breistol, *J. Med. Chem.*, **46**, 3021 (2003).

¹²⁵ C. Eaborn, I. D. Jenkins, and D. R. M. Walton, *J. Chem. Soc., Perkin Trans. 2*, 596 (1974).



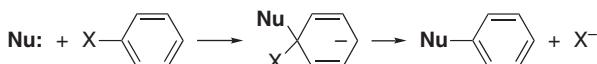
back-side approach of the nucleophile with inversion is impossible

phenyl cation is a high-energy intermediate

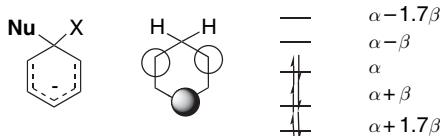
There are several mechanisms by which net nucleophilic aromatic substitution can occur. In this section we discuss the addition-elimination mechanism and the elimination-addition mechanisms. The $S_{RN}1$ mechanism, which involves radical intermediates, is discussed in Chapter 11. Substitutions via organometallic intermediates and via aryl diazonium ions are considered in Chapter 11 of Part B.

9.5.1. Nucleophilic Aromatic Substitution by the Addition-Elimination Mechanism

The addition-elimination mechanism¹²⁶ uses one of the vacant π^* orbitals for bonding interaction with the nucleophile. This permits addition of the nucleophile to the aromatic ring without displacing any of the existing substituents. If attack occurs at a position occupied by a potential leaving group, net substitution can occur by a second step in which the leaving group is expelled.



The addition intermediate is isoelectronic with a pentadienyl anion.



The HOMO is ψ_3 , which has its electron density primarily at the carbons *ortho* and *para* to the position of substitution. The intermediate is therefore strongly stabilized by an EWG *ortho* or *para* to the site of substitution. Such substituents activate the ring to nucleophilic substitution. The most powerful effect is exerted by a nitro group, but cyano and carbonyl groups are also favorable. Generally speaking, nucleophilic aromatic substitution is an energetically demanding reaction, even when electron-attracting substituents are present. The process disrupts the aromatic π system. Without an EWG present, nucleophilic aromatic substitution occurs only under extreme reaction conditions.

The role of the leaving group in determining the reaction rate is somewhat different from S_N2 and S_N1 substitution at alkyl groups. In those cases, the bond strength is

¹²⁶. Reviews: C. F. Bernasconi, in *MTP Int. Rev. Sci., Organic Series One*, Vol. 3, H. Zollinger, ed., Butterworths, London, 1973; J. A. Zolotowicz, *Top. Curr. Chem.*, **59**, 33 (1975); J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier, Amsterdam, 1968.

usually the dominant factor, so the order of reactivity of the halogens is I > Br > Cl > F. In nucleophilic aromatic substitution, the formation of the addition intermediate is usually the rate-determining step, so the ease of C–X bond breaking does not affect the rate. When this is the case, the order of reactivity is often F > Cl > Br > I.¹²⁷ This order is the result of the polar effect of the halogen. The stronger bond dipoles associated with the more electronegative halogens favor the addition step and thus increase the overall rates of reaction.

The broad features of these experimental results, which pertain to solution reactions, are paralleled by computational results on the gas phase reactions.¹²⁸ The barriers for direct halide exchange reactions for Cl⁻, Br⁻, and I⁻ in unsubstituted rings were calculated to be 27 ± 1 kcal/mol, with little difference among the halides. These reactions are calculated to proceed through a single-stage process, without a stable addition intermediate. The situation is quite different for F⁻ exchange. The σ intermediate in this case is calculated to be 3.7 kcal/mol more stable than the reactants, but the barrier for F⁻ elimination is only 1.5 kcal/mol. The addition of one, two, or three nitro groups lowers the Cl⁻ exchange barrier by 22, 39, and 70 kcal/mol, so that the latter two reactions are also calculated to have negative barriers. These reactions all show addition intermediates. Figure 9.12 depicts the contrasting energy profiles for these systems. Besides indicating the important effect of EWGs, these calculations emphasize the special reactivity of the fluoride derivative.

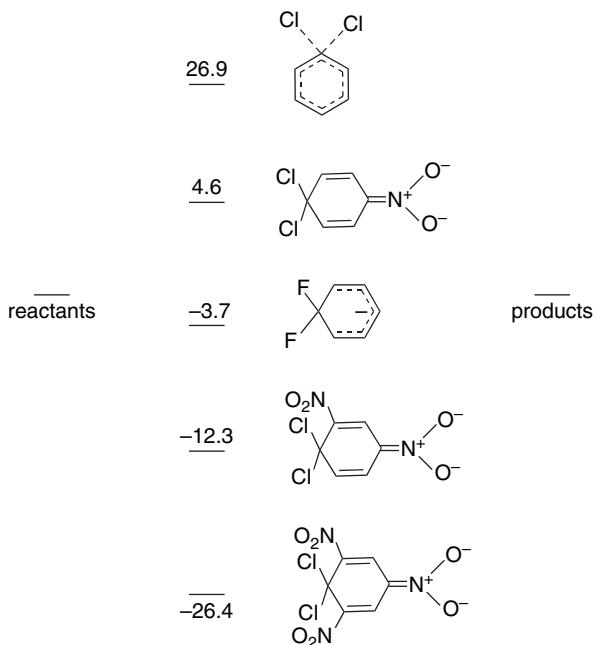
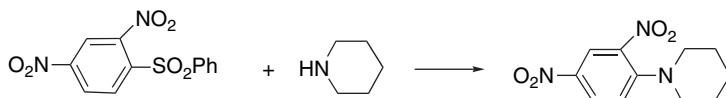


Fig. 9.12. Computed [B3LYP/6-31+G(d)] energy barriers for halide exchange by nucleophilic aromatic substitution. Data from *J. Org. Chem.*, **62**, 4036 (1997).

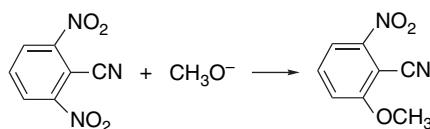
¹²⁷ G. P. Briner, J. Miller, M. Liveris, and P. G. Lutz, *J. Chem. Soc.*, 1265 (1954); J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *J. Am. Chem. Soc.*, **79**, 585 (1957); G. Bartoli and P. E. Todesco, *Acc. Chem. Res.*, **10**, 125 (1977).

¹²⁸ M. N. Glukhovtsev, R. D. Bach, and S. Laiter, *J. Org. Chem.*, **62**, 4036 (1997).

Groups other than halogen can serve as leaving groups. Alkoxy groups are very poor leaving groups in S_N2 reactions but can act as leaving groups in aromatic substitution. The reason is the same as for the inverted order of reactivity for the halogens. The rate-determining step is the addition, and the alkoxide can be eliminated in the energetically favorable rearomatization. Nitro¹²⁹ and sulfonyl¹³⁰ groups can also be displaced.

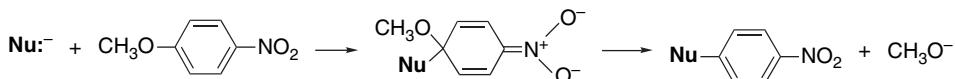


Ref. 131



Ref. 132

The addition intermediates, which are known as *Meisenheimer complexes*, can often be detected spectroscopically and can sometimes be isolated.¹³³ Especially in the case of adducts stabilized by nitro groups, the intermediates are often strongly colored.



The range of nucleophiles that can participate in nucleophilic aromatic substitution is similar to the range of those that participate in S_N2 reactions and includes alkoxides,¹³⁴ phenoxides,¹³⁵ sulfides,¹³⁶ fluoride ion,¹³⁷ and amines.¹³⁸ For reaction with aromatic amines with 1-chloro-2,4-dinitrobenzene, the value of ρ is -4.0 , indicating a substantial buildup of positive charge at nitrogen in the TS.¹³⁹ Substitution by carbanions is somewhat less common. This may be because there are frequently

¹²⁹ J. R. Beck, *Tetrahedron*, **34**, 2057 (1978).

¹³⁰ A. Chisari, E. MacCarone, G. Parisi, and G. Perrini, *J. Chem. Soc., Perkin Trans. 2*, 957 (1982).

¹³¹ J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *J. Am. Chem. Soc.*, **79**, 385 (1957).

¹³² J. R. Beck, R. L. Sobczak, R. G. Suhr, and J. A. Vahner, *J. Org. Chem.*, **39**, 1839 (1974).

¹³³ E. Buncel, A. R. Norris, and K. E. Russel, *Q. Rev. Chem. Soc.*, **22**, 123 (1968); M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970); C. F. Bernasconi, *Acc. Chem. Res.*, **11**, 147 (1978).

¹³⁴ J. P. Idoux, M. L. Madenwald, B. S. Garcia, D. L. Chu, and J. T. Gupton, *J. Org. Chem.*, **50**, 1876 (1985).

¹³⁵ R. O. Brewster and T. Groening, *Org. Synth.*, **II**, 445 (1943).

¹³⁶ M. T. Bogert and A. Shull, *Org. Synth.*, **I**, 220 (1941); N. Kharasch and R. B. Langford, *Org. Synth.*, **V**, 474 (1973); W. P. Reeves, T. C. Bothwell, J. A. Rudis, and J. V. McClusky, *Synth. Commun.*, **12**, 1071 (1982).

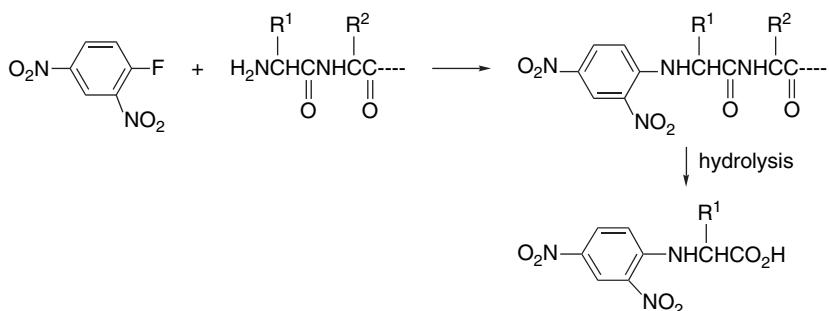
¹³⁷ W. M. S. Berridge, C. Crouzel, and D. Comar, *J. Labelled Compd. Radiopharm.*, **22**, 687 (1985).

¹³⁸ H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*, **31**, 2319 (1966); F. Pietra and F. Del Cima, *J. Org. Chem.*, **33**, 1411 (1968); J. F. Pilichowski and J. C. Gramain, *Synth. Commun.*, **14**, 1247 (1984).

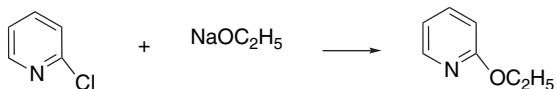
¹³⁹ T. M. Ikramuddeen, N. Chandrasekara, K. Ramarajan, and K. S. Subramanian, *J. Indian Chem. Soc.*, **66**, 342 (1989).

complications resulting from electron transfer processes with nitroaromatics. Solvent effects on nucleophilic aromatic substitutions are similar to those discussed for S_N2 reactions (see Section 3.8). Dipolar aprotic solvents,¹⁴⁰ crown ethers,¹⁴¹ and phase transfer catalysts¹⁴² all can enhance the rate of substitution by providing the nucleophile in a reactive state with weak solvation.

One of the most historically significant examples of aromatic nucleophilic substitution is the reaction of amines with 2,4-dinitrofluorobenzene. This reaction was used by Sanger¹⁴³ to develop a method for identification of the N-terminal amino acid in proteins, and the process opened the way for structural characterization of proteins and other biopolymers.



2-Halopyridines and other π -deficient nitrogen heterocycles are excellent reactants for nucleophilic aromatic substitution.¹⁴⁴



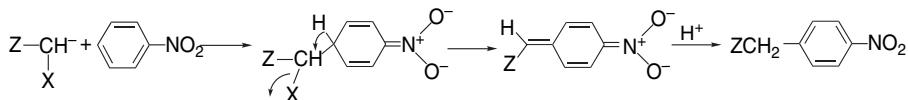
Ref. 145

Substitution reactions also occur readily for other heterocyclic systems, such as 2-haloquinolines and 1-haloisoquinolines, in which a potential leaving group is adjacent to a pyridine-type nitrogen. 4-Halopyridines and related heterocyclic compounds can also undergo substitution by addition-elimination, but are somewhat less reactive.

A variation of the aromatic nucleophilic substitution process in which the leaving group is part of the entering nucleophile has been developed and is known as *vicarious nucleophilic aromatic substitution*. These reactions require a strong EWG substituent

- ¹⁴⁰ F. Del Cima, G. Biggi, and F. Pietra, *J. Chem. Soc., Perkin Trans. 2*, 55 (1973); M. Makosza, M. Jagusztyn-Grochowska, M. Ludwikow, and M. Jawdosiuk, *Tetrahedron*, **30**, 3723 (1974); M. Prato, U. Quintily, S. Salvagno, and G. Scorrano, *Gazz. Chim. Ital.*, **114**, 413 (1984).
- ¹⁴¹ J. S. Bradshaw, E. Y. Chen, R. H. Holes, and J. A. South, *J. Org. Chem.*, **37**, 2051 (1972); R. A. Abramovitch and A. Newman, Jr., *J. Org. Chem.*, **39**, 2690 (1974).
- ¹⁴² M. Makosza, M. Jagusztyn-Grochowska, M. Ludwikow, and M. Jawdosiuk, *Tetrahedron*, **30**, 3723 (1974).
- ¹⁴³ F. Sanger, *Biochem. J.*, **45**, 563 (1949).
- ¹⁴⁴ H. E. Mertel, in *Heterocyclic Chemistry*, Vol 14, Part 2, E. Klingsberg, ed., Interscience, New York, 1961; M. M. Boudakian, in *Heterocyclic Compounds*, Vol 14, Part 2, Supplement, R. A. Abramovitch, ed., Wiley-Interscience, New York, 1974; B. C. Uff, in *Comprehensive Heterocyclic Chemistry*, Vol. 2A, A. J. Boulton and A. McKillop, eds., Pergamon Press, Oxford, 1984, Chap. 2.06.
- ¹⁴⁵ N. Al-Awadi, J. Ballam, R. R. Hemblade, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1175 (1982).

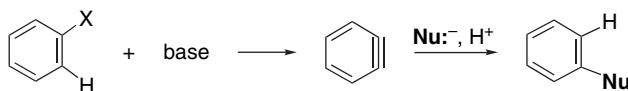
such as a nitro group but do not require a halide or other leaving group. The reactions proceed through addition intermediates.¹⁴⁶



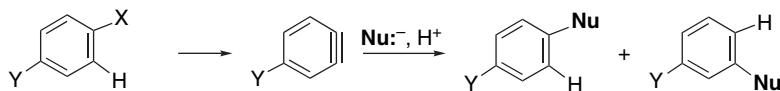
The combinations Z = CN, RSO₂, CO₂R, SR and X = F, Cl, Br, I, ArO, ArS, and (CH₃)₂NCS₂ are among those that have been demonstrated.¹⁴⁷

9.5.2. Nucleophilic Aromatic Substitution by the Elimination-Addition Mechanism

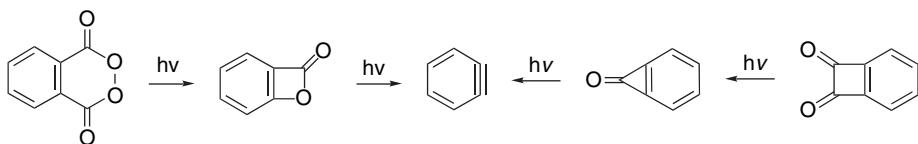
The elimination-addition mechanism involves a highly unstable intermediate, known as *dehydrobenzene* or *benzyne*.¹⁴⁸



A characteristic feature of this mechanism is the substitution pattern in the product. The entering nucleophile need not always enter at the carbon to which the leaving group was bound, since it can add to either of the triply bound carbons.



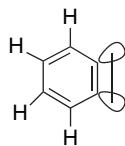
Benzyne can be observed spectroscopically in an inert matrix at very low temperatures.¹⁴⁹ For these studies the molecule is generated photolytically.



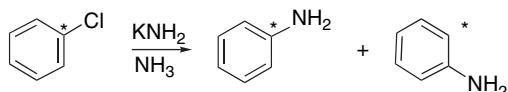
The bonding in benzyne is considered to be similar to benzene, but with an additional weak bond in the plane of the ring formed by overlap of the two *sp*² orbitals.¹⁵⁰

- ^{146.} M. Makosza, T. Lemek, A. Kwast, and F. Terrier, *J. Org. Chem.*, **67**, 394 (2002); M. Makosza and A. Kwast, *J. Phys. Org. Chem.*, **11**, 341 (1998).
- ^{147.} M. Makosza and J. Winiarski, *J. Org. Chem.*, **45**, 1574 (1980); M. Makosza, J. Golinski, and J. Baron, *J. Org. Chem.*, **49**, 1488 (1984); M. Makosza and J. Winiarski, *J. Org. Chem.*, **49**, 1494 (1984); M. Makosza and J. Winiarski, *J. Org. Chem.*, **49**, 5272 (1984); M. Makosza and J. Winiarski, *Acc. Chem. Res.*, **20**, 282 (1987); M. Makosza and K. Wojcienchowski, *Liebigs Ann. Chem./Recueil*, 1805 (1997).
- ^{148.} R. W. Hoffmann, *Dehydrobenzene and Cycloalkynes*, Academic Press, New York (1967); H. H. Wenk, M. Winkler, and W. Sander, *Angew. Chem. Int. Ed. Engl.*, **42**, 502 (2003).
- ^{149.} O. L. Chapman, K. Mattes, C. L. McIntosh, J. Pacansky, G. V. Calder, and G. Orr, *J. Am. Chem. Soc.*, **95**, 6134 (1973); J. W. Laing and R.S. Berry, *J. Am. Chem. Soc.*, **98**, 660 (1976); J. G. Rasdziszewski, B. A. Hess, Jr., and R. Zahradnik, *J. Am. Chem. Soc.*, **114**, 52 (1992).
- ^{150.} H. E. Simmons, *J. Am. Chem. Soc.*, **83**, 1657 (1961).

Comparison of the NMR characteristics¹⁵¹ with MO calculations indicates that the π conjugation is maintained and the benzyne is a strained but aromatic molecule.¹⁵²

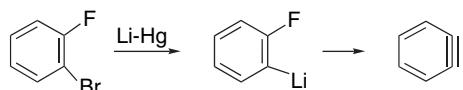


An early case in which the existence of benzyne as an intermediate was established was the reaction of chlorobenzene with potassium amide. ^{14}C -label in the starting material was found to be distributed between C(1) and the *ortho* position in the aniline, consistent with a benzyne intermediate.¹⁵³



The elimination-addition mechanism is facilitated by structural effects that favor removal of a hydrogen from the ring by strong base. Relative reactivity also depends on the halide. The order $\text{Br} > \text{I} > \text{Cl} > \text{F}$ has been established in the reaction of aryl halides with KNH_2 in liquid ammonia.¹⁵⁴ This order has been interpreted as representing a balance between two effects. The polar order favoring proton removal would be $\text{F} > \text{Cl} > \text{Br} > \text{I}$, but this is largely overwhelmed by the order of leaving-group ability $\text{I} > \text{Br} > \text{Cl} > \text{F}$, which reflects bond strengths.

Benzyne can also be generated from *o*-dihaloaromatics. Reaction of lithium-amalgam or magnesium results in formation of a transient organometallic compound that decomposes with elimination of lithium halide. 1-Bromo-2-fluorobenzene is the usual starting material in this procedure.¹⁵⁵



With organometallic compounds as bases in aprotic solvents, the acidity of the *ortho* hydrogen is the dominant factor and the reactivity order, owing to the bond polarity effect, is $\text{F} > \text{Cl} > \text{Br} > \text{I}$.¹⁵⁶

¹⁵¹ R. Warmuth, *Angew. Chem. Int. Ed. Engl.*, **36**, 1347 (1997).

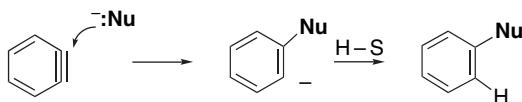
¹⁵² H. Jiao, P.v.R. Schleyer, B. R. Beno, K. N. Houk, and R. Warmuth, *Angew. Chem. Int. Ed. Engl.*, **36**, 2761 (1997).

¹⁵³ J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, *J. Am. Chem. Soc.*, **78**, 601 (1956).

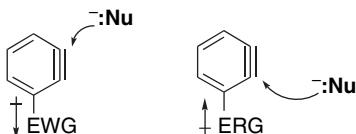
¹⁵⁴ F. W. Bergstrom, R. E. Wright, C. Chandler, and W. A. Gilkey, *J. Org. Chem.*, **1**, 170 (1936).

¹⁵⁵ G. Wittig and L. Pohmer, *Chem. Ber.*, **89**, 1334 (1956); G. Wittig, *Org. Synth.*, **IV**, 964 (1963).

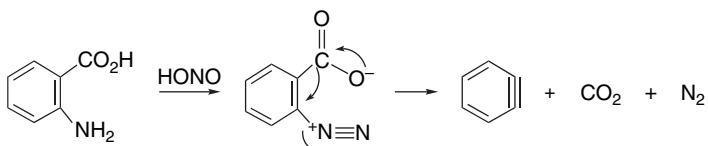
¹⁵⁶ R. Huisgen and J. Sauer, *Angew. Chem.*, **72**, 91 (1960).



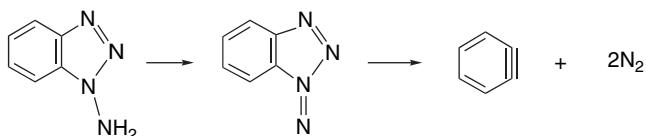
The regiochemistry of the nucleophilic addition is influenced by ring substituents. EWGs tend to favor addition of the nucleophile at the more distant end of the “triple bond,” since this permits maximum stabilization of the developing negative charge. ERGs have the opposite effect. These directive effects probably arise mainly through interaction of the substituent with the electron pair that is localized on the *ortho* carbon by the addition step. Selectivity is usually not high, however, and formation of both possible products from monosubstituted benzenes is common.¹⁵⁸



There are several methods for generation of benzyne in addition to base-catalyzed elimination of hydrogen halide from a halobenzene, and some of these are more generally applicable for preparative work. Probably the most convenient method is diazotization of *o*-aminobenzoic acids.¹⁵⁹ Concerted loss of nitrogen and carbon dioxide follows diazotization and generates benzyne, which can be formed in the presence of a variety of compounds with which it reacts rapidly.



Oxidation of 1-aminobenzotriazole also serves as a source of benzyne under mild conditions. An oxidized intermediate decomposes with loss of two molecules of nitrogen.¹⁶⁰



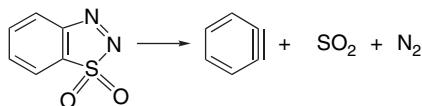
¹⁵⁷ J. F. Bunnett, D. A. R. Happer, M. Patsch, C. Pyun, and H. Takayama, *J. Am. Chem. Soc.*, **88**, 5250 (1966); J. F. Bunnett and J. K. Kim, *J. Am. Chem. Soc.*, **95**, 2254 (1973).

¹⁵⁸ E. R. Biehl, E. Nieh, and K. C. Hsu, *J. Org. Chem.*, **34**, 3595 (1969).

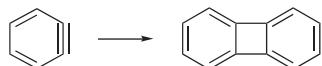
¹⁵⁹ M. Stiles, R. G. Miller, and U. Burckhardt, *J. Am. Chem. Soc.*, **85**, 1792 (1963); L. Friedman and F. M. Longullo, *J. Org. Chem.*, **34**, 3595 (1969); P. C. Buxton, M. Fensome, F. Heaney, and K. G. Mason, *Tetrahedron*, **51**, 2959 (1995).

¹⁶⁰ C. D. Campbell and C. W. Rees, *J. Chem. Soc. C*, 742, 745 (1969).

Another heterocyclic molecule that can serve as a benzyne precursor is benzothiadiazole-1,1-dioxide, which decomposes with elimination of sulfur dioxide and nitrogen.¹⁶¹



Benzyne dimerizes to biphenylene when generated in the absence of either a nucleophile or a reactive unsaturated compound.¹⁶² The lifetime of benzyne is estimated to be on the order of a few seconds in solution near room temperature.¹⁶³



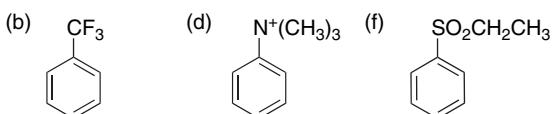
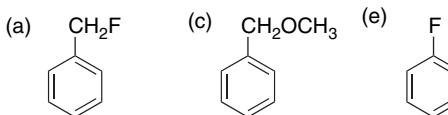
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Problems

(References for these problems will be found on page 1164)

- 9.1. Predict qualitatively the isomer ratio for nitration of each of the following compounds:

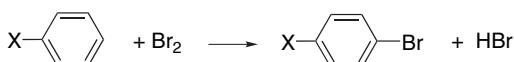


¹⁶¹. G. Wittig and R. W. Hoffmann, *Org. Synth.*, **47**, 4 (1967); G. Wittig and R. W. Hoffmann, *Chem. Ber.*, **95**, 2718, 2729 (1962).

¹⁶². F. M. Logullo, A. H. Seitz, and L. Friedman, *Org. Synth.*, **48**, 12 (1968).

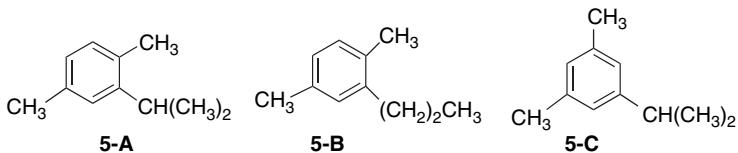
¹⁶³. F. Gavina, S. V. Luis, and A. M. Costero, *Tetrahedron*, **42**, 155 (1986).

- 9.2. Although *N,N*-dimethylaniline is extremely reactive toward electrophilic aromatic substitution and is readily substituted by weak electrophiles, such as diazonium and nitrosonium ions, this reactivity is greatly diminished by introduction of an alkyl substituent in an *ortho* position. Explain.
- 9.3. Toluene is 28 times more reactive than benzene, whereas isopropylbenzene is 14 times more reactive than benzene toward nitration in the organic solvent sulfolane. The *o:m:p* ratio for toluene is 62:3:35. For isopropylbenzene, the ratio is 43:5:52. Calculate the partial rate factors for each position in toluene and isopropylbenzene. Discuss the significance of the partial rate factors. Compare the reactivity at each position of the molecules, and explain any significant differences.
- 9.4. Some bromination rate constants are summarized below. Compare the correlation of the data with both σ and σ^+ substituent constants. What is the value of ρ ? What information do the results provide about the mechanism of bromination?



X	$k (M^{-1}s^{-1})$
H	2.7×10^{-6}
CH_3	1.5×10^{-2}
OCH_3	9.8×10^3
OH	4.0×10^4
$\text{N}(\text{CH}_3)_2$	2.2×10^8

- 9.5. Compare the product distribution results given below for the alkylation of *p*-xylene at two different temperatures after 2 h. The ratio of aromatic reagent:halide: AlCl_3 was 1.0:0.5:0.1.

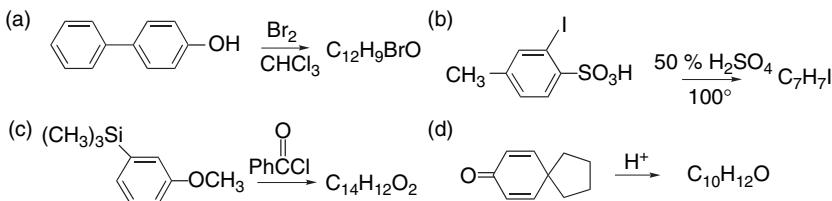


alkyl chloride	temp	Product Composition (%)		
		5-A	5-B	5-C
<i>n</i> -propyl	0°C	34	66	0
<i>n</i> -propyl	50°C	31	53	16
<i>i</i> -propyl	0°C	100	0	0
<i>i</i> -propyl	50°C	62	0	38

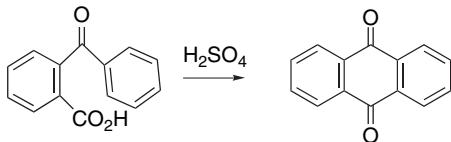
- 9.6. The table below gives first order-rate constants for the reaction of substituted benzenes with *m*-nitrobenzenesulfonyl peroxide. From these data, calculate the relative reactivity and partial rate factors. Does this reaction fit the pattern of an electrophilic aromatic substitution? If so, does the active electrophile exhibit low, intermediate, or high reactivity and position selectivity?

X	$k\text{ (s}^{-1}\text{)}$	product composition		
		<i>o</i>	<i>m</i>	<i>p</i>
H	8.6×10^{-5}	—	—	—
Br	4.8×10^{-5}	21	3	76
CH ₃	1.7×10^{-3}	32	3	65
CH ₃ O	4.3×10^{-2}	14	0	86
CH ₃ O ₂ C	9.1×10^{-6}	24	67	9

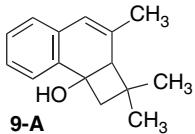
9.7. Propose a structure for the products of the following reactions:



9.8. In 100% H₂SO₄ the cyclization shown below occurs. If one of the *ortho* hydrogens is replaced by deuterium, the rate of cyclization drops from 1.56×10^{-4} to 1.38×10^{-4} s⁻¹. Calculate the kinetic isotope effect. The product from such a reaction contains 60% of the original deuterium. Write a mechanism for this reaction that is consistent with both the magnitude of the kinetic isotope effect and the deuterium retention data.

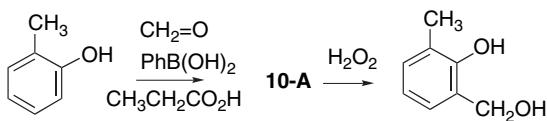


9.9. Reaction of 3,5,5-trimethylcyclohex-2-en-1-one with NaNH₂ (3 equiv) in THF generates an enolate. When bromobenzene is added to this solution and stirred for 4 h, a product **9-A** is isolated in 30% yield. Formulate a mechanism for this reaction.

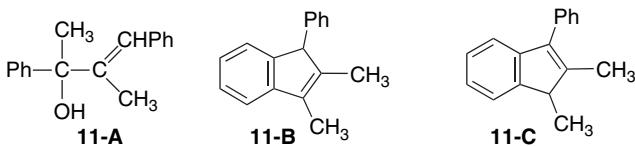


9.10. Several phenols can be selectively hydroxymethylated at the *ortho* position by heating with paraformaldehyde and phenylboronic acid in propanoic acid. An intermediate **10-A** having the formula C₁₄H₁₃O₂B can be isolated in the case

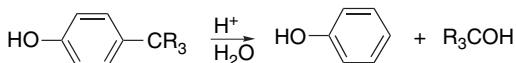
of 2-methylphenol. Propose a structure for the intermediate and indicate the role of phenylboronic acid in the reaction.



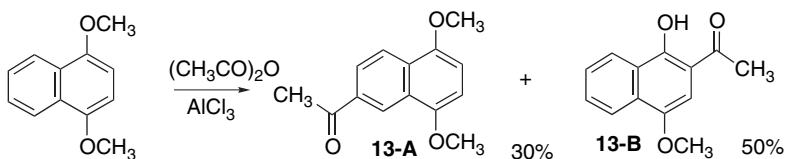
- 9.11. When compound **11-A** is dissolved in FSO₃H at -78°C , the NMR spectrum shows that a carbocation is formed. If the solution is then allowed to warm to -10°C , a different carbocation is formed. When the acidic solution is quenched with 15% NaOH, the first carbocation gives product **11-B**, whereas the second gives **11-C**. What are the likely structures of the two carbocations?



- 9.12. Alkyl groups that are *para* to strong ERG substituents such as hydroxy or methoxy can be removed from aromatic rings under acidic conditions if they can form stable carbocations. A comparison of the cases R = CH₃ and R = Ph showed strikingly different solvent isotope effects. For R = CH₃ $k_{\text{H}}/k_{\text{D}} \sim 0.1$, whereas for R = Ph, $k_{\text{H}}/k_{\text{D}} = 4.3$. How do you account for the difference in the solvent isotope effects in the two systems? What accounts for the inverse isotope effect in the case of R = CH₃?

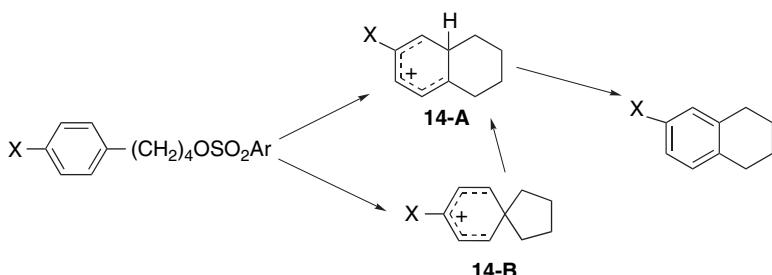


- 9.13. Acylation of 1,4-dimethoxynaphthalene with acetic anhydride (1.2 equiv) and AlCl₃ (2.2 equiv) in dichloroethane at 60°C leads to two products, as shown below. Suggest a rationalization for the formation of these two products. What might account for the demethylation observed in product **13-B**?



- 9.14. The solvolysis of 4-arylbutyl arenesulfonates in nonnucleophilic media leads to formation of tetralins. Two σ intermediates, **14-A** and **14-B**, are conceivable.

14-A would lead directly to product on deprotonation, whereas **14-B** would give product by rearrangement to **14-A**, followed by deprotonation.



Suggest an experiment that could determine how much of the product was formed via each of the two paths. How would you expect the relative importance of the two routes to vary with the substituent group X?

- 9.15. The kinetic expression for chlorination of anisole by HOCl given on p. 799 becomes simpler for both less reactive and more reactive reactants. For benzene the expression is

$$\text{Rate} = k[\text{benzene}][\text{HOCl}][\text{H}^+]$$

and for 1,4-dimethoxybenzene it is

$$\text{Rate} = k[\text{HOCl}][\text{H}^+]$$

Why does the form of the rate expression depend on the reactivity of the aromatic compound? What conclusions can be drawn about the mechanism of chlorination of benzene and 1,4-dimethoxybenzene under these conditions?

- 9.16. Relative reactivity and product distribution data for nitration of the halobenzenes is given below. Calculate the partial rate factors for each position for each halogen. What insight into the substituent activating/directing effects of the halogens can you draw from this data?

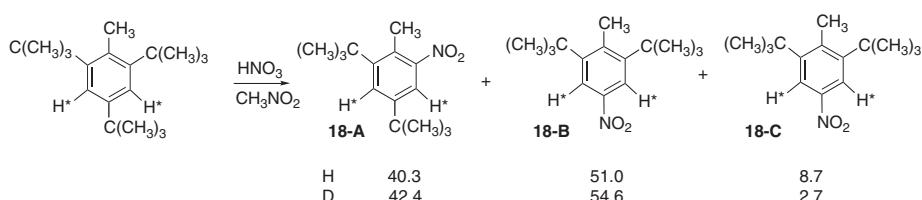
Halogen	Rel rate	%ortho	%meta	%para
F	0.15	13	0	87
Cl	0.033	30	1	69
Br	0.03	37	1	62
I	0.18	38	2	60

- 9.17. *Ipo* substitution is relatively rare in electrophilic aromatic substitution and was not explicitly covered in Section 9.2 in the discussion of substituent effects on reactivity and selectivity. Using qualitative concepts, discuss the effect of the following types of substituents on the TS and intermediate for *ipo* substitution.

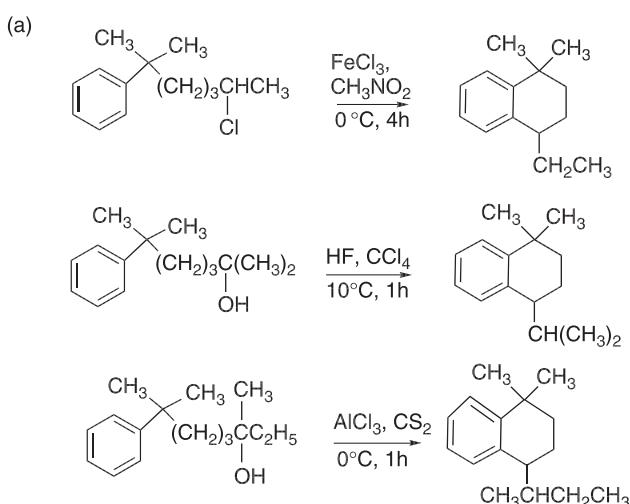
- A π -donor substituent that is more electronegative than carbon, e.g., methoxy.
- A π -acceptor substituent that is more electronegative than carbon, e.g., cyano or nitro.

- c. A very polar EWG that does not have π -conjugation capacity, e.g., $\text{N}^+(\text{CH}_3)_3$.
- d. A group without strong π -conjugating capacity that is less electronegative than carbon, e.g., $\text{Si}(\text{CH}_3)_3$.

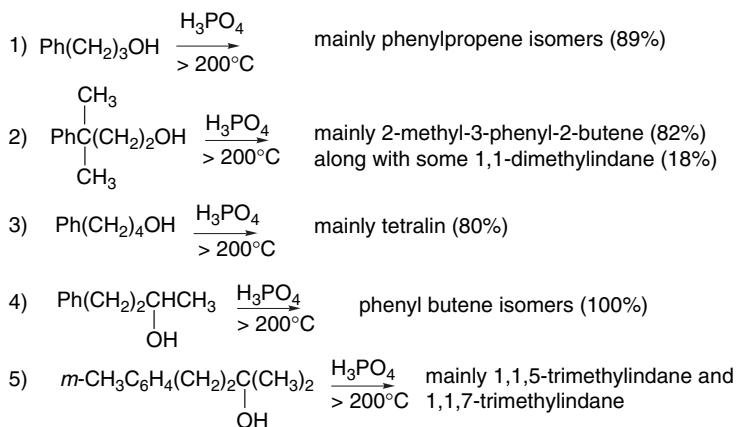
- 9.18. The nitration of 2,4,6-tris-(*t*-butyl)toluene gives rise to three products. The product distribution changes when the 3-position and the 5-position are deuterated, as shown by the data below. Indicate a mechanism for formation of each product. Show why the isotopic labeling results in a change in product composition. Calculate the isotope effect. Does this appear to be a primary isotope effect? Is an isotope effect of this magnitude consistent with your proposed mechanism?



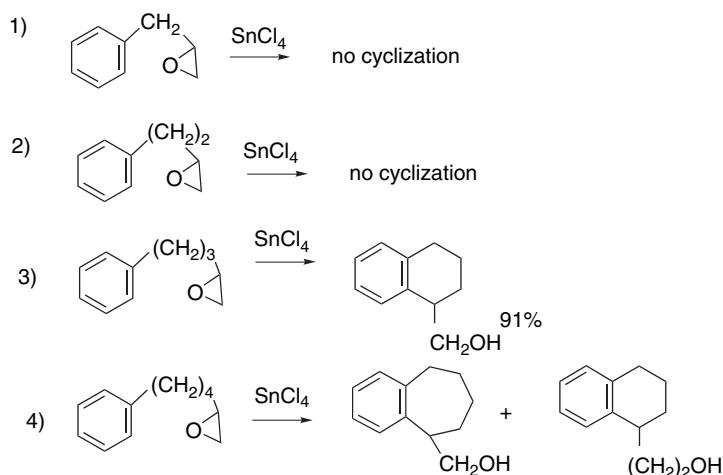
- 9.19. Analyze the results of the studies of intramolecular electrophilic substitution that are described below. Write mechanisms for each of the cyclizations and comment on the relation between ring size and the outcome of cyclization.



(b)

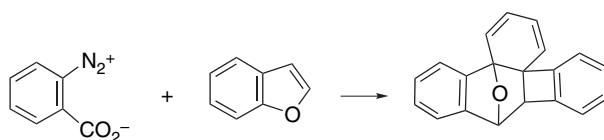


(c)

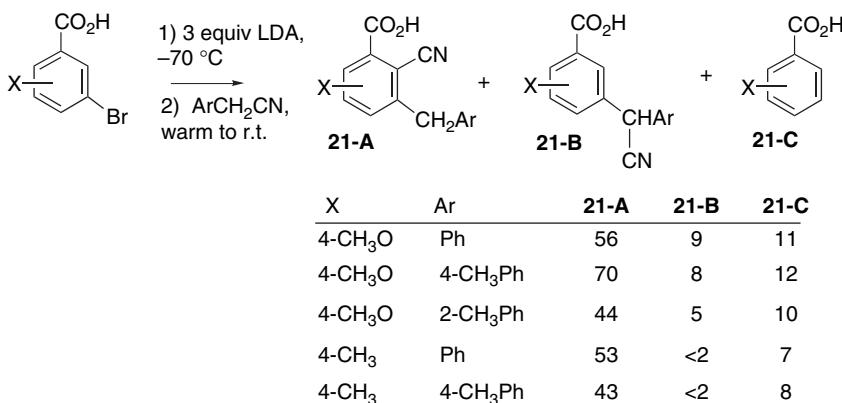


9.20. Explain the outcome of the following reactions by a mechanism showing how the product could be formed.

- 2,6-Di-(*t*-butyl)phenoxide reacts with *o*-nitroaryl halides in NaOH/DMSO at 80°C to give 2,6-di-(*t*-butyl)-4-(2-nitrophenyl)phenol in 60–90% yield. Under similar conditions, 1,4-dinitrobenzene gives 2,6-di-(*t*-butyl)-4-(4-nitrophenyl)phenol.
- 2-(3-Chlorophenyl)-4,4-dimethyloxazoline reacts with alkyllithium reagents to give 2-(2-alkylphenyl)-4,4-dimethyloxazolines.
- Nitrobenzene reacts with cyanomethyl phenyl sulfide in NaOH/DMSO to give a mixture of 2- and 4-nitrophenylacetonitrile.
- The following transformation occurs:



- e. Reaction of benzene with 3,3,3-trifluoropropene in the presence of BF_3 gives 3,3,3-trifluoropropylbenzene.
- f. 3-Chloronitrobenzene reacts with 4-amino-1,2,4-triazole in $\text{K}^+ \cdot^- \text{O}-t\text{-Bu}/\text{DMSO}$ to give 2-chloro-4-nitroaniline.
- g. Good yields of tetralone can be obtained from 4-phenylbutanoic acid or the corresponding acyl chloride in the presence of the strongly acidic resin Nafion-H. With 3-phenylpropanoic acid, only the acyl chloride gives a cyclization product.
- 9.21. Reaction of several 3-bromobenzoic acids with excess LDA at -70°C , followed by addition of benzyl cyanide and warming, gives the product mixtures shown below. Suggest a mechanism for formation of products **21-A** and **21-B** under these conditions.



Concerted Pericyclic Reactions

Introduction

Concerted reactions occur without an intermediate. The transition structure involves both bond breaking and bond formation, although not necessarily to the same degree. There are numerous examples of both unimolecular and bimolecular concerted reactions. A particularly important group consists of the *concerted pericyclic reactions*,¹ which are characterized by a continuous reorganization of electrons through *cyclic transition structures*. Furthermore, the cyclic TS must correspond to an arrangement of the participating orbitals that can maintain a bonding interaction between the reacting atoms throughout the course of the reaction. We shall see shortly that these requirements make pericyclic reactions predictable in terms of relative reactivity, regioselectivity, and stereoselectivity.

A key to understanding the mechanisms of the concerted pericyclic reactions was the recognition by Woodward and Hoffmann that the pathway of such reactions is determined by the symmetry properties of the orbitals that are directly involved.² Specifically, they stated the requirement for *conservation of orbital symmetry*. The idea that the symmetry of each participating orbital must be conserved during the reaction process dramatically transformed the understanding of concerted pericyclic reactions and stimulated much experimental work to test and extend their theory.³ The Woodward and Hoffmann concept led to other related interpretations of orbital properties that are also successful in predicting and interpreting the course of concerted

¹. R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Academic Press, New York, 1970.

². R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395 (1965).

³. For reviews of several concerted reactions within the general theory of pericyclic reactions, see A. P. Marchand and R. E. Lehr, eds., *Pericyclic Reactions*, Vols. I and II, Academic Press, New York, 1977.

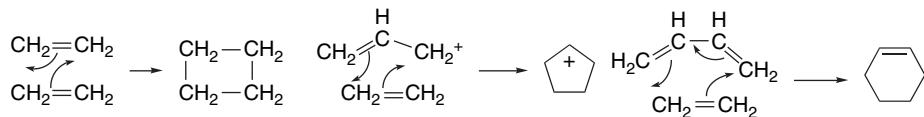
pericyclic reactions.⁴ These various approaches conclude that TSs with certain orbital alignments are energetically favorable (allowed), whereas others lead to high-energy (forbidden) TSs. The stabilized TSs share certain electronic features with aromatic systems, whereas the high-energy TSs are more similar to antiaromatic systems.^{4b,c} As we will see shortly, this leads to rules similar to the Hückel and Möbius relationships for aromaticity (see Section 8.1) that allow prediction of the outcome of the reactions on the basis of the properties of the orbitals of the reactants. Because these reactions proceed through highly ordered cyclic transition structures with specific orbital alignments, the concerted pericyclic reactions often have characteristic and predictable stereochemistry. In many cases, the reactions exhibit regioselectivity that can be directly related to the effect of orbital interactions on TS structure. Similarly, substituent effects on reactivity can be interpreted in terms of the effect of the substituents on the interacting orbitals.

A great deal of effort has been expended to model the transition structures of concerted pericyclic reactions.⁵ All of the major theoretical approaches, semiempirical MO, ab initio MO, and DFT have been applied to the problem and some comparisons have been made.⁶ The conclusions drawn generally parallel the orbital symmetry rules in their prediction of reactivity and stereochemistry and provide additional insight into substituent effects.

We discuss several categories of concerted pericyclic reactions, including Diels-Alder and other *cycloaddition reactions*, *electrocyclic reactions*, and *sigmatropic rearrangements*. The common feature is a concerted mechanism involving a cyclic TS with continuous electronic reorganization. The fundamental aspects of these reactions can be analyzed in terms of orbital symmetry characteristics associated with the TS. For each major group of reactions, we examine how regio- and stereoselectivity are determined by the cyclic TS.

10.1. Cycloaddition Reactions

Cycloaddition reactions involve the combination of two molecules to form a new ring. Concerted pericyclic cycloadditions involve reorganization of the π -electron systems of the reactants to form two new σ bonds. Examples might include cyclodimerization of alkenes, cycloaddition of allyl cation to an alkene, and the addition reaction between alkenes and dienes (Diels-Alder reaction).



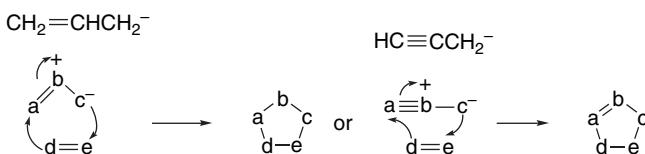
⁴ (a) H. C. Longuet-Higgins and E. W. Abrahamson, *J. Am. Chem. Soc.*, **87**, 2045 (1965); (b) M. J. S. Dewar, *Angew. Chem. Int. Ed. Engl.*, **10**, 761 (1971); M. J. S. Dewar, *The Molecular Orbital Theory of Organic Chemistry*, McGraw-Hill, New York, 1969; (c) H. E. Zimmerman, *Acc. Chem. Res.*, **4**, 272 (1971); (d) K. N. Houk, Y. Li, and J. D. Evanseck, *Angew. Chem. Int. Ed. Engl.*, **31**, 682 (1992).

⁵ O. Wiest, D. C. Montiel, and K. N. Houk, *J. Phys. Chem. A*, **101**, 8378 (1997).

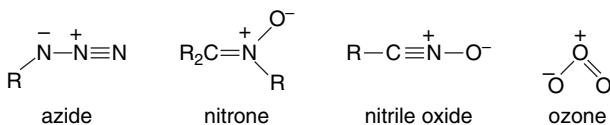
⁶ D. Sperling, H. U. Reissig, and J. Fabian, *Liebigs Ann. Chem.*, 2443 (1997); B. S. Jursic, *Theochem*, **358**, 139 (1995); H.-Y. Yoo and K. N. Houk, *J. Am. Chem. Soc.*, **119**, 2877 (1997); V. Aviente, H. Y. Yoo, and K. N. Houk, *J. Org. Chem.*, **62**, 6121 (1997); K. N. Houk, B. R. Beno, M. Nendal, K. Black, H. Y. Yoo, S. Wilsey, and J. K. Lee, *Theochem*, **398**, 169 (1997); J. E. Carpenter and C. P. Sosa, *Theochem*, **311**, 325 (1994); B. Jursic, *Theochem*, **423**, 189 (1998); V. Brachadell, *Int. J. Quantum Chem.*, **61**, 381 (1997).

The cycloadditions can be characterized by specifying the number of π electrons involved for each species, and for the above three cases, this would be [2 + 2], [2 + 2], and [2 + 4], respectively. Some such reactions occur readily, whereas others are not observed. We will learn, for example, that of the three reactions above, only the alkene-diene cycloaddition occurs readily. The pattern of reactivity can be understood by application of the principle of conservation of orbital symmetry.

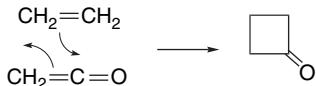
The most important of the concerted cycloaddition reactions is the *Diels-Alder reaction* between a diene and an alkene derivative to form a cyclohexene. The alkene reactant usually has a substituent and is called the *dienophile*. We discuss this reaction in detail in Section 10.2. Another important type of [2 + 4] cycloaddition is *1,3-dipolar cycloaddition*. These reactions involve heteroatomic systems that have four π electrons and are electronically analogous to the allyl or propargyl anions.



Many combinations of atoms are conceivable, among them azides, nitrones, nitrile oxides, and ozone. As these systems have four π electrons, they are analogous to dienes, and cycloadditions with alkenes and alkynes are allowed [4 + 2] reactions. These are discussed in Section 10.3.



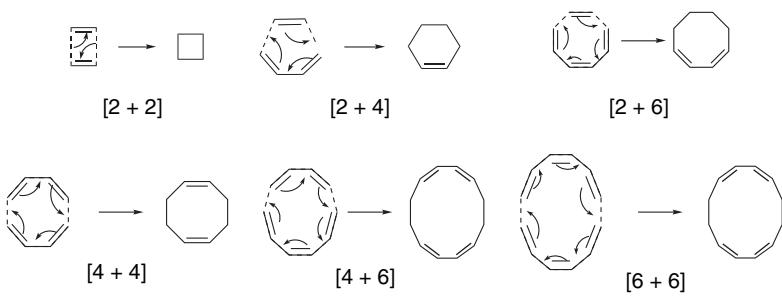
In a few cases [2 + 2] cycloadditions are feasible, particularly with ketenes, and these reactions are dealt with in Section 10.4.



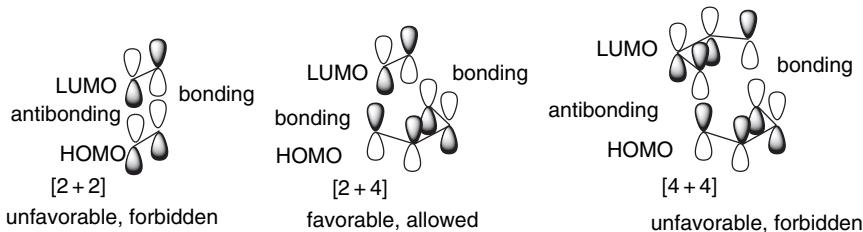
We begin the discussion of concerted cycloaddition reactions by exploring how the orbital symmetry requirements distinguish between reactions that are favorable and those that are unfavorable. Cycloaddition reactions that occur through a pericyclic concerted mechanism can be written as a continuous rearrangement of electrons. If we limit consideration to conjugated systems with from two to six π electrons, the reactions shown in Scheme 10.1 are conceivable.

We recognize immediately that some of these combinations would encounter strain and/or entropic restrictions. However, orbital symmetry considerations provide a fundamental insight into the electronic nature of the cycloaddition reactions and allow us to see that some of the TS structures are electronically favorable, whereas others are not. Woodward and Hoffmann formulated the orbital symmetry principles for cycloaddition reactions in terms of the frontier orbitals. An energetically accessible TS requires overlap of the frontier orbitals to permit smooth formation of the new

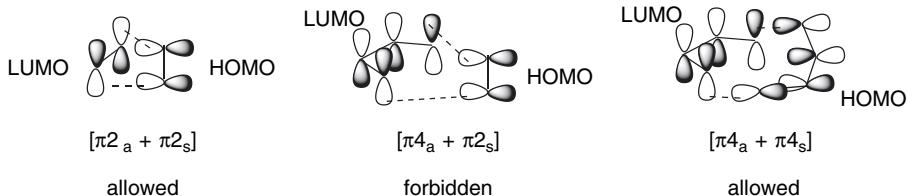
Scheme 10.1. Possible Combinations for Cycloaddition Reactions of Conjugated Polyenes



σ bonds. If it is assumed that the reactants approach one another face-to-face, as would be expected for reactions involving π orbitals, the requirement for bonding interactions between the HOMO and LUMO are met for [2 + 4] but not for [2 + 2] or [4 + 4] cycloadditions. (See Section 1.2 to review the MOs of conjugated systems.) More generally, systems involving $4n + 2 \pi$ electrons are favorable (allowed), whereas systems with $4n \pi$ electrons are not.



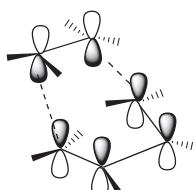
There is another aspect of cycloaddition TS structure that must be considered. It is conceivable that some systems might react through an arrangement with Möbius rather than Hückel topology (see p. 736). Möbius systems can also be achieved by addition to opposite faces of the π system. This mode of addition is called *antarafacial* and the face-to-face addition is called *suprafacial*. In order to specify the topology of cycloaddition reactions, subscripts *s* and *a* are added to the numerical classification. For systems of Möbius topology, as for aromaticity, $4n$ combinations are favored and $4n + 2$ combinations are unfavorable.^{4c}



The generalized Woodward-Hoffmann rules for cycloaddition are summarized below.

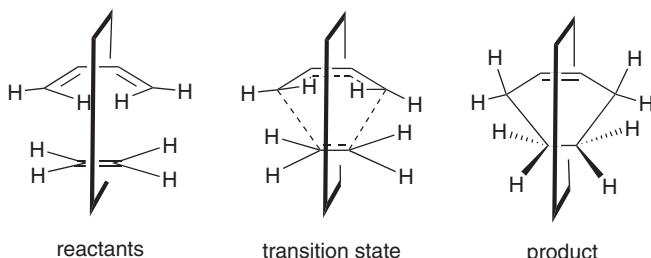
$m + n$	Orbital Symmetry Rules for $m + n$ Cycloaddition		
	Supra/supra	Supra/antara	Antara/antara
$4n$	Forbidden	Allowed	Forbidden
$4n + 2$	Allowed	Forbidden	Allowed

The selection rules for $[\pi 4_s + \pi 2_s]$ and other cycloaddition reactions can also be derived from consideration of the aromaticity of the TS.^{4b,c} In this approach, the basis set p orbitals are aligned to correspond with the orbital overlaps that occur in the TS. The number of nodes in the array of orbitals is counted. If the number is zero or even, the system is classified as a Hückel system. If the number is odd, it is a Möbius system. Just as was the case for ground state molecules (see p. 736), Hückel systems are stabilized with $4n + 2$ electrons, whereas Möbius systems are stabilized with $4n$ electrons. For the $[\pi 4 + \pi 2]$ suprafacial-suprafacial cycloaddition the transition state is aromatic.



Basis set orbitals for *supra, supra* $[\pi 2 + \pi 4]$ cycloaddition. Six electrons, zero nodes: aromatic

The orbital symmetry principles can also be applied by constructing an *orbital correlation diagram*.^{4a} Let us construct a correlation diagram for the addition of butadiene and ethene to give cyclohexene. For concerted addition to occur, the diene must adopt the *s-cis* conformation. Because the electrons that are involved are the π electrons in both the diene and dienophile, the reaction occurs via a face-to-face rather than an edge-to-edge orientation. When this orientation of the reacting complex and TS is adopted, it can be seen that a plane of symmetry perpendicular to the planes of the reacting molecules is maintained during the course of the cycloaddition.



An orbital correlation diagram can be constructed by examining the symmetry of the reactant and product orbitals with respect to this plane, as shown in Figure 10.1. An additional feature must be taken into account in the case of cyclohexene. The cyclohexene orbitals σ_1 , σ_2 , σ_1^* , and σ_2^* are called *symmetry-adapted orbitals*. We might be inclined to think of the σ and σ^* orbitals as being localized between specific pairs of carbon atoms, but this is not the case for the MO treatment because localized

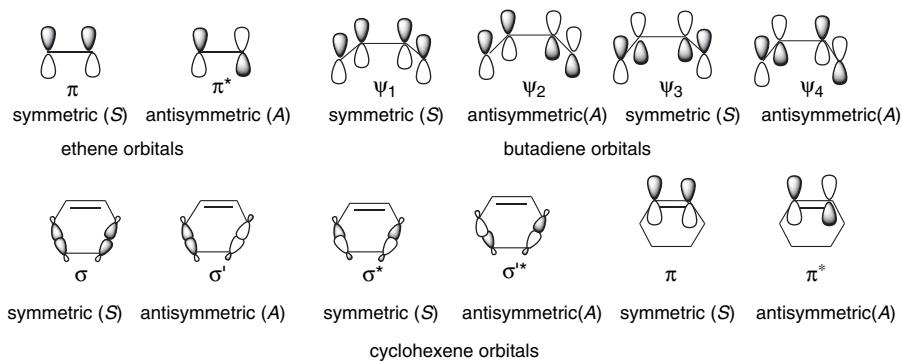


Fig. 10.1. Symmetry properties of ethene, butadiene, and cyclohexene orbitals with respect to a plane bisecting the reacting system.

orbitals would fail the test of being either symmetric or antisymmetric with respect to the plane of symmetry (see p. 37). In the construction of orbital correlation diagrams, *all* of the orbitals involved must be either symmetric or antisymmetric with respect to the element of symmetry being considered.

When the orbitals have been classified with respect to symmetry, they are arranged according to energy and the correlation lines are drawn as in Figure 10.2. From the orbital correlation diagram, it can be concluded that the thermal concerted cycloaddition reaction between butadiene and ethylene is allowed. All bonding levels of the reactants correlate with product ground state orbitals. Extension of orbital correlation analysis to cycloaddition reactions with other numbers of π electrons leads to the conclusion that suprafacial-suprafacial addition is allowed for systems with $[4n + 2]$ π electrons but forbidden for systems with $4n$ π electrons.

The frontier orbital analysis, basis set orbital aromaticity, and orbital correlation diagrams can be applied to a particular TS geometry to determine if the reaction is symmetry allowed. These three methods of examining TS orbital symmetry are equivalent and interchangeable. The orbital symmetry rules can be generalized from conjugated polyenes to any type of conjugated π system. Conjugated anions and cations such as allylic and pentadienyl systems fall within the scope of the rules. The orbital symmetry considerations can also be extended to isoelectronic systems

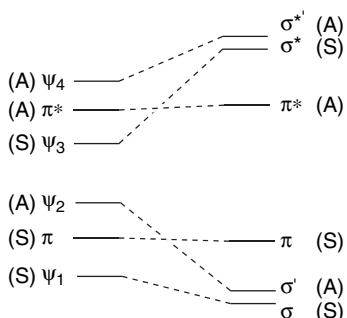
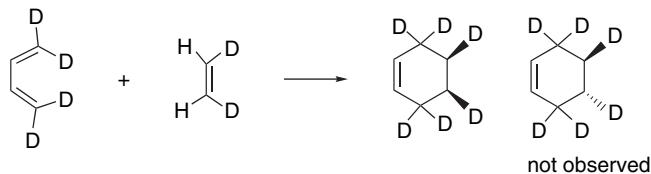


Fig. 10.2. Orbital symmetry correlation diagram for $[\pi_{2s} + \pi_{4s}]$ cycloaddition of ethene and 1,3-butadiene.

10.2. The Diels-Alder Reaction

10.2.1. Stereochemistry of the Diels-Alder Reaction

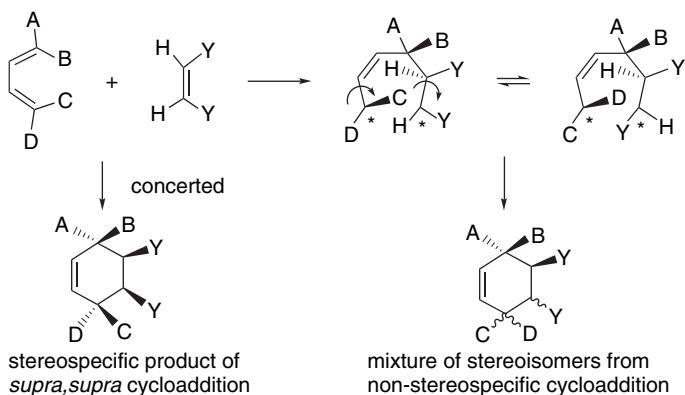
The $[\pi 4_s + \pi 2_s]$ cycloaddition of alkenes and dienes is a very useful method for forming substituted cyclohexenes. This reaction is known as the Diels-Alder (abbreviated D-A in this chapter) reaction.⁷ The transition structure for a concerted reaction requires that the diene adopt the *s-cis* conformation. The diene and substituted alkene (called the *dienophile*) approach each other in approximately parallel planes. This reaction has been the object of extensive mechanistic and computational study, as well as synthetic application. For most systems, the reactivity pattern, regioselectivity, and stereoselectivity are consistent with a concerted process. In particular, the reaction is a stereospecific *syn* (suprafacial) addition with respect to both the alkene and the diene. This stereospecificity has been demonstrated with many substituted dienes and alkenes and also holds for the simplest possible example of the reaction, ethene with butadiene, as demonstrated by isotopic labeling.⁸



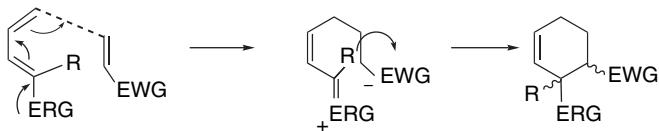
The issue of the concertedness of the D-A reaction has been studied and debated extensively. It has been argued that there might be an intermediate that is diradical in character.⁹ D-A reactions are almost always stereospecific, which implies that if an intermediate exists, it cannot have a lifetime sufficient to permit rotation or inversion. The prevailing opinion is that the majority of D-A reactions are concerted reactions and most theoretical analyses agree with this view.¹⁰ It is recognized that in reactions between unsymmetrical alkenes and dienes, bond formation might be more advanced at one pair of termini than at the other. This is described as being an *asynchronous*

7. L. W. Butz and A. W. Rytina, *Org. React.*, **5**, 136 (1949); M. C. Kloetzel, *Org. React.*, **4**, 1 (1948); A. Wasserman, *Diels-Alder Reactions*, Elsevier, New York (1965); R. Huisgen, R. Grashey, and J. Sauer, in *Chemistry of Alkenes*, S. Patai, ed., Interscience, New York, 1964, pp. 878–928; J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961); J. Hamer, ed., *1,4-Cycloaddition Reactions: The Diels-Alder Reaction in Heterocyclic Syntheses*, Academic Press, New York, 1967; J. Sauer and R. Sustmann, *Angew. Chem. Int. Ed. Engl.*, **19**, 779 (1980); R. Gleiter and M. C. Boehm, *Pure Appl. Chem.*, **55**, 237 (1983); R. Gleiter and M. C. Boehm, in *Stereochemistry and Reactivity of Systems Containing π Electrons*, W. H. Watson, ed., Verlag Chemie, Deerfield Beach, FL, 1983; F. Fringuelli and A. Taticchi, *The Diels-Alder Reaction: Selected Practical Methods*, Wiley, Chichester, 2002.
8. K. N. Houk, Y.-T. Lin, and F. K. Brown, *J. Am. Chem. Soc.*, **108**, 554 (1986).
9. M. J. S. Dewar, S. Olivella, and J. P. Stewart, *J. Am. Chem. Soc.*, **108**, 5771 (1986).
10. J. J. Gajewski, K. B. Peterson, and J. R. Kagel, *J. Am. Chem. Soc.*, **109**, 5545 (1987); K. N. Houk, Y.-T. Lin, and F. K. Brown, *J. Am. Chem. Soc.*, **108**, 554 (1986); E. Goldstein, B. Beno, and K. N. Houk, *J. Am. Chem. Soc.*, **118**, 6036 (1996); V. Branchadell, *Int. J. Quantum Chem.*, **61**, 381 (1997).

process. Loss of stereospecificity is expected only if there is an intermediate in which one bond is formed and the other is not, permitting rotation or inversion at the unbound termini.

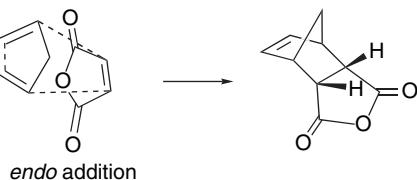


Loss of stereospecificity is observed when ionic intermediates are involved. This occurs when the reactants are of very different electronic character, with one being strongly electrophilic and the other strongly nucleophilic. Usually more than one substituent of each type is required for the ionic mechanism to occur.



For a substituted dienophile, there are two possible stereochemical orientations with respect to the diene. In the *endo* TS the reference substituent on the dienophile is oriented toward the π orbitals of the diene. In the *exo* TS the substituent is oriented away from the π system. The two possible orientations are called *endo* and *exo*, as illustrated in Figure 10.3.

For many substituted butadiene derivatives, the two TSs lead to two different stereoisomeric products. The *endo* mode of addition is usually preferred when an EWG substituent such as a carbonyl group is present on the dienophile. This preference is called the *Alder rule*. Frequently a mixture of both stereoisomers is formed and sometimes the *exo* product predominates, but the Alder rule is a useful initial guide to prediction of the stereochemistry of a D-A reaction. The *endo* product is often the more sterically congested. For example, the addition of dienophiles to cyclopentadiene usually favors the *endo*-stereoisomer, even though this is the sterically more congested product.



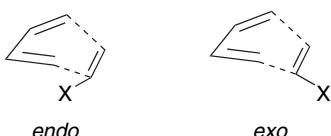
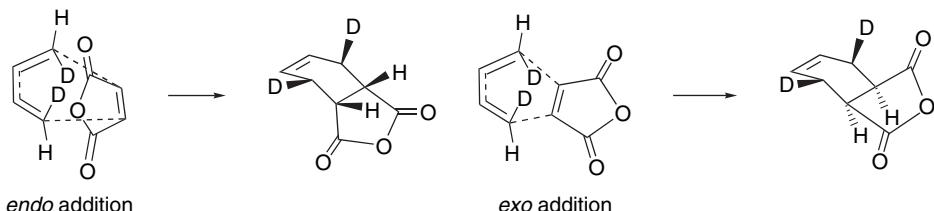
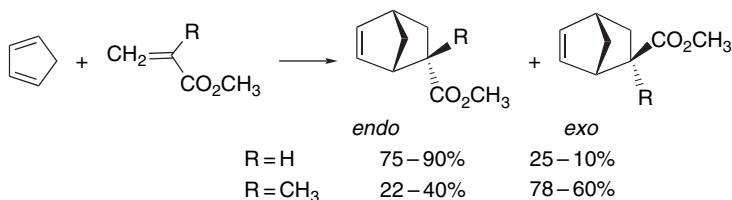


Fig. 10.3. *Exo* and *endo* transition structures for the Diels-Alder reaction.

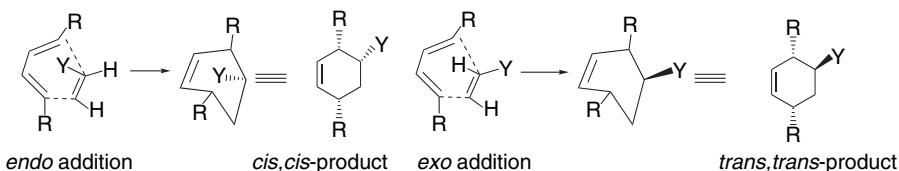
The preference for the *endo* mode of addition is not restricted to cyclic dienes such as cyclopentadiene. By using deuterium labels it has been shown that in the addition of 1,3-butadiene and maleic anhydride, 85% of the product arises from the *endo* TS.¹¹



The stereoselectivity predicted by the Alder rule is independent of the requirement for suprafacial-suprafacial cycloaddition because both the *endo* and *exo* TSs meet this requirement. There are many exceptions to the Alder rule and in most cases the preference for the *endo* isomer is relatively modest. For example, although cyclopentadiene reacts with methyl acrylate in decalin solution to give mainly the *endo* adduct (75%), the ratio is solvent sensitive and ranges up to 90% *endo* in methanol. When a methyl substituent is added to the dienophile (methyl methacrylate) the *exo* product predominates.¹²



Stereochemical predictions based on the Alder rule are made by aligning the diene and dienophile in such a way that the unsaturated substituent on the dienophile overlaps the diene π system.



There are probably several factors that contribute to determining the *endo:exo* ratio in any specific case, including steric effects, electrostatic interactions, and London

¹¹. L. M. Stephenson, D. E. Smith, and S. P. Current, *J. Org. Chem.*, **47**, 4170 (1982).

¹². J. A. Berson, Z. Hamlet, and W. A. Mueller, *J. Am. Chem. Soc.*, **84**, 297 (1962).

dispersion forces.¹³ Molecular orbital interpretations emphasize *secondary orbital interactions* between the π orbitals on the dienophile substituent(s) and the developing π bond between C(2) and C(3) of the diene.

D-A cycloadditions are sensitive to steric effects. Bulky substituents on the dienophile or on the termini of the diene can hinder the approach of the two components to each other and decrease the rate of reaction. This effect can be seen in the relative reactivity of 1-substituted butadienes toward maleic anhydride.¹⁴

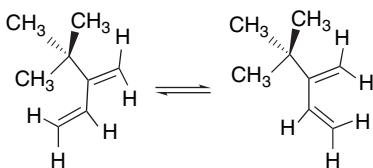
	R	$k_{\text{rel}} (25^\circ \text{C})$
	H	1
	CH ₃	4.2
	C(CH ₃) ₃	<0.05

Substitution of hydrogen by methyl results in a slight rate *increase* as a result of the electron-releasing effect of the methyl group. A *t*-butyl substituent produces a large rate *decrease* because the steric effect is dominant.

Another type of steric effect has to do with interactions between diene substituents. Adoption of the *s-cis* conformation of the diene in the TS brings the *cis*-oriented 1- and 4-substituents on diene close together. *trans*-1,3-Pentadiene is 10³ times more reactive than 4-methyl-1,3-pentadiene toward the very reactive dienophile tetracyanoethene, owing to the unfavorable steric interaction between the additional methyl substituent and the C(1) hydrogen in the *s-cis* conformation.¹⁵

	R	k_{rel}
	H	1
	CH ₃	10 ⁻³

Relatively small substituents at C(2) and C(3) of the diene exert little steric influence on the rate of D-A addition. 2,3-Dimethylbutadiene reacts with maleic anhydride about ten times faster than butadiene because of the electron-releasing effect of the methyl groups. 2-*t*-Butyl-1,3-butadiene is 27 times more reactive than butadiene. The *t*-butyl substituent favors the *s-cis* conformation because of the steric repulsions in the *s-trans* conformation.



¹³. Y. Kobuke, T. Sugimoto, J. Furukawa, and T. Funco, *J. Am. Chem. Soc.*, **94**, 3633 (1972); K. L. Williamson and Y.-F. L. Hsu, *J. Am. Chem. Soc.*, **92**, 7385 (1970).

¹⁴. D. Craig, J. J. Shipman, and R. B. Fowler, *J. Am. Chem. Soc.*, **83**, 2885 (1961).

¹⁵. C. A. Stewart, Jr., *J. Org. Chem.*, **28**, 3320 (1963).

The presence of a *t*-butyl substituent on *both* C(2) and C(3), however, prevents attainment of the *s-cis* conformation, and D-A reactions of 2,3-di-(*t*-butyl)-1,3-butadiene have not been observed.¹⁶

10.2.2. Substituent Effects on Reactivity, Regioselectivity and Stereochemistry

There is a strong electronic substituent effect on the D-A cycloaddition. It has long been known that the reaction is particularly efficient and rapid when the dienophile contains one or more EWG and is favored still more if the diene also contains an ERG. Thus, among the most reactive dienophiles are quinones, maleic anhydride, and nitroalkenes. α,β -Unsaturated esters, ketones, and nitriles are also effective dienophiles. The D-A reaction between unfunctionalized alkenes and dienes is quite slow. For example, the reaction of cyclopentadiene and ethene occurs at around 200°C.¹⁷ These substituent effects are illustrated by the data in Table 10.1. In the case of the diene, reactivity is increased by ERG substituents. Data for some dienes are given in Table 10.2. Note that ERG substituents at C(1) have a larger effect than those at C(2). Scheme 10.2 gives some representative examples of dienophiles activated by EWG substitution.

It is significant that if an electron-poor diene is utilized, the preference is reversed and electron-rich alkenes, such as vinyl ethers and enamines, are the best dienophiles. Such reactions are called *inverse electron demand Diels-Alder reactions*, and the reactivity relationships are readily understood in terms of frontier orbital theory. Electron-rich dienes have high-energy HOMOs that interact strongly with the LUMOs of electron-poor dienophiles. When the substituent pattern is reversed and the diene is electron poor, the strongest interaction is between the dienophile HOMO and the diene LUMO. The FMO approach correctly predicts both the relative reactivity and regioselectivity of the D-A reaction for a wide range of diene-dienophile combinations.

Table 10.1. Relative Reactivity toward Cyclopentadiene in the Diels-Alder Reaction

Dienophile	Relative rate ^a
Tetracyanoethene	43,000,000
1,1-Dicyanoethene	450,000
Maleic anhydride	56,000
<i>p</i> -Benzoquinone	9,000
Z-1,2-Dicyanoethene	91
<i>E</i> -1,2-Dicyanoethene	81
Dimethyl fumarate	74
Dimethyl maleate	0.6
Methyl acrylate	1.2
Cyanoethene	1.0

a. From second-order rate constants in dioxane at 20°C, as reported by J. Sauer, H. Wiest, and A. Mielert, *Chem. Ber.*, **97**, 3183 (1964).

¹⁶. H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, **58**, 643 (1939).

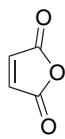
¹⁷. J. Meinwald and N. J. Hudak, *Org. Synth.*, **IV**, 738 (1963).

Scheme 10.2. Representative Electrophilic Dienophiles

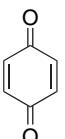
CHAPTER 10

Concerted Pericyclic Reactions

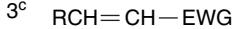
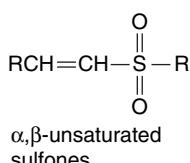
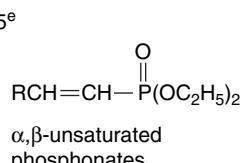
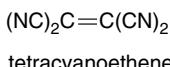
A. Substituted Alkenes.

^{1^a}

Maleic anhydride

^{1^b}

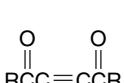
Benzoquinone

^{3^c} $\text{EWG} = \text{CH}=\text{O}, \text{RC}=\text{O}$ $\text{CO}_2\text{R}, \text{C}\equiv\text{N}, \text{NO}_2$ α,β -unsaturated aldehydes, ketones, esters, nitriles and nitro compounds^{4^d}^{5^e}^{6^f}

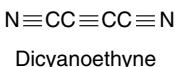
B. Substituted Alkynes

^{7^g}

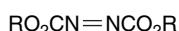
Esters of acetylene-dicarboxylic acid

^{8^h}

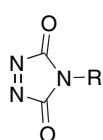
Dibenzoyl-acetylene

^{9ⁱ}

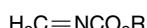
C. Heteroatomic dienophiles

^{10^j}

Esters of azodicarboxylic acids

^{11^k}

N-substituted 1,2,4-triazoline-3,5-diones

^{12^l}

iminocarbonates

a. M. C. Kloetzel, *Org. React.*, **4**, 1 (1948).b. L. W. Butz and A. W. Rytina, *Org. React.*, **5**, 136 (1949).c. H. L. Holmes, *Org. React.*, **4**, 60 (1948).d. J. C. Phillips and M. Oku, *J. Org. Chem.*, **37**, 4479 (1972).e. W. M. Daniewski and C. E. Griffin, *J. Org. Chem.*, **31**, 3236 (1966).f. E. Ciganek, W. J. Linn, and O. W. Webster, *The Chemistry of the Cyano Group*, Z. Rappoport, ed., John Wiley & Sons, New York, 1970, pp. 423–638.g. J. Sauer, H. Wiest, and A. Mieler, *Chem. Ber.*, **97**, 3183 (1964).h. J. D. White, M. E. Mann, H. D. Kirshenbaum, and A. Mitra, *J. Org. Chem.*, **36**, 1048 (1971).i. C. D. Weis, *J. Org. Chem.*, **28**, 74 (1963).j. B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **28**, 3177 (1963).k. B. T. Gillis and J. D. Hagarty, *J. Org. Chem.*, **32**, 330 (1967).l. M. P. Cava, C. K. Wilkins, Jr., D. R. Dalton, and K. Bessho, *J. Org. Chem.*, **30**, 3772 (1965); G. Krow, R. Rodebaugh, R. Carmosin, W. Figures, H. Panella, G. De Vicaris, and M. Grippi, *J. Am. Chem. Soc.*, **95**, 5273 (1973).

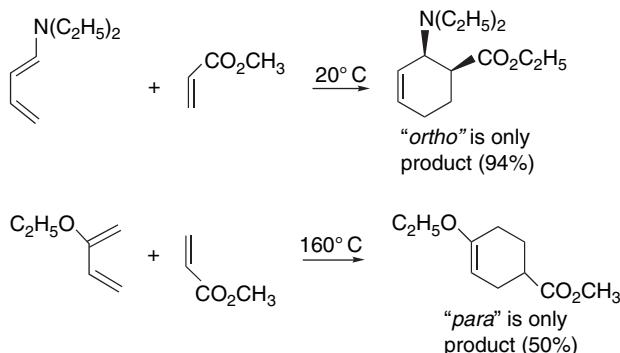
The question of regioselectivity arises when both the diene and alkene are unsymmetrically substituted. Generally, there is a preference for the “*ortho*” and “*para*” orientations, respectively, as in the examples shown.¹⁸

¹⁸. J. Sauer, *Angew. Chem. Int. Ed. Engl.*, **6**, 16 (1967).

Table 10.2. Relative Reactivity of Some Substituted Butadienes in the Diels-Alder Reaction^a

Diene Substituents	Tetracyanoethene	Dienophile	Maleic anhydride
None	1		1
1-Methyl	103		3.3
2-Methyl	45		2.3
1,4-Dimethyl	1,660		
1-Phenyl	385		1.65
2-Phenyl	191		8.8
1-Methoxy	50,900		12.4
2-Methoxy	1,750		
1,4-Dimethoxy	49,800		
Cyclopentadiene	2,100,000		1,350

a. C. Rücker, D. Lang, J. Sauer, H. Friege, and R. Sustmann, *Chem. Ber.*, **113**, 1663 (1980).



The regioselectivity of the D-A reaction is determined by the nature of the substituents on the diene and dienophile. FMO theory has been applied by calculating the energy and orbital coefficients of the frontier orbitals.¹⁹ When the dienophile bears an EWG and the diene an ERG, the strongest interaction is between the HOMO of the diene and the LUMO of the dienophile, as indicated in Figure 10.4. The reactants are preferentially oriented with the carbons having the highest coefficients of the two frontier orbitals aligned for bonding. Scheme 10.3 shows the preferred regiochemistry for various substitution patterns. The combination of an electron donor in the diene and an electron acceptor in the dienophile gives rise to cases **A** and **B**. Inverse electron demand D-A reactions give rise to combinations **C** and **D**. In reactions of types **A** and **B**, the frontier orbitals will be the diene HOMO and the dienophile LUMO. The strongest interaction is between ψ_2 and π^* because the donor substituent on the diene raises the diene orbitals in energy, whereas the acceptor substituent lowers the dienophile orbitals. In reaction types **C** and **D**, the pairing of the diene LUMO and dienophile HOMO is the strongest interaction.

The regiochemical relationships summarized in Scheme 10.3 can be understood by considering the atomic coefficients of the frontier orbitals. Figure 10.5 gives the approximate energies and orbital coefficients for the various classes of dienes and dienophiles. 1-ERG substituents (X:) raise the HOMO level and increase the coefficient

¹⁹. K. N. Houk, *J. Am. Chem. Soc.*, **95**, 4092 (1973).

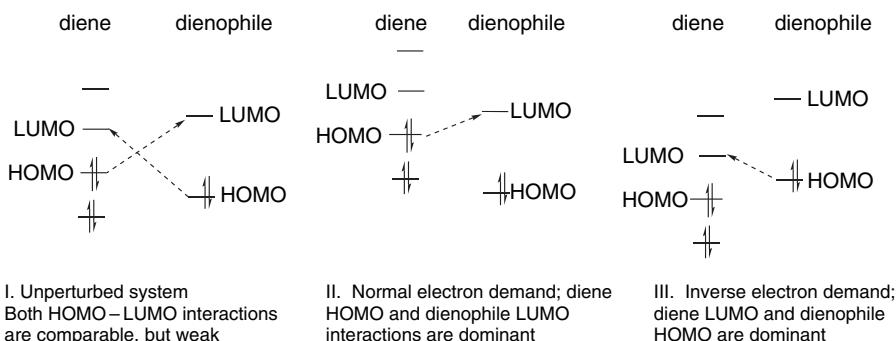
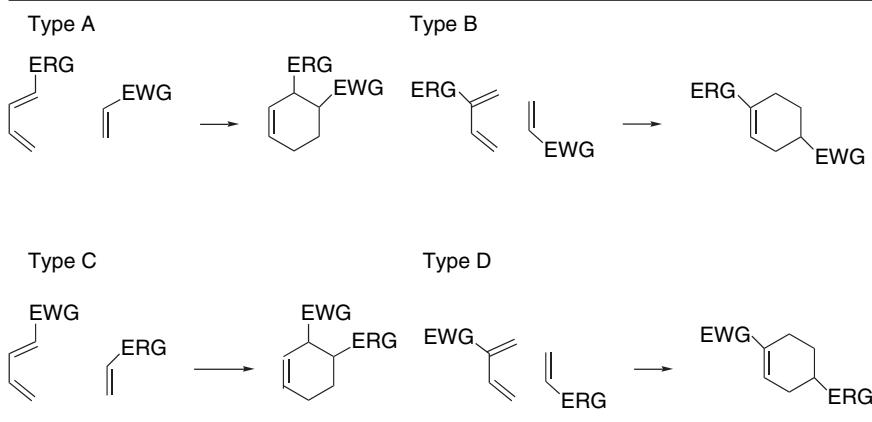


Fig. 10.4. Frontier orbital interactions in Diels-Alder reactions.

on C(4) of the diene. 2-ERG substituents raise the HOMO and result in the largest HOMO coefficient at C(1). For EWG substituents, the HOMO and LUMO are lowered in energy. For dienophiles, the largest LUMO coefficient is at C(2).

The regiochemistry can be predicted by the generalization that the strongest interaction is between the centers on the frontier orbitals having the largest orbital coefficients. For dienophiles with EWG substituents, π^* has its largest coefficient on the β -carbon atom. For dienes with ERG substituents at C(1) of the diene, the HOMO has its largest coefficient at C(4). This is the case designated A in Scheme 10.3, and is the observed regiochemistry for the type A Diels-Alder addition. A similar analysis of each of the other combinations in Scheme 10.3 using the orbitals in Figure 10.5 leads to the prediction of the favored regiochemistry. Note that in the type A and C reactions this leads to preferential formation of the more sterically congested 1,2-disubstituted cyclohexene. The predictive capacity of these frontier orbital relationships for D-A reactions is excellent.²⁰

Scheme 10.3. Regioselectivity of the Diels-Alder Reaction



²⁰ For discussion of the development and application of frontier orbital concepts in cycloaddition reactions, see K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975); K. N. Houk, *Topics Current Chem.*, **79**, 1 (1979); R. Sustmann and R. Schubert, *Angew. Chem. Int. Ed. Engl.*, **11**, 840 (1972); J. Sauer and R. Sustmann, *Angew. Chem. Int. Ed. Engl.*, **19**, 779 (1980).

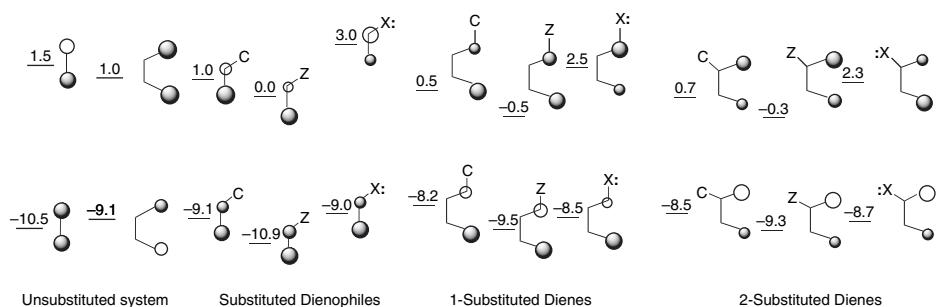


Fig. 10.5. Coefficients and relative energies of dienophile and diene frontier MOs. Orbital energies are given in eV. The sizes of the circles give a relative indication of the orbital coefficient. Z stands for a conjugated EWG, e.g., $\text{C}\equiv\text{O}$, $\text{C}\equiv\text{N}$, NO_2 ; C is a conjugated substituent without strong electronic effect, e.g., phenyl, vinyl; X is a conjugated ERG, e.g., OCH_3 , NH_2 . From *J. Am. Chem. Soc.*, **95**, 4092 (1973).

From these ideas, we see that for substituted dienes and dienophiles there is *charge transfer* in the process of formation of the TS. The more electron-rich reactant acts as an electron donor (*nucleophilic*) and the more electron-poor reactant accepts electron density (*electrophilic*). It also seems from the data in Tables 10.1 and 10.2 that reactions are faster, the *greater the extent of charge transfer*. The reactivity of cyclopentadiene increases with the electron-acceptor capacity of the dienophile. Note also that the very strongly electrophilic dienophile, tetracyanoethene, is more sensitive to substituent effects in the diene than the more moderately electrophilic dienophile, maleic anhydride. These relationships can be understood in terms of FMO theory by noting that the electrophile LUMO and nucleophile HOMO are closer in energy the stronger the substituent effect, as illustrated schematically in Figure 10.6.

The FMO considerations are most reliable when one component is clearly more electrophilic and the other more nucleophilic. When a diene with a 2-EWG substituent reacts with an electrophilic dienophile, the major product is the *para* product, even

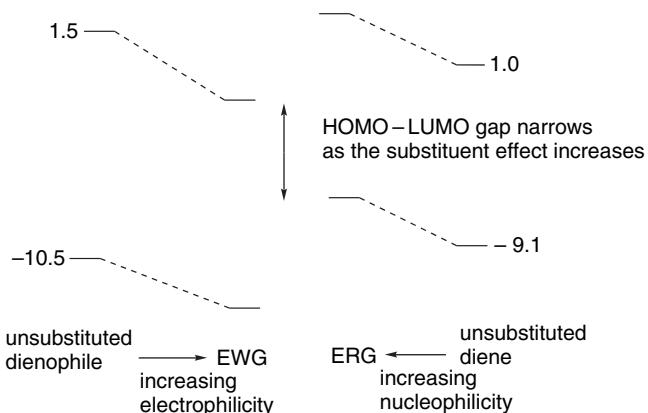
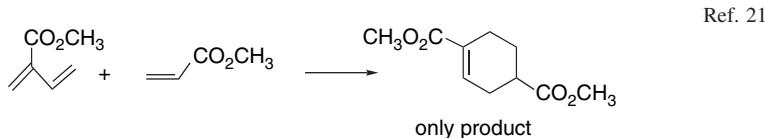
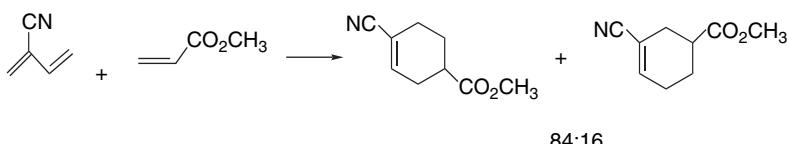


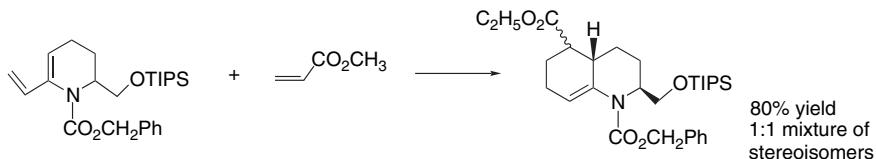
Fig. 10.6. Schematic diagram illustrating substituent effect on reactivity in terms of FMO theory. HOMO-LUMO gap narrows, transition state is stabilized, and reactivity is increased in normal electron-demand Diels-Alder reaction as the nucleophilicity of diene and the electrophilicity of dienophile increase.

though simple resonance consideration would suggest that the *meta* product might be preferred.



Ref. 22

Another case that goes contrary to simple resonance or FMO predictions are reactions of 2-amido-1,3-dienes. The main product has a *meta* rather than a *para* orientation. These reactions also show little *endo:exo* stereoselectivity.

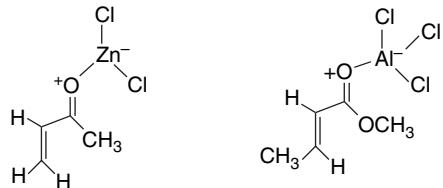


Ref. 23

Thus, there seems to be reason for caution in application of simple resonance or FMO predictions to 2-substituted dienes. We say more about this Topic 10.1.

10.2.3. Catalysis of Diels-Alder Reactions by Lewis Acids

Diels-Alder reactions are catalyzed by many Lewis acids, including SnCl_4 , ZnCl_2 , AlCl_3 , and derivatives of AlCl_3 such as $(\text{CH}_3)_2\text{AlCl}$ and $(\text{C}_2\text{H}_5)_2\text{AlCl}$.²⁴ A variety of other Lewis acids are effective catalysts. The types of dienophiles that are subject to catalysis are typically those with carbonyl substituents. Lewis acids form complexes at the carbonyl oxygen and this increases the electron-withdrawing capacity of the carbonyl group. The basic features are well modeled by HF/3-21G level computations on the TS structures.²⁵



²¹. T. Inukai and T. Kojima, *J. Org. Chem.*, **36**, 924 (1971).

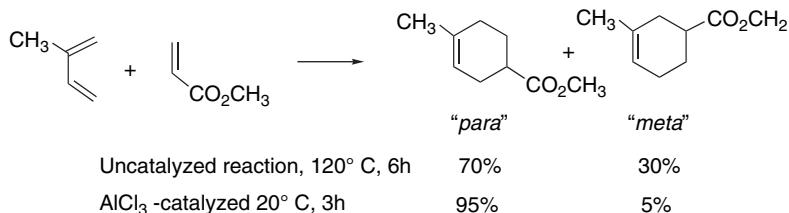
²². C. Spino, J. Crawford, Y. Cui, and M. Gugelchuk, *J. Chem. Soc., Perkin Trans. 2*, 1499 (1998).

²³. J. D. Ha, C. H. Kang, K. A. Belmore, and J. K. Cha, *J. Org. Chem.*, **63**, 3810 (1998).

²⁴. P. Laszlo and J. Lucche, *Actual. Chim.*, 42 (1984).

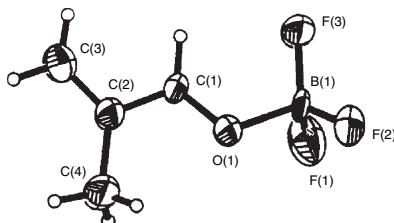
²⁵. D. M. Birney and K. N. Houk, *J. Am. Chem. Soc.*, **112**, 4127 (1990); M. I. Menendez, J. Gonzalez, J. A. Sordo, and T. L. Sordo, *Theochem*, **120**, 241 (1994).

This complexation accentuates both the energy and orbital distortion effects of the substituent and enhances both the reactivity and selectivity of the dienophile relative to the uncomplexed compound.²⁶ Usually, both regioselectivity and *exo,endo* stereoselectivity increase. Part of this may be due to the lower reaction temperature. However, the catalysts also shift the reaction toward a higher degree of charge transfer by making the EWG substituent more electrophilic.

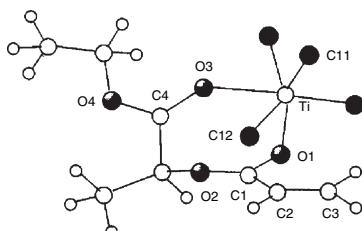


Ref. 27

The stereoselectivity of any particular D-A reaction depends on the details of the TS structure. The structures of several enone-Lewis acid complexes have been determined by X-ray crystallography.²⁸ The site of complexation is the carbonyl oxygen, which maintains a trigonal geometry, but with somewhat expanded angles (130°–140°). The Lewis acid is normally *anti* to the larger carbonyl substituent. Boron trifluoride complexes are tetrahedral, but Sn(IV) and Ti(IV) complexes can be trigonal bipyramidal or octahedral. The structure of the 2-methylpropenal-BF₃ complex is illustrative.²⁹



Chelation can favor a particular structure. For example, *O*-acryloyl lactates adopt a chelated structure with TiCl₄.³⁰



²⁶ K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, **95**, 4094 (1973).

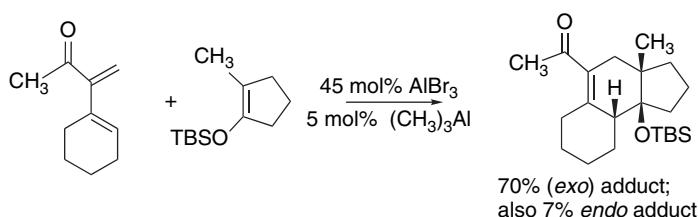
²⁷ T. Inukai and T. Kojima, *J. Org. Chem.*, **31**, 1121 (1966).

²⁸ S. Shambayati, W. E. Crowe, and S. L. Schreiber, *Angew. Chem. Int. Ed. Engl.*, **29**, 256 (1990).

²⁹ E. J. Corey, T.-P. Loh, S. Sarshar, and M. Azimioara, *Tetrahedron Lett.*, **33**, 6945 (1992).

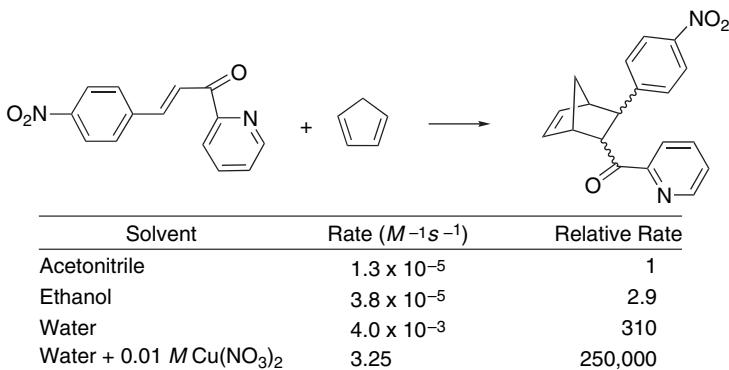
³⁰ T. Poll, J. O. Metter, and G. Helmchen, *Angew. Chem. Int. Ed. Engl.*, **24**, 112 (1985).

Lewis acid catalysis can also be applied to inverse electron demand D-A reactions, but with the proviso that the strongest interaction must be with the diene in this case.



Ref. 31

Metal cations can catalyze reactions of certain dienophiles. For example, Cu^{2+} strongly catalyzes addition reactions of 2-pyridyl styryl ketones, presumably through a chelate.³² DFT (B3LYP/6-31G*) computations indicate that this reaction shifts to a stepwise ionic mechanism in the presence of the Lewis acid.³³



The solvent also has an important effect on the rate of D-A reactions. The traditional solvents were nonpolar organic solvents such as aromatic hydrocarbons. However, water and other highly polar solvents, such as ethylene glycol and formamide, accelerate a number of D-A reactions.³⁴ The accelerating effect of water is attributed to “enforced hydrophobic interactions.”³⁵ That is, the strong hydrogen-bonding network in water tends to exclude nonpolar solutes and forces them together, resulting in higher effective concentrations. There may also be specific stabilization of the developing TS.³⁶ For example, hydrogen bonding with the TS can contribute to the rate acceleration.³⁷

- ³¹. M. E. Jung and P. Davidov, *Angew. Chem. Int. Ed. Engl.*, **41**, 4125 (2002).
- ³². S. Otto and J. B. F. N. Engberts, *Tetrahedron Lett.*, **36**, 2645 (1995).
- ³³. L. R. Domingo, J. Andres, and C. N. Alves, *Eur. J. Org. Chem.*, 2557 (2002).
- ³⁴. D. Rideout and R. Breslow, *J. Am. Chem. Soc.*, **102**, 7816 (1980); R. Breslow and T. Guo, *J. Am. Chem. Soc.*, **110**, 5613 (1988); T. Dunams, W. Hoekstra, M. Pentaleri, and D. Liotta, *Tetrahedron Lett.*, **29**, 3745 (1988).
- ³⁵. S. Otto and J. B. F. N. Engberts, *Pure Appl. Chem.*, **72**, 1365 (2000).
- ³⁶. R. Breslow and C. J. Rizzo, *J. Am. Chem. Soc.*, **113**, 4340 (1991).
- ³⁷. W. Blokzijl, M. J. Blandamer, and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **113**, 4241 (1991); W. Blokzijl and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **114**, 5440 (1992); S. Otto, W. Blokzijl, and J. B. F. N. Engberts, *J. Org. Chem.*, **59**, 5372 (1994); A. Meijer, S. Otto, and J. B. F. N. Engberts, *J. Org. Chem.*, **65**, 8989 (1998); S. Kong and J. D. Evanseck, *J. Am. Chem. Soc.*, **122**, 10418 (2000).

The idea of complementary electronic interactions between the diene and dienophile provides a reliable qualitative guide to the regio- and stereoselectivity of the D-A reaction. Structural and substituent effects can be explored in more detail by computational analysis of TS structure and energy. Comparison of the relative energy of competing TSs allows prediction and interpretation of the course of the reaction. Ab initio HF calculations often can be relied on to give the correct order of isomeric TS structures. Accurate E_a estimates require a fairly high-level treatment of electron correlation. Reliable results have been achieved with B3LYP/6-31G*, MP3/6-31G*, and CCSD(T)/6-31G* computations.³⁸ These calculations permit prediction and interpretation of relative reactivity and regio- and stereoselectivity by comparison of competing TSs. There are other aspects of TS character that can be explored, including the degree of asynchronicity in bond formation and the nature of the electronic reorganization within the TS. Kinetic isotope effects can be calculated from the TS and provide a means of validation of TS characteristics by comparison with experimental results.³⁹

A range of quantum chemical computations were applied to Diels-Alder reactions as the methods were developed. The consensus that emerged is illustrated by typical recent studies.^{25,40} For symmetrical dienes and dienophiles without strong EWG substituents, the reaction is *synchronous*, that is the degree of bond making of the C(1)–C(1') and C(4)–C(2') bonds is the same. As we will see shortly, this does not always seem to be the case for strongly electrophilic dienophiles, even when they are symmetric. The TS displays aromaticity, as indicated by the computed NICS value (see Section 8.1.3),⁴¹ which implies that there is enhanced delocalization of the six electrons that participate in bonding changes. Fradera and co-workers have used the AIM localization and delocalization parameters λ and δ to investigate the electron distribution in the TS for ethene/butadiene cycloaddition.⁴² At the HF/6-31G* level, the delocalization indices are about 0.4 for all the reacting bonds (plus 1.0 for the residual bonds). There is stronger delocalization between the *para* than the *meta* positions. Both of these parameters are very similar to those found for benzene.⁴³ These similarities support the idea that the electronic distribution in the TS for the D-A reaction resembles that of the π system of benzene, an idea that goes back to the 1930s.⁴⁴

^{38.} T. C. Dinadayalane, R. Vijaya, A. Smitha, and G. N. Sastry, *J. Phys. Chem. A*, **106**, 1627 (2002); B. R. Beno, S. Wilsey, and K. N. Houk, *J. Am. Chem. Soc.*, **121**, 4816 (1999).

^{39.} B. R. Beno, K. N. Houk, and D. A. Singleton, *J. Am. Chem. Soc.*, **118**, 9984 (1996); E. Goldstein, B. Beno, and K. N. Houk, *J. Am. Chem. Soc.*, **118**, 6036 (1996).

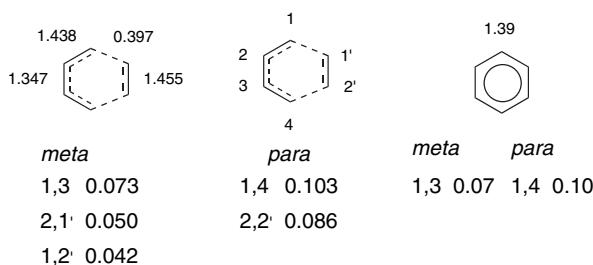
^{40.} S. Sakai, *J. Phys. Chem. A*, **104**, 922 (2000); R. D. J. Froese, J. M. Coxon, S. C. West, and K. Morokuma, *J. Org. Chem.*, **62**, 6991 (1997).

^{41.} H. Jiao and P. v. R. Schleyer, *J. Phys. Org. Chem.*, **11**, 655 (1998).

^{42.} J. Poater, M. Sola, M. Duran, and X. Fradera, *J. Phys. Chem. A*, **105**, 2052 (2001).

^{43.} X. Fradera, M. A. Austen, and R. F. W. Bader, *J. Phys. Chem. A*, **103**, 304 (1999).

^{44.} M. G. Evans, *Trans. Faraday Soc.*, **35**, 824 (1939).



The TS of D-A reactions can also be characterized with respect to *synchronicity*. If both new bonds are formed to the same extent the reaction is synchronous, but if they differ it is asynchronous. Synchronicity has been numerically defined in terms of Wiberg bond order indices.⁴⁵

$$S_y^1 = 1 - \frac{\sum_{i=1}^n |\delta B_i - \delta B_{av}| / \delta B_{av}}{2n - 2} \quad (10.1)$$

where n is the number of bonds directly involved in the reaction, δB_i is the relative variation in the B_i at the TS. The terms δB_i and δB_{av} are defined as follows:

$$\delta B_i = \frac{B_i^{TS} - B_i^R}{B_i^P - B_i^R} \quad (10.2)$$

$$\delta B_{av} = n^{-1} \sum_{i=1}^n \delta B_i \quad (10.3)$$

Computations have also been applied to the analysis of *exo:endo* ratios. The computed differences in energies of the *exo* and *endo* TS are often small and are subject to adjustments when solution models are used.⁴⁶ Cyclopentadiene has been a common subject, since there is more experimental data for this compound than for any other. MP3/6-31G*-level computations were used to compare the *exo* and *endo* TS E_a for the reactions with acrylonitrile and but-2-en-3-one (methyl vinyl ketone), and ZPE and thermal corrections were included in the calculations.⁴⁷ Good qualitative agreement was achieved with the experimental results, which is little stereoselectivity for acrylonitrile and *endo* stereoselectivity for but-3-en-2-one.

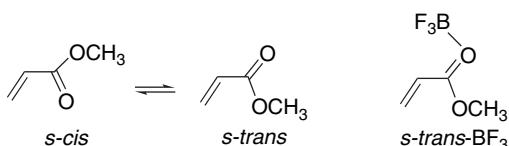
	Acrylonitrile		But-3-en-2-one	
	E_a	ΔG^\ddagger	E_a	G^\ddagger
<i>exo</i>	18.49	31.72	16.16	29.86
<i>endo</i>	18.53	31.69	15.92	29.42
Difference	-0.04	+0.03	+0.24	+0.44

⁴⁵ A. Moyano, M. A. Pericas, and E. Valenti, *J. Org. Chem.*, **54**, 573 (1989); B. Lecea, A. Arrieta, G. Roa, F. P. Ugalde, and F. P. Cossio, *J. Am. Chem. Soc.*, **116**, 9613 (1994).

⁴⁶ M. F. Ruiz-Lopez, X. Assfeld, J. I. Garcia, J. A. Mayoral, and L. Salvatella, *J. Am. Chem. Soc.*, **115**, 8780 (1993).

⁴⁷ W. L. Jorgensen, D. Lim, and J. F. Blake, *J. Am. Chem. Soc.*, **115**, 2936 (1993).

Computational studies have revealed some of the distinctive effects of Lewis acid catalysis on TS structure. MO (HF/6-31G*, MP2/6-31G*) and DFT (B3LYP/6-311+G(2d,p)) calculations have been used to compare the structure and energy of four possible TSs for the D-A reaction of the BF_3 complex of methyl acrylate with 1,3-butadiene. The results are summarized in Figure 10.7. The uncatalyzed reaction favors the *exo-cis* TS by 0.38 kcal/mol over the *endo-cis* TS. For the catalyzed reaction, the *endo* TS with the *s-trans* conformation of the dienophile is preferred to the two *exo* TSs by about 0.8 kcal/mol.⁴⁸ Part of the reason for the shift in preferred TS is the difference in the ground state dienophile conformation. The *s-trans* conformation minimizes repulsions with the BF_3 group. There is also a significant difference in the degree of charge transfer between the uncatalyzed and catalyzed reactions, as reflected by the NPA δ values. The catalyzed reaction has a much larger net transfer of electron density to the dienophile. The catalyzed reactions are less synchronous than the uncatalyzed reactions, as can be seen by comparing the differences in the lengths of the forming bonds.



Relative Transition State Energies					
Uncatalyzed reaction			BF_3 -catalyzed reaction		
	Rel E	NPA δ		Rel E	NPA δ
<i>s-cis</i> Acrylate	0.00	–	<i>s-cis</i> Acrylate- BF_3	1.71	–
<i>s-trans</i> Acrylate	0.65	–	<i>s-trans</i> Acrylate- BF_3	0.00	–
<i>endo-cis</i> TS	0.38	0.005	<i>endo-cis</i> BF_3 TS	2.23	0.276
<i>endo-trans</i> TS	1.65	0.005	<i>endo-trans</i> BF_3 TS	0.00	0.225
<i>exo-cis</i> TS	0.00	0.006	<i>exo-cis</i> BF_3 TS	0.82	0.260
<i>exo-trans</i> TS	1.44	0.006	<i>exo-trans</i> BF_3 TS	0.83	0.216

Visual models, additional information and exercises on the Diels-Alder Reaction can be found in the Digital Resource available at: Springer.com/carey-sundberg.

Similar calculations have been done for propenal.⁴⁹ For the uncatalyzed reaction, the *endo-cis* TS is slightly favored over the *exo-cis*; the two *trans* TSs are more than 1 kcal/mol higher. The order is the same for the catalyzed reaction, but the differences are accentuated. The TSs for the catalyzed reactions are considerably more asynchronous than those for the uncatalyzed reactions. For example, for the reaction of butadiene and acrolein, the asynchronicity was measured as the difference in bond length of the two forming bonds.

$$\Delta d = [\text{C}(1)-\text{C}(1'')] - [\text{C}(4)-\text{C}(2')]$$

⁴⁸. J. I. Garcia, J. A. Mayoral, and L. Salvatella, *Tetrahedron*, **53**, 6057 (1997).

⁴⁹. J. I. Garcia, J. A. Mayoral, and L. Salvatella, *J. Am. Chem. Soc.*, **118**, 11680 (1996); J. I. Garcia, V. Martinez-Merino, J. A. Mayoral, and L. Salvatella, *J. Am. Chem. Soc.*, **120**, 2415 (1998).

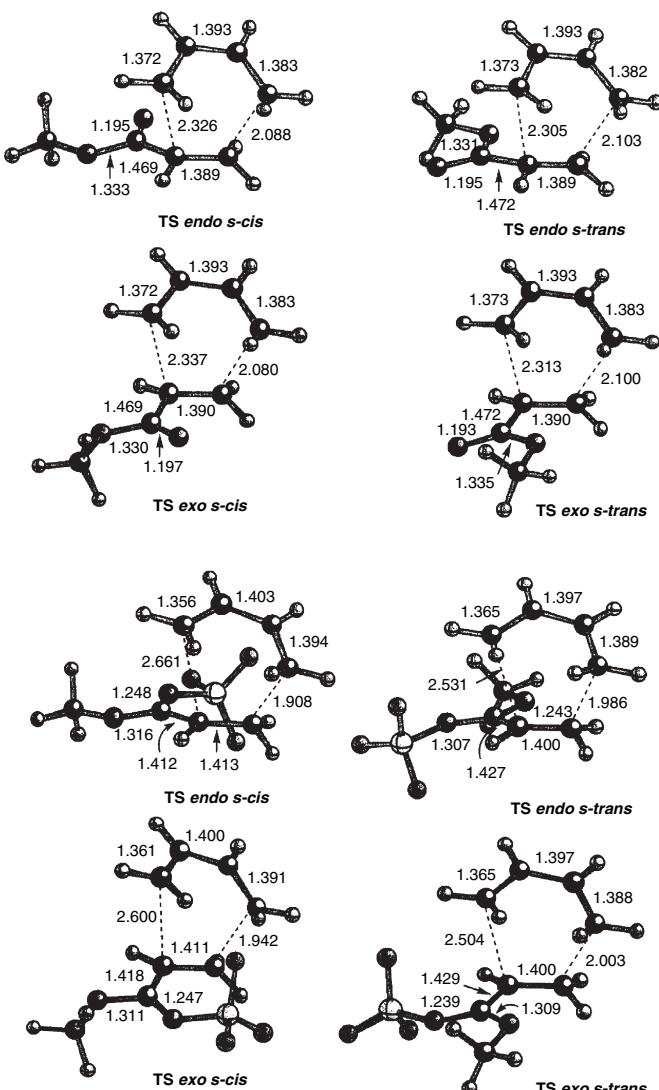


Fig. 10.7. Computed transition structures for uncatalyzed and BF_3 -catalyzed Diels-Alder reaction of 1,3-butadiene with methyl acrylate. Reproduced from *Tetrahedron*, **53**, 6057 (1997), by permission of Elsevier.

The value of Δd increases from 0.617 to 0.894 going from the uncatalyzed to the BF_3 -catalyzed reaction.

Another feature of the catalyzed TS is stronger interaction between the diene and the complexed EWG by a type of secondary orbital interaction. For example, in the butadiene-acrolein/ BH_3 catalytic complex,⁵⁰ there is a quite close approach of diene C(1) to the complexed carbonyl carbon.⁵¹ This aspect of the TS was examined for the BF_3 -catalyzed reaction by comparing the electron density between C(1) and

⁵⁰ D. M. Birney and K. N. Houk, *J. Am. Chem. Soc.*, **112**, 4127 (1990).

⁵¹ D. A. Singleton, *J. Am. Chem. Soc.*, **114**, 6563 (1992).

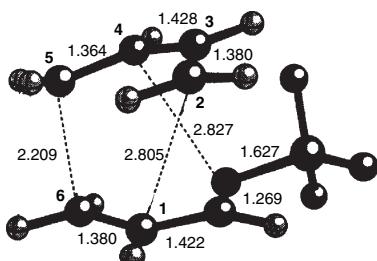
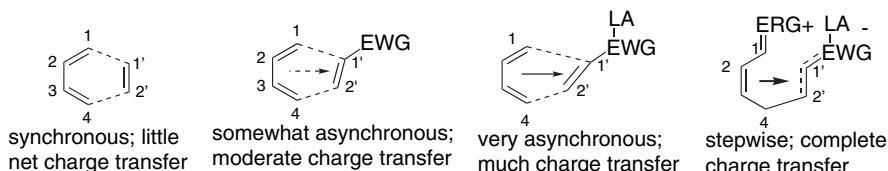


Fig. 10.8. Secondary orbital interaction between carbonyl oxygen and butadiene in BF_3 -catalyzed transition structure. Reproduced from *J. Am. Chem. Soc.*, **120**, 2415 (1998), by permission of the American Chemical Society.

the carbonyl carbon as shown in Figure 10.8. Significant bonding was noted and is represented by the second dashed line in the TS structure.⁴⁹

The extent of this interaction is different in the *endo* and *exo* TSs and contributes to the enhanced *endo* stereoselectivity that is observed in catalyzed reactions. This structural feature is consistent with the catalyzed reaction having more extensive charge transfer, owing to the more electrophilic character of the complexed dienophile. In the limiting case, the reaction can become a stepwise ionic process.



One might expect that a D-A reaction of butadiene with any *symmetrical* dienophile would have a synchronous TS, since the new bonds that are being formed are *identical*. However, that does not seem to be the case, at least for highly electrophilic dienophiles. For example, highly asynchronous TSs are found for maleic acid⁵² and 1,2,4-triazoline, as shown in Figure 10.9.⁵³

There is, however, disagreement in the case of the results for another very reactive dienophile, dimethyl acetylenedicarboxylate. Froese and co-workers also found the TS of cyclopentadiene and dimethyl acetylenedicarboxylate to be unsymmetrical by B3LYP/6-31G computation,⁵⁴ but another group discovered that a symmetrical TS was favored for 1,3-butadiene.⁵⁵ These unsymmetrical TSs seem to reflect the same trend noted in comparing Lewis acid-catalyzed reactions with uncatalyzed reactions.

⁵². D. A. Singleton, B. E. Schulmeier, C. Hang, A. A. Thomas, S.-W. Leung, and S. R. Merrigan, *Tetrahedron*, **57**, 5149 (2001).

⁵³. J. S. Chen, K. N. Houk, and C. S. Foote, *J. Am. Chem. Soc.*, **120**, 12303 (1998).

⁵⁴. R. D. J. Froese, J. M. Coxon, S. C. West, and K. Morokuma, *J. Org. Chem.*, **62**, 6991 (1997).

⁵⁵. L. R. Domingo, M. Arno, R. Contreras, and P. Perez, *J. Phys. Chem. A*, **106**, 952 (2002).

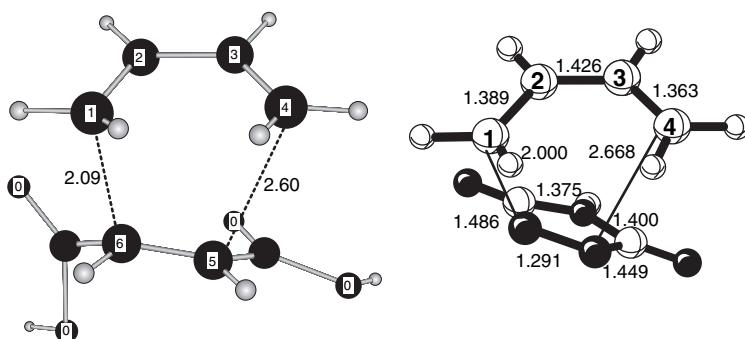
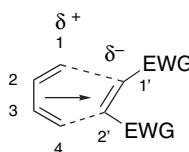
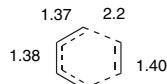


Fig. 10.9. Asynchronous transition structures for Diels-Alder reactions of butadiene with maleic acid and 1,2,4-triazoline using B3LYP/6-31G* calculations. Reproduced from *Tetrahedron*, **57**, 5149 (2001) and *J. Am. Chem. Soc.*, **120**, 12303 (1998), by permission of Elsevier and the American Chemical Society, respectively.

The asynchronous TS results from an increase in the extent of charge transfer, leading to partial ionic character in the TS.



There seems to be another element of asynchronicity associated with bond formation in D-A reactions. The formation of the new double bond and the lengthening of the reacting dienophile bond seem to *run ahead* of the formation of the new σ bonds. For example, in the MP4SDTQ/6-31G* TS for the reaction of butadiene and ethene, the new σ bonds are only 22% formed at the TS. The same picture emerges by following the transformations of the orbitals during the course of the reaction.⁵⁶ The transfer of π -electronic characteristics from the dienophile π bond to the product π bond seems to occur ahead of the reorganization of electrons to form the two new σ bonds.



Visual models, additional information and exercises on the Diels-Alder Reaction can be found in the Digital Resource available at: Springer.com/carey-sundberg.

A wide variety of diene substituents were surveyed using B3LYP/6-31G(*d,p*) calculations to determine the effect on the E_a for D-A addition with ethene.⁵⁷ There was stabilization of the TS by EWG substituents, which was accompanied by a small positive charge (NPA) on ethene. This indicates that the electronic interaction involves

⁵⁶ C. Spino, M. Pesant, and Y. Dory, *Angew. Chem. Int. Ed. Engl.*, **37**, 3262 (1998).

⁵⁷ R. Robiette, J. Marchand-Brynaert, and D. Peeters, *J. Org. Chem.*, **67**, 6823 (2002).

the diene as a net electron acceptor; that is, the reactions are diene LUMO-controlled inverse electron demand reactions. The size of the stabilization and the charge transfer correlated reasonably well with a *combination* of the polar and resonance substituent constants. A polarization effect was also noted in several series. In each instance, the stabilization *increased* with substituent size and polarizability ($\text{F} < \text{Cl} < \text{Br}; \text{CH}_3 < \text{CF}_3 < \text{CCl}_3 < \text{CBr}_3; \text{OCH}_3 < \text{SCH}_3 < \text{SeCH}_3$).

Computation on TS structure may be useful in predicting and interpreting trends in reactivity, regioselectivity, and stereoselectivity. To the extent observed trends are in agreement with the computations, the validity of the TS structure is supported. One experimental measurement that can be directly connected to TS structure is the kinetic isotope effect (review Section 3.5), which can be measured with good experimental accuracy as well as calculated from the TS structure.⁵⁸ Comparisons can be used to examine TS structure at a very fine level of detail. The computed TS for the $(\text{CH}_3)_2\text{AlCl}$ -catalyzed reaction of isoprene with acrolein, ethyl acrylate, and but-3-en-2-one indicated highly asynchronous TSs and gave calculated isotope effects in agreement with experiment.⁵⁹ For example, the study of the $(\text{CH}_3)_2\text{AlCl}$ -catalyzed D-A reaction of isoprene with propenal found good agreement between observed and computed isotope effects, except at one position. A later study located an alternative TS that gave better agreement with the isotope effect at this position.⁶⁰ This structure incorporates a formyl H bond, as postulated in other Lewis acid-catalyzed reactions of aldehydes.⁶¹ Although this structure was computed to be slightly higher in energy, it was favored when a PCM solvent model was used. The TSs are shown in Figure 10.10.

Several studies have looked at the TS of D-A reactions in which the extent of aromaticity increases or decreases in going from reactants to products. For example, aromaticity is enhanced with *o*-quinodimethanes, where a new benzene ring is formed. The benzo[c] fused heterocycles contain an *o*-quinoid structure. The aromaticity of the heterocyclic ring is lost, but a new benzenoid ring is formed by cycloaddition. When polycyclic aromatic compounds undergo D-A reactions, the aromaticity of the reacting central ring is lost, but the peripheral rings have increased aromaticity per carbon.

Calculated E_a 's in several cases are in accord with the experimental trends.⁶² Quinodimethanes are more reactive than benzo[c]heterocycles and the reactivity of the linear polycyclic hydrocarbons increases with the number of rings. The changes in the NICS values for the rings is consistent with the changing aromaticity. In the case of polycyclic hydrocarbons, the aromaticity in the peripheral rings increases. The aromaticity of the center ring is transformed to the aromaticity of the TS and then diminishes as the reaction is completed.⁶³

- ^{58.} B. R. Beno, K. N. Houk, and D. A. Singleton, *J. Am. Chem. Soc.*, **118**, 9984 (1996); E. Goldstein, B. Beno, and K. N. Houk, *J. Am. Chem. Soc.*, **118**, 6036 (1996).
- ^{59.} D. A. Singleton, S. R. Merrihan, B. R. Beno, and K. N. Houk, *Tetrahedron Lett.*, **40**, 5817 (1999).
- ^{60.} O. Acevedo and J. D. Evanscek, *Org. Lett.*, **5**, 649 (2003).
- ^{61.} E. J. Acevedo Corey, J. J. Rohde, A. Fischer, and M. D. Alimiora, *Tetrahedron Lett.*, **38**, 33 (1997).
- ^{62.} C. Di Valentin, M. Freccero, M. Sarzi-Amade, and R. Zanaletti, *Tetrahedron*, **56**, 2547 (2000).
- ^{63.} M. Manoharan, F. De Proft, and P. Geerlings, *J. Chem. Soc., Perkin Trans. 2*, 1767 (2000); M.-F. Cheng and W.-K. Li, *Chem. Phys. Lett.*, **368**, 630 (2003).

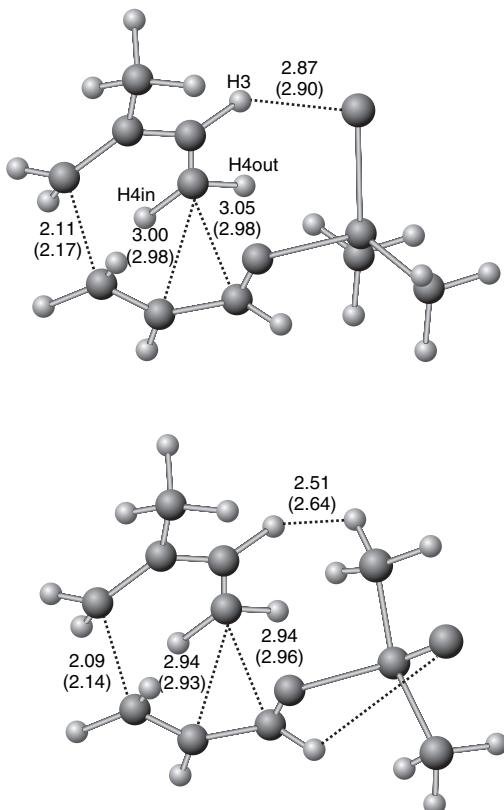
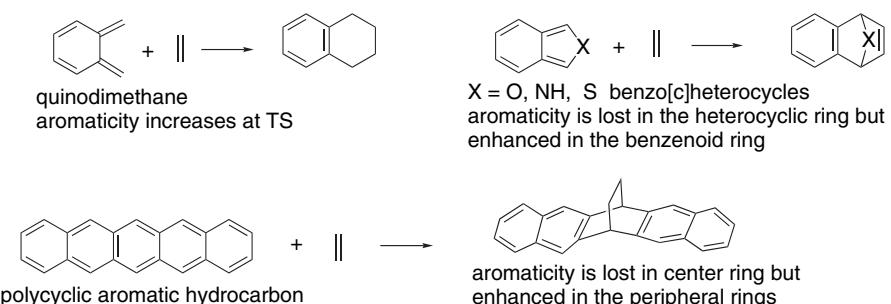


Fig. 10.10. Alternate transition structures for Diels-Alder reaction of isoprene with propenal: (a) structure without formyl hydrogen bond; (b) structure with formyl hydrogen bond. Dimensions are from B3LYP/6-31G(*d*) computations in the gas phase and in PMC with $\epsilon = 4.335$ (shown in parentheses). Adapted from *Org. Lett.*, **5**, 649 (2003), by permission of the American Chemical Society.



In the case of the benzo[c] heterocycles, the ΔE , E_a , and degree of charge transfer in the TS were calculated. The E_a correlated with the exothermicity of the reaction for the second-row elements. The extent of charge transfer at the TS increased from carbon to oxygen to nitrogen, but was low for the benzo[c]thiophene.⁶⁴

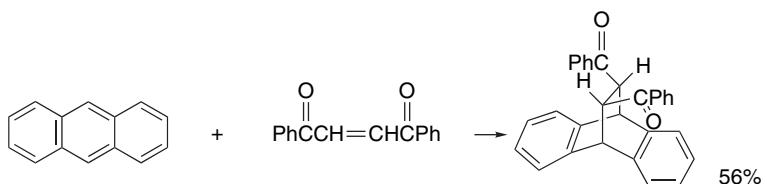
⁶⁴. T. C. Dinadayalane and G. N. Sastry, *J. Chem. Soc., Perkin Trans. 2*, 1902 (2002).

SECTION 10.2

The Diels-Alder Reaction

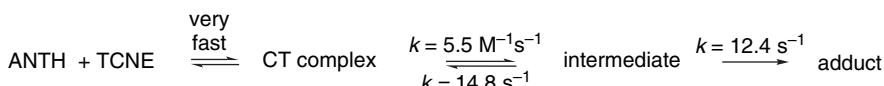
E_a	10.8	21.4	15.4
ΔE	-48.8	-16.2	-29.8
c.t.	0.022	0.092	0.043
			24.7
			-27.1
			0.001

These results are consistent with experimental results. Polycyclic aromatic hydrocarbons are moderately reactive as the diene component of Diels-Alder reactions. Although benzene and naphthalene show no reactivity toward maleic anhydride at 90°C, anthracene does give an adduct.⁶⁵ A variety of dienophiles react with anthracene, including benzoquinone, dimethyl fumarate, nitroethene, and phenyl vinyl sulfoxide.⁶⁶ The addition occurs at the center ring. There is no net loss of resonance stabilization, since the anthracene ring (resonance energy = 1.60 eV) is replaced by two benzenoid rings (total resonance energy = $2 \times 0.87 = 1.74$ eV).⁶⁷



A B3LYP/6-31+G(*d,p*) computational investigation of the reaction between anthracene and tetracyanoethene indicates that the reaction proceeds through a charge transfer complex.⁶⁹ Mulliken population analysis was used to follow the transfer of charge at the various stages of the reaction. At the CT complex, 0.20 electron had been transferred. This increased to 0.46 electron at the TS, but then dropped to 0.32 electron in the product. There is partial pyramidalization of both the dienophile and anthracene in the CT complex. This distortion is believed to make the transformation of the reactants to the TS more facile. The formation of the CT complex also begins the process of decreasing the aromaticity of the center ring, which makes the distortion of the ring toward the TS easier.

In the case of the reaction of anthracene with tetracyanoethene, there is kinetic evidence for an intermediate that is distinct from the rapidly formed charge transfer complex.⁷⁰ The intermediate is proposed to be a tight complex with a geometry favorable for formation of the adduct. The formation of the charge transfer complex is fast and reversible and may also lie on the overall reaction path.



⁶⁵. B. Biermann and W. Schmidt, *J. Am. Chem. Soc.*, **102**, 3163 (1980).

⁶⁶. J. C. C. Atherton and S. Jones, *Tetrahedron*, **59**, 9039 (2003).

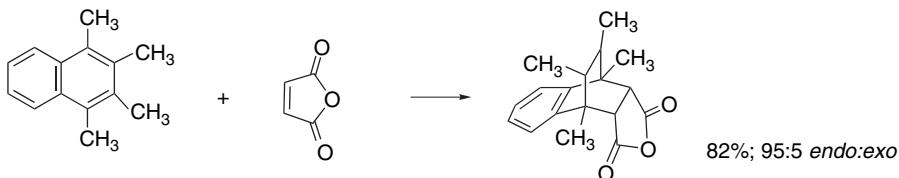
⁶⁷. M. J. S. Dewar and C. de Llano, *J. Am. Chem. Soc.*, **91**, 789 (1969).

⁶⁸. D. M. McKinnon and J. Y. Wong, *Can. J. Chem.*, **49**, 3178 (1971).

⁶⁹. K. E. Wise and R. A. Wheeler, *J. Phys. Chem. A*, **103**, 8279 (1999).

⁷⁰. K. L. Handoo, Y. Lu, and V. D. Parker, *J. Am. Chem. Soc.*, **125**, 9381 (2003).

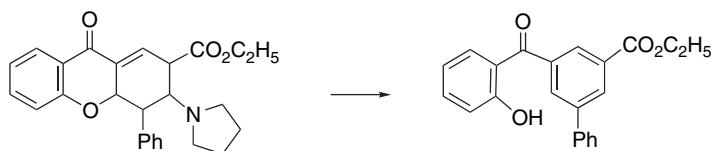
The naphthalene ring is much less reactive. Polymethylnaphthalenes are more reactive than the parent molecule and 1,2,3,4-tetramethylnaphthalene gives an adduct with maleic anhydride in 82% yield. Reaction occurs exclusively in the substituted ring because it is more electron rich.⁷¹ The steric repulsions between the methyl groups, which are relieved in the nonplanar adduct, may also exert an accelerating effect.



10.2.5. Scope and Synthetic Applications of the Diels-Alder Reaction

Examples of some compounds that exhibit a high level of reactivity as dienophiles are shown in Scheme 10.2 (p. 844). Scheme 10.4 presents some typical uncatalyzed D-A reactions. Part A shows normal electron demand reactions. Each of the reactive dienophiles has at least one strongly electron-attracting substituent on the carbon-carbon double or triple bond. Part B shows several inverse electron demand D-A reactions. Ethene, ethyne, and their alkyl derivatives are poor dienophiles and react only under vigorous conditions.

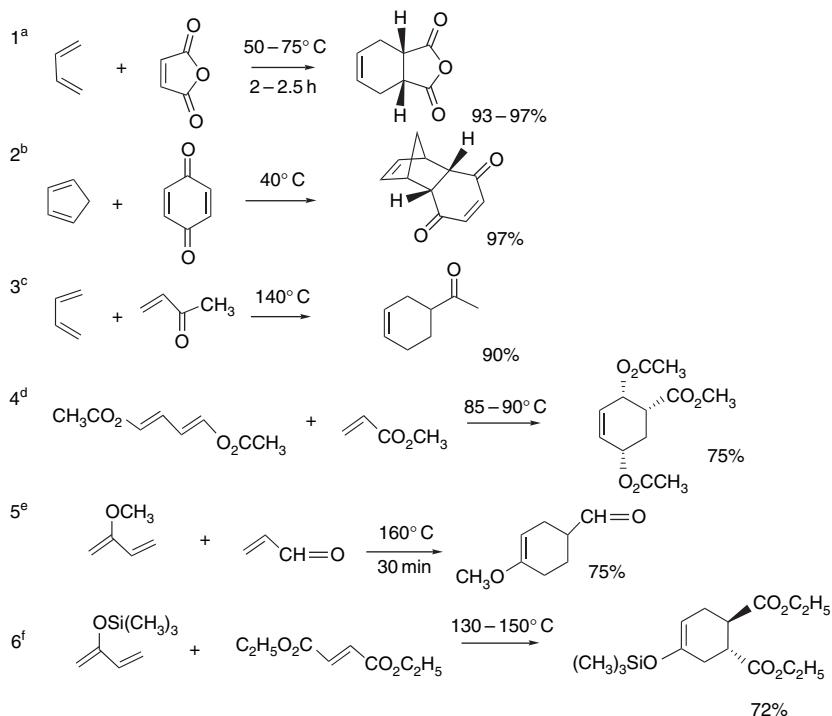
Entries 1 to 3 are classical examples of D-A reactions between simple dienes and electrophilic dienophiles. Note the *endo* stereoselectivity in Entry 2. Entries 4 to 6 are examples with dienes having activating ERG substituents. There is no regiochemical issue with the symmetrical diene in Entry 4, but the all-*cis* stereochemistry results from an *endo* TS. Entry 5 exhibits the expected regiochemistry, with C(1) of the diene bonded to the more electrophilic β -carbon of the dienophile. Entries 7 and 8 are inverse electron demand reactions with ERGs in the dienophiles and an EWG in the diene. The reaction in Entry 8 leads to formation of an aromatic ring by elimination of pyrrolidine and opening of the pyrone ring.



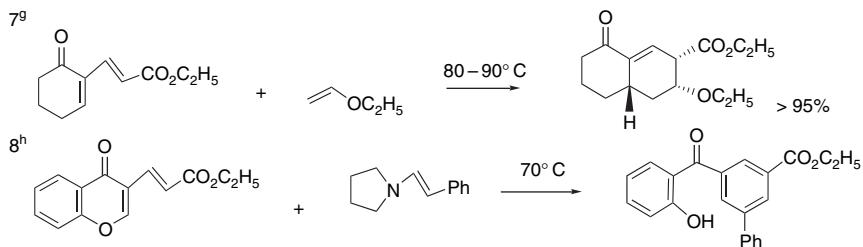
The regiochemistry of this reaction is consistent with expectation. The more nucleophilic β -carbon of the enamine bonds to C(2) of the pyrone ring, which is activated by both the C(4) ring carbonyl and the ester substituent.

⁷¹. A. Oku, Y. Ohnishi, and F. Mashio, *J. Org. Chem.*, **37**, 4264 (1972).

A. Normal Electron Demand



B. Inverse Electron Demand



a. A. C. Cope and E. C. Herrichy, *Org. Synth.*, **IV**, 890 (1963).

b. A. Wasserman, *J. Chem. Soc.*, 1511 (1935).

c. W. K. Johnson, *J. Org. Chem.*, **29**, 864 (1959).

d. R. McCrindle, K. H. Overton, and R. A. Raphael, *J. Chem. Soc.*, 1560 (1960); R. K. Hill and G. R. Newkome, *Tetrahedron Lett.*, 1851 (1968).

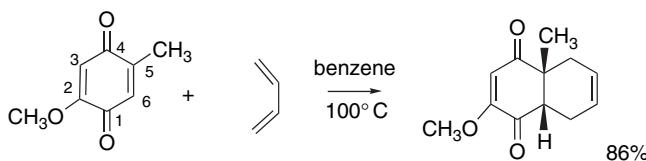
e. J. I. DeGraw, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 1156 (1961).

f. M. E. Jung and C. A. McCombs, *Org. Synth.*, **VL**, 445 (1988).

g. G. J. Bodwell and Z. Pi, *Tetrahedron Lett.*, **38**, 309 (1997).

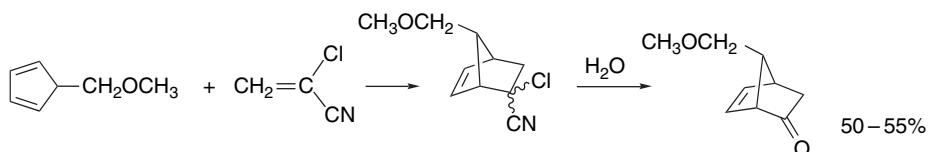
h. G. J. Bodwell, K. M. Hawco, and R. P. da Silva, *Synlett*, 179 (2003).

10.2.5.1. Dienophiles There are many examples of synthetic applications of D-A reactions where it is necessary to have additional substituents. The reaction of a substituted benzoquinone and 1,3-butadiene, for example, was the first step in early syntheses of steroids. The angular methyl group was introduced via the quinone and the other functional groups were used for further elaboration.

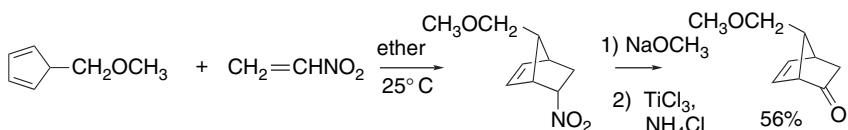


Note that the unsymmetrically substituted quinone exhibits excellent regioselectivity. The stronger donor effect of the methoxy group deactivates the C(4) carbonyl relative to the C(1) carbonyl, making the C(5)–C(6) double bond the more reactive dienophile.

The synthetic utility of the D-A reaction can be expanded by the use of dienophiles that contain *masked functionality* and are the *synthetic equivalent* of unreactive or inaccessible species. For example, α -chloroacrylonitrile shows satisfactory reactivity as a dienophile. The α -chloronitrile functionality in the adduct can be hydrolyzed to a carbonyl group, so α -chloroacrylonitrile can function as the equivalent of ketene, $\text{CH}_2=\text{C=O}$.⁷³ Ketene itself is not a suitable dienophile because it reacts with dienes by [2 + 2] cycloaddition, rather than in the desired [4 + 2] fashion.



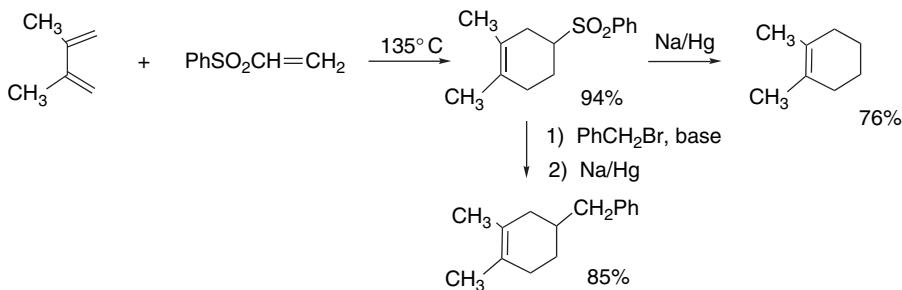
Nitroalkenes are good dienophiles and the variety of transformations that are available for nitro groups makes them versatile intermediates.⁷⁵ Nitro groups can be converted to carbonyl groups by reductive hydrolysis, so nitroethene can also be used as a ketene equivalent.⁷⁶



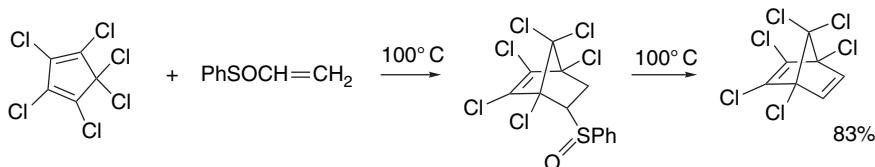
The adducts from both the α -chloroacrylonitrile and nitroethene and 5-methoxymethylcyclopentadiene are intermediates for the synthesis of prostaglandins.

Vinyl sulfones are useful dienophiles. The sulfonyl group can be removed reductively with sodium amalgam. In this two-step reaction sequence, the vinyl sulfone functions as an ethene equivalent. The sulfonyl group also allows for alkylation of the

- ⁷². R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).
- ⁷³. V. K. Aggarwal, A. Ali, and M. P. Coogan, *Tetrahedron*, **55**, 293 (1999).
- ⁷⁴. E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).
- ⁷⁵. D. Ranganathan, C. B. Rao, S. Ranganathan, A. K. Mehrotra, and R. Iyengar, *J. Org. Chem.*, **45**, 1185 (1980).
- ⁷⁶. For a review of ketene equivalents, see S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *Synthesis*, 289 (1977).
- ⁷⁷. S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *J. Am. Chem. Soc.*, **96**, 5261 (1974).

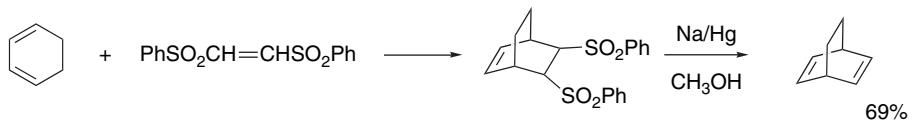


Phenyl vinyl sulfoxide can serve as an ethyne equivalent. Its Diels-Alder adducts can undergo thermal elimination of benzenesulfenic acid.



Ref. 79

E- and *Z*-bis-(benzenesulfonyl)ethene are also ethyne equivalents. The two sulfonyl groups undergo reductive elimination on reaction with sodium amalgam.



Ref. 80

Vinylphosphonium salts are reactive as dienophiles as a result of the electron-withdrawing capacity of the phosphonium substituent. The D-A adducts can be deprotonated to give ylides that undergo the Wittig reaction to introduce an exocyclic double bond (see Part B, Section 2.4.1). This sequence of reactions corresponds to a D-A reaction employing allene ($\text{CH}_2=\text{C}=\text{CH}_2$) as the dienophile.⁸¹



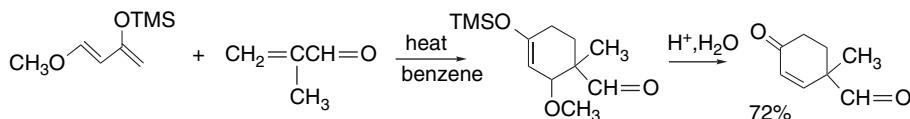
⁷⁸. R. V. C. Carr and L. A. Paquette, *J. Am. Chem. Soc.*, **102**, 853 (1980); R. V. C. Carr, R. V. Williams, and L. A. Paquette, *J. Org. Chem.*, **48**, 4976 (1983); W. A. Kinney, G. O. Crouse, and L. A. Paquette, *J. Org. Chem.*, **48**, 4986 (1983).

⁷⁹. L. A. Paquette, R. E. Moerck, B. Harirchian, and P. D. Magnus, *J. Am. Chem. Soc.*, **100**, 1597 (1978).

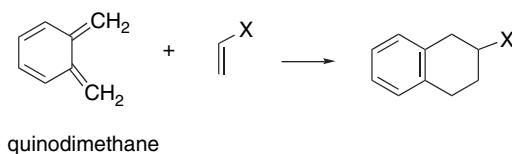
⁸⁰. O. DeLucchi, V. Lucchini, L. Pasquato, and G. Modena, *J. Org. Chem.*, **49**, 596 (1984).

⁸¹. R. Bonjouklian and R. A. Buden, *J. Org. Chem.*, **42**, 4095 (1977).

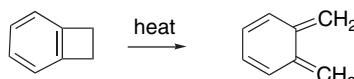
10.2.5.2. Dienes Simple dienes react readily with good dienophiles in D-A reactions. Functionalized dienes are also important in organic synthesis. One example that illustrates the versatility of such reagents is 1-methoxy-3-trimethylsiloxy-1,3-butadiene (*Danishefsky's diene*).⁸² Its D-A adducts are trimethylsilyl enol ethers that can be readily hydrolyzed to ketones. The β -methoxy group is often eliminated during hydrolysis, leading to an enone.



Unstable dienes can be generated *in situ* in the presence of a dienophile. Among the most useful examples of this type of diene are the quinodimethanes.⁸³ These compounds are especially reactive as dienes because the cycloaddition reestablishes a benzenoid ring and results in aromatic stabilization (see p. 858).

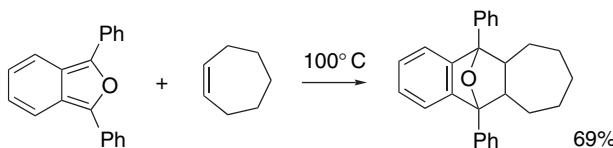


There are several possible routes to quinodimethanes, including pyrolysis of benzocyclobutenes.⁸⁴



The reaction is accelerated by ERG substituents, particularly trialkylsiloxy groups, on the cyclobutene ring.⁸⁵ Quinodimethanes have been especially useful in intramolecular Diels-Alder reactions, as is illustrated in Section 10.2.7.

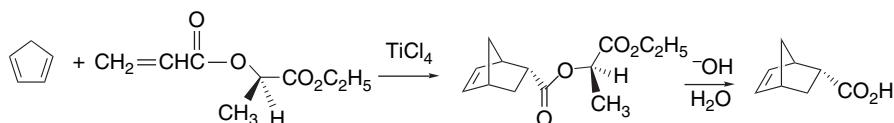
Another group of dienes with extraordinarily high reactivity is made up of the derivatives of benzo[c]furan (isobenzofuran).⁸⁶ Here again, the high reactivity can be traced to the gain of aromatic stabilization in the adduct.



Ref. 87

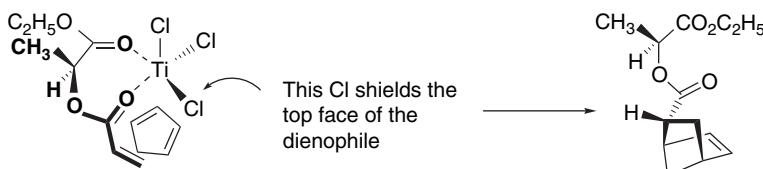
- ⁸². S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974).
- ⁸³. W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, **16**, 10 (1977); T. Kametani and K. Fukumoto, *Heterocycles*, **3**, 29 (1975); J. J. McCullough, *Acc. Chem. Res.*, **13**, 270 (1980); W. Oppolzer, *Synthesis*, 793 (1978); J. L. Charlton and M. M. Alauddin, *Tetrahedron*, **43**, 2873 (1987); H. N. C. Wong, K.-L. Lau, and K. F. Tam, *Top. Curr. Chem.*, **133**, 85 (1986); P. Y. Michellys, H. Pellissier, and M. Santelli, *Org. Prep. Proc. Int.*, **28**, 545 (1996); J. L. Segura and N. Martin, *Chem. Rev.*, **99**, 3199 (1999).
- ⁸⁴. M. P. Cava and M. J. Mitchell, *Cyclobutadiene and Related Compounds*, Academic Press, New York, 1967, Chap. 6; I. L. Klundt, *Chem. Rev.*, **70**, 471 (1970); R. P. Thummel, *Acc. Chem. Res.*, **13**, 70 (1980); G. Mehta and S. Kotha, *Tetrahedron*, **57**, 625 (2001); A. K. Sadana, R. K. Saini, and W. E. Billups, *Chem. Rev.*, **103**, 1539 (2003).
- ⁸⁵. J. G. Allen, M. F. Hentemann, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **122**, 571 (2000).
- ⁸⁶. M. J. Haddadin, *Heterocycles*, **9**, 865 (1978); W. Friedrichsen, *Adv. Heterocycl. Chem.*, **26**, 135 (1980).
- ⁸⁷. G. Wittig and T. F. Burger, *Liebigs Ann. Chem.*, **632**, 85 (1960).

10.2.6.1. Chiral Auxiliaries for Diels-Alder Reactions The highly ordered cyclic TS of the Diels-Alder reaction permits design of reactants and catalysts that lead to a preference between diastereomeric or enantiomeric adducts. (See Section 2.4) to review the principles of diastereoselectivity and enantioselectivity.) One way to achieve diastereoselectivity is to install a chiral auxiliary.⁸⁸ The cycloaddition proceeds to give two diastereomeric products that can be separated and purified. Because of the lower temperature and the greater stereoselectivity, the best diastereoselectivity is often observed in Lewis acid–catalyzed reactions. Chiral esters and amides of acrylic acid are particularly useful because the chiral auxiliary can be easily recovered by hydrolysis of the purified adduct to give the enantiomerically pure carboxylic acid.



Ref. 89

Prediction and analysis of diastereoselectivity is based on steric, stereoelectronic, and chelating interactions in the TS.⁹⁰ For example, the facial selectivity of the reaction above is governed by a chloride ligand on titanium, which shields one face of the dienophile.



The lactone of 2,4-dihydroxy-3,3-dimethylpentanoic acid (known as pantolactone) has been successfully employed as a chiral auxiliary in several D-A reactions. For example, in conjunction with TiCl_4 , it provides a 92% de in the reaction of 2,3-dimethylbutadiene with α -cyanocinnamic acid.⁹¹ The diastereoselectivity is consistent with a chelated structure similar to that shown above for acryloyl lactate. In the absence of TiCl_4 , this same ester gives a 64% de of the opposite configuration. This

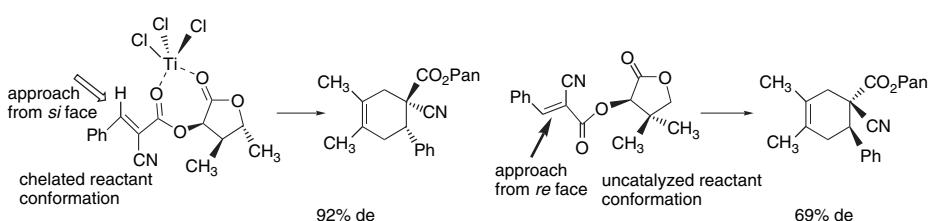
⁸⁸. W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, **23**, 876 (1984); M. J. Tascher, in “*Organic Synthesis, Theory and Applications*,” Vol. 1, T. Hudlicky, ed., JAI Press, Greenwich, CT, 1989, pp. 1–101; H. B. Kagan and O. Riant, *Chem. Rev.*, **92**, 1007 (1992); K. Narasaka, *Synthesis*, 16 (1991).

⁸⁹. T. Poll, G. Helmchen, and B. Bauer, *Tetrahedron Lett.*, **25**, 2191 (1984).

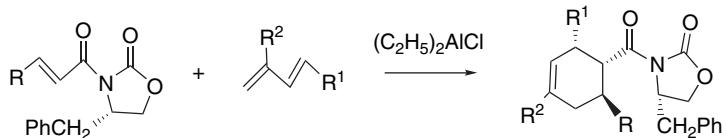
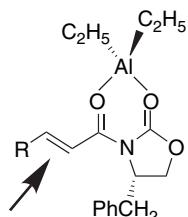
⁹⁰. For example, see T. Poll, A. Sobczak, H. Hartmann, and G. Helmchen, *Tetrahedron Lett.*, **26**, 3095 (1985).

⁹¹. A. Avenoza, C. Cativiela, J. A. Mayoral, and J. M. Peregrina, *Tetrahedron: Asymmetry*, **3**, 913 (1992); C. Cativiela, J. A. Mayoral, A. Avenoza, J. M. Peregrina, F. J. Lahoz, and S. Gimeno *J. Org. Chem.*, **57**, 4664 (1992).

result suggests that the uncatalyzed reaction goes through a conformation in which the two carbonyl groups are *anti* to one another.



α, β -Unsaturated derivatives of chiral oxazolidinones have proven to be especially useful for enantioselective D-A additions.⁹² Reaction occurs at low temperatures in the presence of such Lewis acids as $SnCl_4$, $TiCl_4$, and $(C_2H_5)_2AlCl$.⁹³ Both the 4-isopropyl (derived from valine) and the 4-benzyl (derived from phenylalanine) derivative are frequently used. Both carbonyl oxygens are coordinated with the Lewis acid and the oxazolidione substituent provides steric shielding of one face of the dienophile. We discuss a number of other chiral auxiliaries for D-A reactions in Section 6.1.5 of Part B.



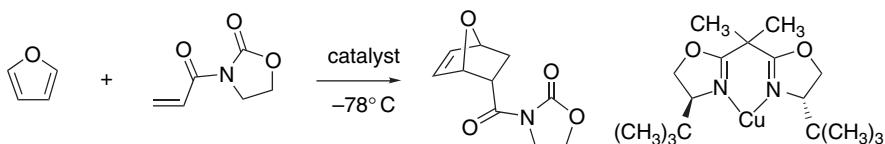
R	R ¹	R ²	Yield (%)	dr
H	H	CH ₃	85	95:5
H	CH ₃	H	84	>100:1
CH ₃	H	CH ₃	83	94:6
CH ₃	CH ₃	H	77	95:5

⁹². D. J. Ager, J. Prakash, and D. R. Schaad, *Chem. Rev.*, **96**, 835 (1996); D. J. Ager, J. Prakash, and D. R. Schaad, *Aldrichimica Acta*, **30**, 3 (1997).

⁹³. D. A. Evans, K. T. Chapman, and J. Bisaha, *J. Am. Chem. Soc.*, **110**, 1238 (1988).

10.2.6.2. Enantioselective Catalysts for Diels-Alder Reactions Enantioselectivity can also be achieved with chiral catalysts.⁹⁴ Many of the most efficient catalysts involve a chiral ligand in conjunction with a metal ion that acts as a Lewis acid. The metal ion provides the electron-attracting capacity and in conjunction with the ligand establishes a chiral environment at the catalytic site. Several boron compounds are also good catalysts, with the boron playing the role of the Lewis acid. The ligands typically have bulky substituents, often substituted aromatic rings. The ligands are usually derived from readily available chiral substances, such as amino acids. In addition to the Lewis acid complexation and steric effects, π stacking and hydrogen bonding can contribute to the structure of the catalytic complex. The effectiveness of the catalyst is related to the proximity of the chiral features to the reaction center. If the chiral environment is too remote from the catalytic site, it does not control the enantioselectivity effectively. This proposition was tested for a number of catalysts for the D-A reaction and generally found to be true.⁹⁵

One group of chiral catalysts consists of metal ion complexes, usually Cu^{2+} ,⁹⁶ of bis-oxazolines (referred to as box catalysts).⁹⁷



Ref. 98

Based on a crystal structure of the catalyst and PM3 modeling of the complex, the reaction is proposed to proceed preferentially from the *re* face as a result of steric shielding by a *t*-butyl group, as shown in Figure 10.11.

Chiral oxazaborolidines have also been found to be useful catalysts in D-A reactions. The tryptophan-derived catalyst shown in TS A, for example, can achieve 99% enantioselectivity in the D-A reaction between 5-benzyloxymethyl-1,3-cyclopentadiene and 2-bromopropenal. The adduct is an important intermediate in the synthesis of prostaglandins.⁹⁹ The aldehyde is bound to the catalyst by a Lewis interaction. There is also believed to be a hydrogen bond between the formyl C–H and the oxygen bound to boron. This type of hydrogen bonding has been recognized in several Lewis acid complexes of aldehydes.¹⁰⁰ The upper face of the aldehyde is shielded by the indole ring. The benzyloxymethyl substituent provides a steric differentiation of the two faces of the cyclopentadiene ring, as shown in TS A.

⁹⁴ Y. Hayashi, in *Cycloaddition Reactions in Organic Synthesis*, S. Kobayashi and K. A. Jorgensen, eds., Wiley-VCH, Weinheim, 2002, pp. 5–55.

⁹⁵ K. B. Lipkowitz, C. A. D'Hue, T. Sakamoto, and J. N. Stack, *J. Am. Chem. Soc.*, **124**, 14255 (2002).

⁹⁶ D. A. Evans, S. J. Miller, and T. Lectka, *J. Am. Chem. Soc.*, **115**, 6460 (1993); D. A. Evans, J. P. Murry, P. von Matt, R. D. Norcross, and S. J. Miller, *Angew. Chem. Int. Ed. Engl.*, **34**, 798 (1995); J. S. Johnson and D. A. Evans, *Acc. Chem. Res.*, **33**, 325 (2000).

⁹⁷ A. K. Ghosh, P. Mathivanan, and J. Cappiello, *Tetrahedron: Asymmetry*, **9**, 1 (1998).

⁹⁸ D. A. Evans and D. M. Barnes, *Tetrahedron Lett.*, **38**, 57 (1997).

⁹⁹ E. J. Corey and T. P. Loh, *J. Am. Chem. Soc.*, **113**, 8966 (1991).

¹⁰⁰ E. J. Corey, J. J. Rohde, A. Fischer, and M. D. Azimioara, *Tetrahedron Lett.*, **38**, 33 (1997).

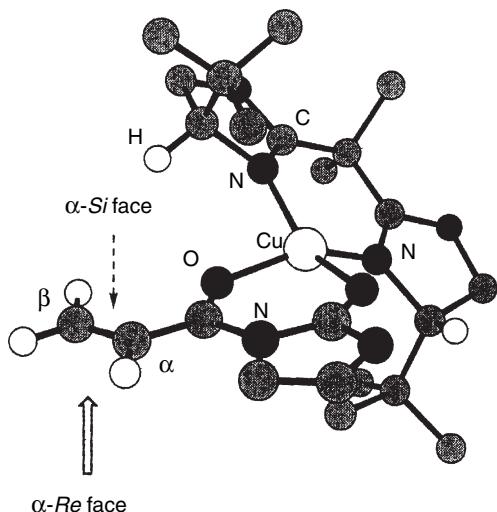
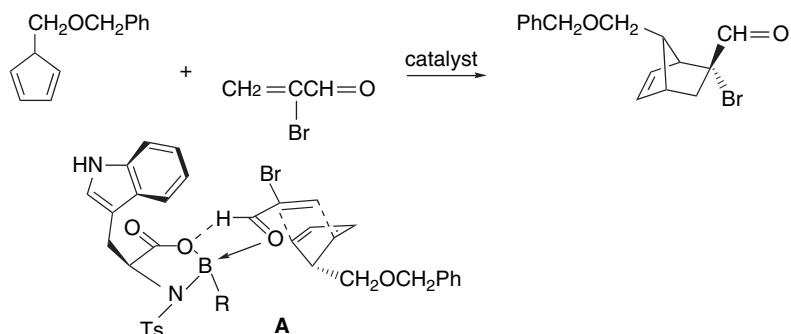


Fig. 10.11. Model of Cu(*S,S*-*t*-BuBox catalyst with *N*-acryloyloxazolidinone showing facial stereodifferentiation. Reproduced from *J. Am. Chem. Soc.*, **121**, 7559 (1999), by permission of the American Chemical Society.



Other enantioselective catalysts for the D-A reactions have been developed. The chiral ligands used include the TADDOLs ($\alpha, \alpha, \alpha, \alpha$ -tetraaryl-1,3-dioxolane-4,5-dimethanols)¹⁰¹ and BINOL derivatives.¹⁰² These are discussed in Section 6.4 of Part B.

10.2.7. Intramolecular Diels-Alder Reactions

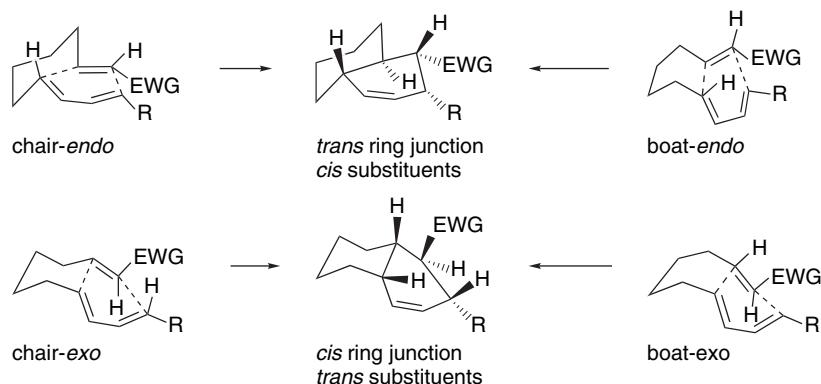
Intramolecular Diels-Alder (IMDA) reactions are very useful in the synthesis of polycyclic compounds.¹⁰³ Two new rings are created by the reaction, and the stereochemistry of the ring junction is determined by TS geometry. In addition to the *exo*

¹⁰¹. D. Seebach, A. K. Back, and A. Heckel, *Angew. Chem. Int. Ed. Engl.*, **40**, 93 (2001).

¹⁰². K. Ishihara, H. Kurihara, M. Matsumoto, and H. Yamamoto, *J. Am. Chem. Soc.*, **120**, 6920 (1995); S. Kobayashi, M. Araki, and I. Hachiya, *J. Org. Chem.*, **59**, 3758 (1994); S. Kobayashi, M. Sugiura, H. Kitagawa, and W.-L. Lam, *Chem. Rev.*, **102**, 2227 (2002).

¹⁰³. W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, **16**, 10 (1977); G. Brieger and J. N. Bennett, *Chem. Rev.*, **80**, 63 (1980); E. Ciganek, *Org. React.*, **32**, 1 (1984); D. F. Taber, *Intramolecular Diels-Alder and Alder Ene Reactions*, Springer-Verlag, Berlin, 1984.

and *endo* relationships present in intermolecular D-A reactions, the conformation of the intervening linkage influences the stereochemistry. For example, in the case of an *E,E*-undeca-1,7,9-trienes with 1-EWG substituents, four TSs are possible. Two lead to a *trans* ring junction with *cis* orientation of the substituents, whereas the other two lead to a *cis* ring junction and *trans* orientation of the substituents. As for intermolecular D-A reactions, the reaction is stereospecific with respect to the diene and dienophile substituents, so that the *Z,E*- , *E,Z*- , and *Z,Z*-reactants also give specific stereoisomers.



One of the factors that affect TS structure is the length of the connecting chain. Sastry and co-workers looked systematically at this factor in the unsubstituted triene system with from one to four linking CH_2 groups.¹⁰⁴ Single-point B3LYP/6-31G* energies were calculated at the PM3 structural minima. Because of strain, a *cis* ring juncture is strongly favored for $n = 1$ and $n = 2$ and slightly for $n = 3$. The *trans* ring juncture is favored somewhat for $n = 4$. The effect of strain is reflected in the energy of both the TS and the product and indicates the rudimentary features associated with the linking group. The E_a and reaction energies are given below and are plotted in Figure 10.12. The synchronicity of the reaction was computed. (See p. 852 for the numerical definition of synchronicity.) Synchronicity was quite high for $n = 2$ to $n = 4$, but was lower (0.669) for $n = 1$ (*cis*), where the formation of the peripheral bond is leading. According to these results, formation of a bicyclo[4.3.0]non-2-ene ring system ($n = 3$) is slightly preferred kinetically to a bicyclo[4.4.0]dec-2-ene ring for both *cis* and *trans* ring junctions.



n	E_{act}		ΔE_{react}		Synchronicity	
	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>
1	35.7	57.2	-11.0	+25.6	0.6692	0.8987
2	37.0	41.1	-18.2	-4.3	0.9816	0.9730
3	17.9	19.6	-40.9	-38.8	0.9248	0.9473
4	26.1	23.3	-41.8	-47.7	0.9267	0.9054

¹⁰⁴ R. Vijaya and G. N. Sastry, *Theochem*, **618**, 201 (2002).

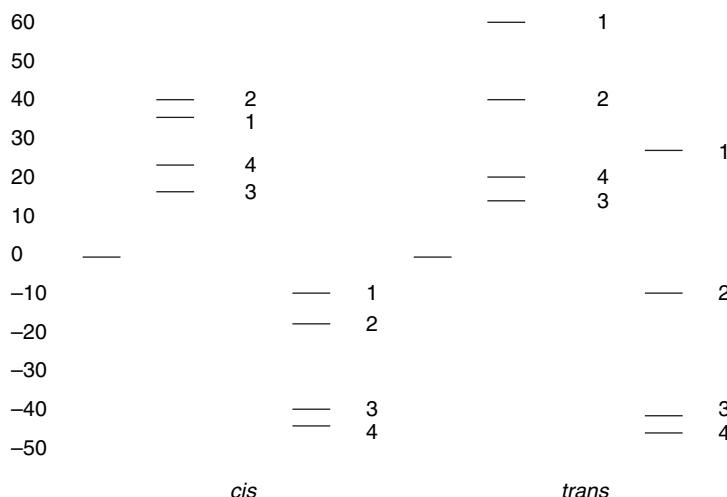
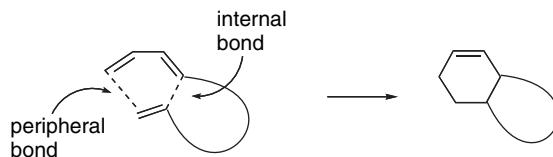


Fig. 10.12. Activation and reaction energies (B3LYP/6-31G*) in kcal/mol for intramolecular Diels-Alder reactions of $\text{CH}_2=\text{CH}(\text{CH}_2)_n\text{CH}=\text{CHCH}=\text{CH}_2$ for $n = 1$ to 4. Adapted from *Theochem*, **618**, 201 (2002).

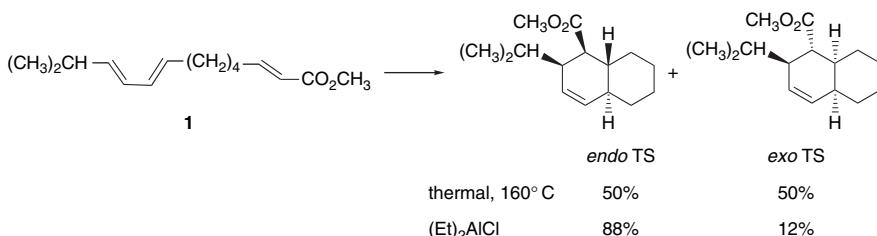
In several IMDA reactions involving substituted systems, the direction of the asynchronicity appears to be controlled by steric and torsional, rather than electronic, factors. Often the internal bond formation is more advanced than the peripheral bond, regardless of the location and electronic characteristics of the substituents.¹⁰⁵ This is presumably due to the proximity (entropic) factor and is in contrast to intermolecular D-A reactions, where electronic effects are dominant.



Lewis acid catalysis usually substantially improves the stereoselectivity of IMDA reactions, just as it does in intermolecular cases. For example, the thermal cyclization of **1** at 160°C gives a 50:50 mixture of two stereoisomers, but the use of $(\text{C}_2\text{H}_5)_2\text{AlCl}$ as a catalyst permits the reaction to proceed at room temperature, and *endo* addition is favored by 7:1.¹⁰⁶

¹⁰⁵. C. I. Turner, R. M. Williamson, M. N. Paddon-Row, and M. S. Sherburn, *J. Org. Chem.*, **66**, 3963 (2001); T. N. Cayzer, L. S. M. Wong, P. Turner, M. N. Paddon-Row, and M. S. Sherburn, *Chem. Eur. J.*, **8**, 739 (2002).

¹⁰⁶. W. R. Roush and H. R. Gillis, *J. Org. Chem.*, **47**, 4825 (1982).

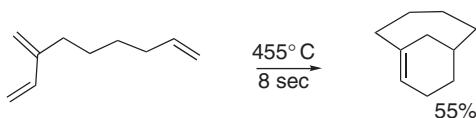


The general pattern of IMDA stereoselectivity suggests that although electronic interactions govern the regioselectivity, conformational effects are the main factors in determining stereoselectivity.¹⁰⁷ Because the conformational interactions depend on the substituent pattern in the specific case, no general rules for stereoselectivity can be put forward. Molecular modeling can frequently identify the controlling structural features.¹⁰⁸

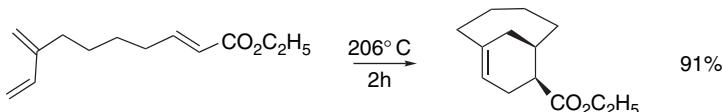
A less common type of IMDA reaction leads to bicyclic rings with bridgehead double bonds.¹⁰⁹



Both activated and unactivated systems have been observed to react, and the reaction is subject to Lewis acid catalysis.



Ref. 110



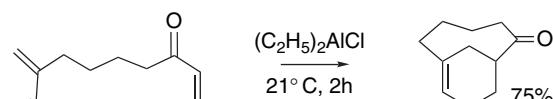
Ref. 110

¹⁰⁷ W. R. Roush, A. I. Ko, and H. R. Gillis, *J. Org. Chem.*, **45**, 4264 (1980); R. K. Boeckman, Jr., and S. S. Ko, *J. Am. Chem. Soc.*, **102**, 7146 (1980); W. R. Roush and S. E. Hall, *J. Am. Chem. Soc.*, **103**, 5200 (1981); J. A. Marshall, J. E. Audia, and J. Grote, *J. Org. Chem.*, **49**, 5277 (1984); T.-C. Wu and K. N. Houk, *Tetrahedron Lett.*, **26**, 2293 (1985); K. A. Parker and T. Iqbal, *J. Org. Chem.*, **52**, 4369 (1987); W. R. Roush, A. P. Eisenfeld, and J. S. Warmus, *Tetrahedron Lett.*, **28**, 2447 (1987).

¹⁰⁸ K. J. Shea, L. D. Burke, and W. P. England, *J. Am. Chem. Soc.*, **110**, 860 (1988); L. Raimondi, F. K. Brown, J. Gonzalez, and K. N. Houk, *J. Am. Chem. Soc.*, **114**, 4796 (1992); D. P. Dolata and L. M. Harwood, *J. Am. Chem. Soc.*, **114**, 10738 (1992); F. K. Brown, U. C. Singh, P. A. Kollman, L. Raimondi, K. N. Houk, and C. W. Bock, *J. Org. Chem.*, **57**, 4862 (1992); J. D. Winkler, H. S. Kim, S. Kim, K. Ando, and K. N. Houk, *J. Org. Chem.*, **62**, 2957 (1997).

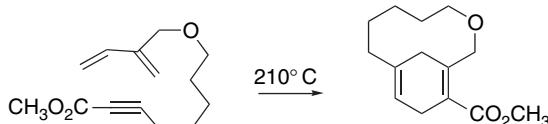
¹⁰⁹ B. R. Bear, S. M. Sparks, and K. J. Shea, *Angew. Chem. Int. Ed. Engl.*, **40**, 821 (2001).

¹¹⁰ K. J. Shea, S. Wise, L. D. Burke, P. D. Davis, J. W. Gilman, and A. C. Greeley, *J. Am. Chem. Soc.*, **104**, 5708 (1982).



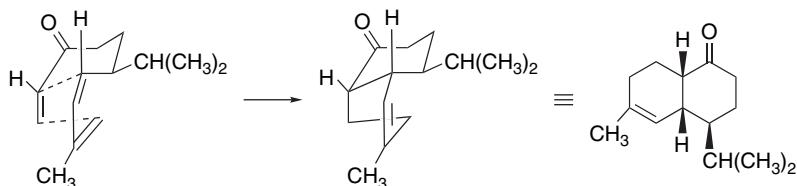
Ref. 111

Alkynes give cyclohexadienes.

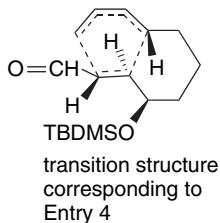


Ref. 112

We can illustrate some of the features of the IMDA reaction by considering some specific examples given in Scheme 10.5. In Entry 1 the dienophilic portion bears a carbonyl substituent and cycloaddition occurs easily. Two stereoisomeric products are formed, but both have *cis* ring fusion, which is the stereochemistry expected for an *endo* TS.



In Entry 2 a similar triene that lacks the activating carbonyl group undergoes reaction, but a much higher temperature is required. In this case the ring junction is *trans*. This corresponds to an *exo*-transition state and may reflect the absence of secondary orbital interaction between the diene and dienophile. Entry 3 is an example of the use of a benzocyclobutene to generate a quinodimethane intermediate. The IMDA reaction creates the steroidal skeleton.¹¹³ Entries 4 and 5 illustrate the use of Lewis acid catalysts in IMDA. The *trans* ring junctions arise from *endo* TSs.

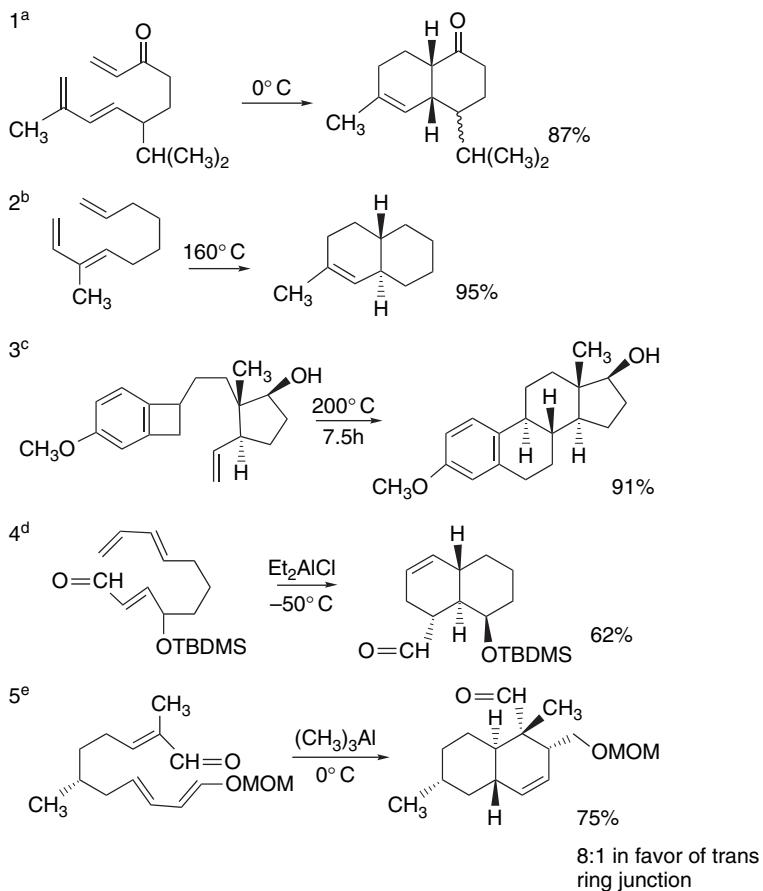


Note that all the reactions are stereospecific with respect to the configuration at the diene and dienophile double bonds.

¹¹¹ K. J. Shea and J. W. Gilman, *Tetrahedron Lett.*, **24**, 657 (1983).

¹¹² K. J. Shea, L. D. Burke, and W. P. England, *J. Am. Chem. Soc.*, **110**, 860 (1988).

¹¹³ H. Nemoto and K. Fukumoto, *Tetrahedron*, **54**, 5425 (1998).

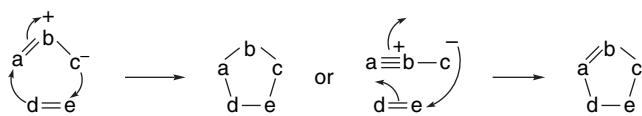


- a. D. F. Taber and B. P. Gunn, *J. Am. Chem. Soc.*, **101**, 3992 (1979); T. Kitahara, H. Kurata, T. Matsuoka, and K. Mori, *Tetrahedron*, **41**, 5475 (1985).
 b. S. R. Wilson and D. T. Mao, *J. Am. Chem. Soc.*, **100**, 6289 (1978).
 c. P. A. Grieco, T. Takigawa, and W. J. Schilling, *J. Org. Chem.*, **45**, 2247 (1980).
 d. J. A. Marshall, J. E. Audia, and J. Grote, *J. Org. Chem.*, **49**, 5277 (1984).
 e. K. Yuki, M. Shindo, and K. Shishido, *Tetrahedron Lett.*, **42**, 2517 (2001).

10.3. 1,3-Dipolar Cycloaddition Reactions

There is a large class of reactions known as *1,3-dipolar cycloaddition reactions* (1,3-DPCA) that are analogous to the Diels-Alder reaction in that they are concerted [$\pi 4_s + \pi 2_s$] cycloadditions.¹¹⁴ 1,3-DPCA reactions can be represented as shown in the following diagram. The entity *a-b-c* is called the *1,3-dipole* and *d-e* is the *dipolarophile*.

¹¹⁴. (a) R. Huisgen, *Angew. Chem. Int. Ed. Engl.*, **2**, 565 (1963); (b) R. Huisgen, R. Grashey, and J. Sauer, in *The Chemistry of the Alkenes*, S. Patai, ed., Interscience, London, 1965, pp. 806–878; (c) G. Bianchi, C. DeMicheli, and R. Gandolfi, in *The Chemistry of Double Bonded Functional Groups*, Part I, Supplement A, S. Patai, ed., Wiley-Interscience, New York, 1977, pp. 369–532; (d) A. Padwa, ed., *1,3-Dipolar Cycloaddition Chemistry*, Wiley, New York, 1984; (e) For a review of intramolecular 1,3-dipolar cycloaddition reactions, see A. Padwa, *Angew. Chem. Int. Ed. Engl.*, **15**, 123 (1976).



The 1,3-dipoles have a π -electron system consisting of two filled and one empty orbital and are analogous with the allyl or propargyl anion. Each 1,3-dipole has at least one charge-separated resonance structure with opposite charges in a 1,3-relationship. It is this structural feature that leads to the name 1,3-dipole for this class of reactants. The dipolarophiles are typically substituted alkenes or alkynes but all that is essential is a π bond, and other multiply bonded functional groups such as carbonyl, imine, azo, and nitroso can also act as dipolarophiles. The reactivity of dipolarophiles depends both on the substituents present on the π bond and on the nature of the 1,3-dipole involved in the reaction. Owing to the wide range of structures that can serve either as a 1,3-dipole or as a dipolarophile, the 1,3-DPCA is a very useful reaction for the construction of five-membered heterocyclic rings. Scheme 10.6 gives some examples using both ethenyl and ethynyl dipolarophiles. Some of the structures shown can undergo hydrogen shifts to more stable heterocyclic molecules, if there is one or more $R = H$.

10.3.1. Relative Reactivity, Regioselectivity, Stereoselectivity, and Transition Structures

The bonding changes for 1,3-DPCA reactions involve four π electrons from the 1,3-dipole and two from the dipolarophile. In most cases, the reaction is a concerted $[\pi 2_s + \pi 4_s]$ cycloaddition.¹¹⁵ As in the D-A reaction, the reactants approach one another in parallel planes. There is interaction between the complementary HOMO-LUMO combinations, and depending on the combination, either reactant can be the electrophilic or the nucleophilic component. Generally speaking, the reactant 1,3-dipoles are more polar than the TS or the reaction product. The rate of reaction is not strongly sensitive to solvent polarity.



¹¹⁵. P. K. Kadaba, *Tetrahedron*, **25**, 3053 (1969); R. Huisgen, G. Szeimes, and L. Möbius, *Chem. Ber.*, **100**, 2494 (1967); P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Am. Chem. Soc.*, **87**, 306 (1965).

Scheme 10.6. 1,3-Dipolar Cycloadditions

875

1,3-Dipole		Alkenyl dipolarophile	Alkynyl dipolarophile	SECTION 10.3 1,3-Dipolar Cycloaddition Reactions
$\begin{array}{c} - \\ \\ \text{RN}-\text{N}\equiv\text{N} \\ \\ \text{azide} \end{array}$	+ RCH=CHR			1,2,3-triazoline 1,2,3-triazole
$\begin{array}{c} - \\ \\ \text{R}_2\text{C}-\text{N}\equiv\text{N} \\ \\ \text{diazoalkane} \end{array}$	+ RCH=CHR			1-pyrazoline 3 <i>H</i> -pyrazole
$\begin{array}{c} - \\ \\ \text{R}_2\text{C}-\text{N}\equiv\text{CR} \\ \\ \text{nitrile ylide} \end{array}$	+ RCH=CHR			1-pyrroline 2 <i>H</i> -pyrrole
$\begin{array}{c} - \\ \\ \text{RN}-\text{N}\equiv\text{CR} \\ \\ \text{nitrile imine} \end{array}$	+ RCH=CHR			2-pyrazoline pyrazole
$\begin{array}{c} - \\ \\ \text{O}-\text{N}\equiv\text{CR} \\ \\ \text{nitrile oxide} \end{array}$	+ RCH=CHR			2-isoxazoline isoxazole
$\begin{array}{c} - \\ \\ \text{R}_2\text{C}-\text{N}=\text{CR}_2 \\ \\ \text{azomethine ylide} \end{array}$	+ RCH=CHR			pyrrolidine 3-pyrroline
$\begin{array}{c} - \\ \\ \text{RN}-\text{N}=\text{CR}_2 \\ \\ \text{azomethine imine} \end{array}$	+ RCH=CHR			pyrazolidine 3-pyrazoline
$\begin{array}{c} - \\ \\ \text{O}-\text{N}=\text{CR}_2 \\ \\ \text{nitrone} \end{array}$	+ RCH=CHR			isoxazolidine 4-isoxazoline

There have been many computational analyses of 1,3-DPCA TSs, and they are generally regarded to be aromatic in character. Typical TSs are characterized by aromatic NICS values.¹¹⁶ The ring current associated with this aromaticity is primarily due to the six electrons undergoing bonding changes.¹¹⁷ The orbital interactions in the cyclic TS serve as the focal point for discussion of relative reactivity, regioselectivity, and stereoselectivity of 1,3-DPCA reactions.

The most widely applied interpretation of substituent effects on relative reactivity is based on FMO theory. According to FMO theory, interacting orbitals are most stabilized when they are closest in energy. Substituent effects on dipolar cycloadditions can be interpreted in terms of matching of HOMO and LUMO orbitals of the two reactants.¹¹⁸ This is the same concept used in applying FMO theory to D-A reactions (see p. 844–848). In the D-A reaction, it is fairly clear which reactant is electrophilic and which is nucleophilic, and the interpretation of substituent effects follows directly. This choice is not always so obvious for 1,3-DPCA reactions. In fact, for several of the 1,3-dipoles both EWGs and ERGs in the dipolarophile enhance reactivity. These 1,3-dipoles are called *ambiphilic*. Let us look carefully to see why they have this property.

Much of the relative reactivity data on 1,3-DPCA reactions has been tabulated and discussed in reviews by R. Huisgen, a pioneer researcher in the field.^{114b} Some representative data are presented in Table 10.3. The dipolarophiles are shown in decreasing order of electrophilicity. The data from these monosubstituted dipolarophiles should be relatively free of steric influences on reactivity. Note that for phenyl azide and benzonitrile oxide, reactivity is at a minimum for unfunctionalized alkenes and is increased by both donor and acceptor substituents.

Table 10.3. Representative Relative Rate Data for 1,3-Dipolar Cycloadditions^a

CH ₂ =CHX	Ph ₂ CN ₂ ^b	PhN ₃ ^c	PhC≡NO ^d	PhCH=NCH ₃ ^e	PhC≡NNPh ^f	CH ₂ N ₂ ^g
Dimethyl fumarate	996	31	94	18.3	283	
Dimethyl maleate	27.8	1.25	1.61	6.25	7.94	
Ethyl acrylate	288	36.5	66	11.1	48.2	175
Ethyl crotonate	1.0	1.0	1.0	1.0	1.0	1.0
Norbornene	1.15	700	97	0.13	3.12	3.3 × 10 ⁻²
1-Alkene		0.8	2.6	0.072	0.146	6.9 × 10 ⁻⁴
Styrene	0.57	1.5	9.3	0.32	1.60	6.9 × 10 ⁻²
Cyclopentene		6.9	1.04	0.022	0.128	4.2 × 10 ⁻⁴
Cyclohexene			0.055		0.011	1.6 × 10 ⁻⁵
Vinyl ether		1.5	15			8.5 × 10 ⁻⁶
Vinyl amine		~ 1 × 10 ⁵				

a. Relative to ethyl crotonate as tabulated in Ref. 114b.

b. R. Huisgen, H. Stangl, H. J. Sturm, and H. Wagenhofer, *Angew. Chem.*, **73**, 170 (1961).

c. R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.*, **100**, 2494 (1967).

d. K. Bast, M. Christl, R. Huisgen, and W. Mack, *Chem. Ber.*, **106**, 3312 (1973).

e. R. Huisgen, H. Seidl, and I. Brunig, *Chem. Ber.*, **102**, 1102 (1969).

f. E. Eckell, R. Huisgen, R. Sustmann, D. Wallbillich, D. Grashey, and E. Spindler, *Chem. Ber.*, **100**, 2192 (1967).

g. J. Geittner, R. Huisgen, and R. Sustmann, *Tetrahedron Lett.*, 881 (1977).

¹¹⁶ F. P. Cossio, I. Marao, H. Jiao, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **121**, 6737 (1999).

¹¹⁷ I. Marao, B. Lecea, and F. P. Cossio, *J. Org. Chem.*, **62**, 7033 (1997); I. Marao and F. P. Cossio, *J. Org. Chem.*, **64**, 1868 (1999).

¹¹⁸ R. Sustmann and H. Trill, *Angew. Chem. Int. Ed. Engl.*, **11**, 838 (1972); R. Sustmann, *Pure Appl. Chem.*, **40**, 569 (1974).

In addition to the electronic effects of substituents, several other structural features affect the reactivity of dipolarophiles. Strain increases reactivity. Norbornene, for example, is consistently more reactive than cyclopentene in 1,3-dipolar cycloadditions. Cyclopentene is also more reactive than cyclohexene. Conjugating substituents, such as the phenyl group in styrene, usually increase reactivity of dipolarophiles (compare styrene with 1-alkenes in Table 10.3).

An interesting series of compounds for which a fairly broad range of data exists is diazomethane, methyl diazoacetate, and diethyl diazomalonate, in which each additional ester group should make the 1,3-dipole successively more electrophilic. The data are given in Table 10.4. We see that diazomethane is primarily nucleophilic in character, dropping sharply in reactivity from electrophilic to nucleophilic dipolarophiles. The other two reactants clearly show an ambiphilic reactivity. These reagents show increased reactivity with both EWG and ERG dipolarophiles, with the diazomalonate shifted somewhat more toward electrophilic character.

Sustmann and Trill¹¹⁸ summarized these and related reactivity relationships in terms of FMO theory and pointed out that 1,3-DPCA reactions could be of three types, depending on relative placement of the frontier orbitals: (A) $\text{HOMO}_{\text{dipole}}\text{-LUMO}_{\text{dipolarophile}}$ dominant; (B) $\text{LUMO}_{\text{dipole}}\text{-HOMO}_{\text{dipolarophile}}$ dominant; (C) both HOMO-LUMO interactions are significant. The first type should be accelerated by ERG in the dipole and EWG in the dipolarophile. The second type should be facilitated by an EWG in the dipole and an ERG in the dipolarophile. These relationships suggest a parabolic substituent effect as the Type C reactions shift from $\text{LUMO}_{\text{dipolarophile}}$ to mixed to $\text{HOMO}_{\text{dipolarophile}}$ controlled. Figure 10.13 illustrates this relationship for aryl azides. The Hammett ρ is positive for reaction with nucleophilic enamines but negative for the electrophilic dipolarophile maleic anhydride, showing that the direction of the substituent effect depends on the relative importance of the two HOMO-LUMO interactions. The unfunctionalized alkenes cyclopentene and norbornene are nucleophilic in character, but less so than the enamine. Using a wider range of reactants, Sustmann and Trill demonstrated a parabolic rate relationship and developed a mathematical treatment in terms of FMO theory that provided a semiquantitative explanation of relative reactivity.¹¹⁸ We pursue the application of FMO theory to the regiochemistry of the 1,3-DPCA reaction in more detail below.

As with the D-A reaction, the concerted pericyclic mechanism can account for many aspects of the stereochemistry and regiochemistry of the 1,3-DPCA reaction. Most 1,3-DPCA reactions are highly *stereospecific* with respect to the dipolarophile. In one case, it was established that a pair of isomeric dipolarophiles both reacted

Table 10.4. Relative Reactivity for Diazo Compounds

$\text{CH}_2=\text{CHX}$	$\text{CH}_2\text{N}_2^{\text{a}}$	$\text{RO}_2\text{CCHN}_2^{\text{b}}$	$(\text{RO}_2\text{C})_2\text{CN}_2^{\text{c}}$
Acrylate	250,000	930	35
1-Alkene	1	1	1
Styrene	100	2.5	1.5
Vinyl ether	0.02	0.1	0.15
Vinyl amine	0.07	470	620

a. J. Geittner, R. Huisgen, and R. Sustmann, *Tetrahedron Lett.*, 881 (1977).

b. W. Bihlmaier, R. Huisgen, H.-U. Reissig and S. Voss, *Tetrahedron Lett.*, 2621 (1979).

c. H. U. Reissig, Ph. D. Thesis, University of Munich, 1978, as quoted in Ref. 114b.

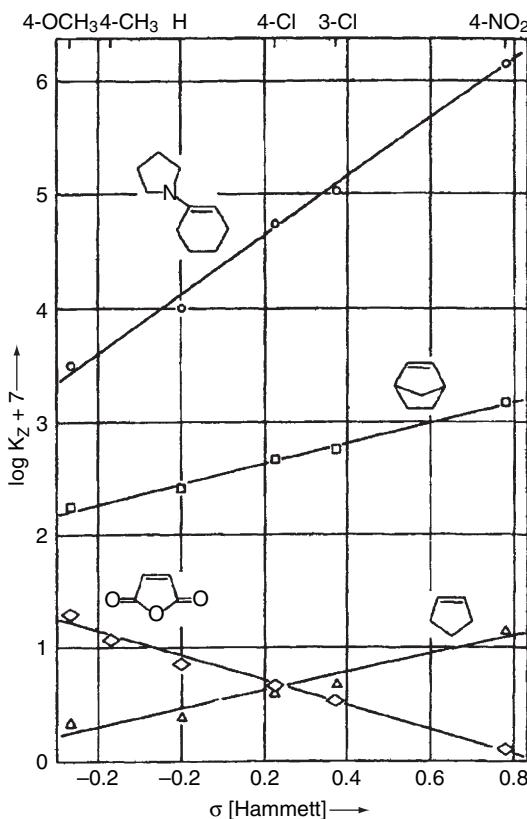
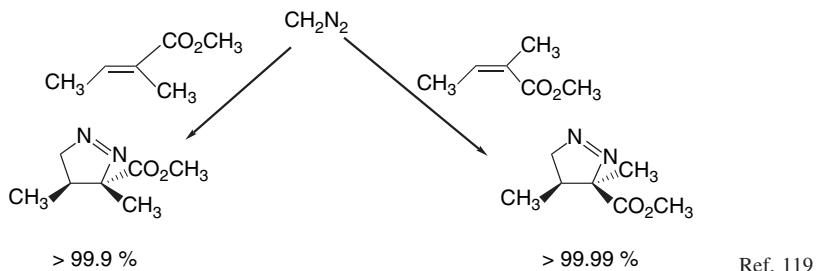


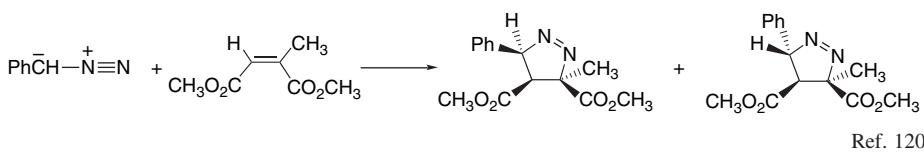
Fig. 10.13. Hammett plots of cycloaddition rates of substituted aryl azides with nucleophilic, electrophilic, and unsubstituted alkenes showing the ambiphilic character of the azide cycloaddition. Reaction with maleic anhydride (electrophilic) is favored by donor substituents. Reaction with pyrrolidinoclohexene (nucleophilic) is favored by acceptor substituents. Reactions with cyclopentene and norbornene are modestly favored by acceptor substituents. Reproduced from *Chem. Ber.*, **100**, 2494 (1967), by permission of Wiley-VCH.

with more than 99.9% stereospecificity, and there are numerous other examples of stereospecific additions.



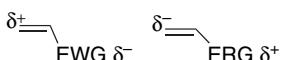
With some 1,3-dipoles, two possible stereoisomers can be formed. These products result from two differing orientations of the reacting molecules and are analogous to

¹¹⁹ W. Bihlmaier, J. Geittner, R. Huisgen, and H. U. Reissig, *Heterocycles*, **10**, 147 (1978).



For unsymmetrical dipolarophiles, two regioisomeric products are also possible. The prediction and interpretation of the stereo- and regioselectivity of 1,3-DPCA reactions have been of ongoing interest. The issues are the same as in the D-A reaction. The reactions are usually under kinetic control, so TS energy is the controlling factor. As the reactants come together, charge transfer and polarization occur, with one reactant donating electron density to the other. As the TS is reached, the degree of bond formation and electron delocalization are important. The TS can be characterized by the extent of orbital interaction, charge transfer, and the degree of bond formation.¹²¹ Reactant conformation may also be a factor in distinguishing between *exo* and *endo* TSs. For any given reaction, computational comparison of TS energies can be informative, but there is also a need for qualitative understanding of the factors that contribute to TS energy and therefore to regio- and stereocontrol.

The polarity of the common dipolarophiles can be recognized from the nature of the substituent.



When both the 1,3-dipole and the dipole are unsymmetrical, there are two possible orientations for addition. Both steric and electronic factors play a role in determining the regioselectivity of the addition. The most generally satisfactory interpretation of the regiochemistry of 1,3-DPCA is based on frontier orbital concepts.¹²² As with the D-A reaction, the most favorable orientation is the one that gives the strongest interaction between the frontier orbitals of the 1,3-dipole and the dipolarophile. Most 1,3-DPCA are of the type in which the frontier orbitals are the LUMO of the dipolarophile and the HOMO of the 1,3-dipole. There are a number of systems in which the relationship is reversed, as well as some in which the two possible HOMO-LUMO interactions are of comparable magnitude.

The analysis of the regioselectivity of a 1,3-dipolar cycloaddition by FMO theory requires information about the energy and atomic coefficients of the frontier orbitals of the 1,3-dipole and the dipolarophile. Most of the more common 1,3-dipoles have been examined using CNDO/2 calculations.^{122b} Figure 10.14 gives estimates of the energies of the HOMO and LUMO orbitals of some representative 1,3-dipoles. By using these orbital coefficients and calculating or estimating the relative energies

¹²⁰ R. Huisgen and P. Eberhard, *Tetrahedron Lett.*, 4343 (1971).

¹²¹ P. Merino, J. Revuelta, T. T. Tejero, U. Chiacchio, A. Rescifina, and G. Romeo, *Tetrahedron*, **59**, 3581 (2003).

¹²² (a) R. Sustmann and H. Trill, *Angew. Chem. Int. Ed. Engl.*, **11**, 838 (1972); (b) K. N. Houk, J. Sims, B. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, **95**, 7287 (1973); (c) R. Sustmann, *Pure Appl. Chem.*, **40**, 569 (1974); (d) I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, New York, 1977; (e) K. N. Houk, in *Pericyclic Reactions*, Vol. II, A. P. Marchand and R. E. Lehr, eds., Academic Press, New York, 1977, pp. 181–271; (f) K. N. Houk, *Top. Curr. Chem.*, **79**, 1 (1979).

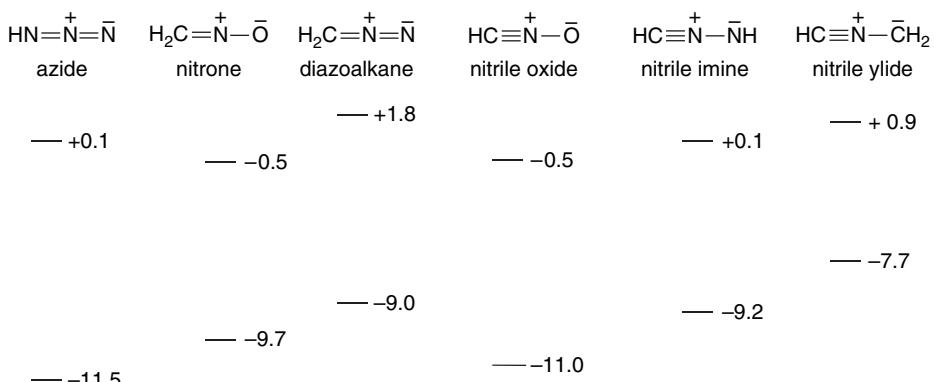


Fig. 10.14. Estimated energies (eV) of frontier π MOs for some 1,3-dipoles. Data from *J. Am. Chem. Soc.*, **95**, 7287 (1973).

of the interacting orbitals, it is possible to make predictions of the regiochemistry of 1,3-DPCA reactions. The most important dipolarophiles are the same types of compounds that are dienophiles in the D-A reaction. The orbital coefficients given in Figure 10.5 can be used in analyses of 1,3-DPCA reactions. In conjunction with the orbital coefficients given in Figure 10.15, this information allows conclusions as to which HOMO-LUMO combination will interact most strongly for a given pair of reactants.

This procedure is illustrated for two specific cases in Figure 10.16. The reaction of a nitrile oxide with an alkene is considered on the left. The smallest energy gap is for the alkene HOMO and the 1,3-dipole LUMO. This is qualitatively reasonable in that the atoms in the 1,3-dipole are more electronegative than those in the dipolarophile. Reference to Figure 10.15 shows that the LUMO coefficient is largest at carbon for the nitrile oxide group. The largest coefficient for a terminal alkene HOMO is at C(1). The matching of the largest coefficients of the 1,3-dipole LUMO and the dipolarophile HOMO leads to the predicted (and observed) product. The same procedure can be applied to the case shown at the right of Figure 10.16. In this case, the 1,3-dipole is the nucleophile and the dipolarophile is the electrophile. The largest coefficient of the nitrone HOMO is at oxygen and the largest coefficient for the acrylate ester LUMO is at the β -carbon.

Although the FMO approach provides a good foundation for understanding the regioselectivity of 1,3-cycloadditions, there are many specific cases in which it fails to provide a complete understanding. Steric factors are not considered by the FMO analysis and in many instances steric factors control regiochemistry. 1,3-DPCA can be broadly classified as *sterically controlled* or *electronically controlled*. There may also be specific interactions in the TSs that are not considered by the FMO analysis.

There have been many studies of individual systems by MO and DFT methods and these provide further insight into the factors that control regio- and stereoselectivity. For example, there are two possible regioisomers from the reaction of diazomethane and methyl vinyl ether, but only the 3-methoxy isomer is formed. Calculations at several levels of theory (AM1, HF/6-31G, and MP2/6-31G*) found lower activation

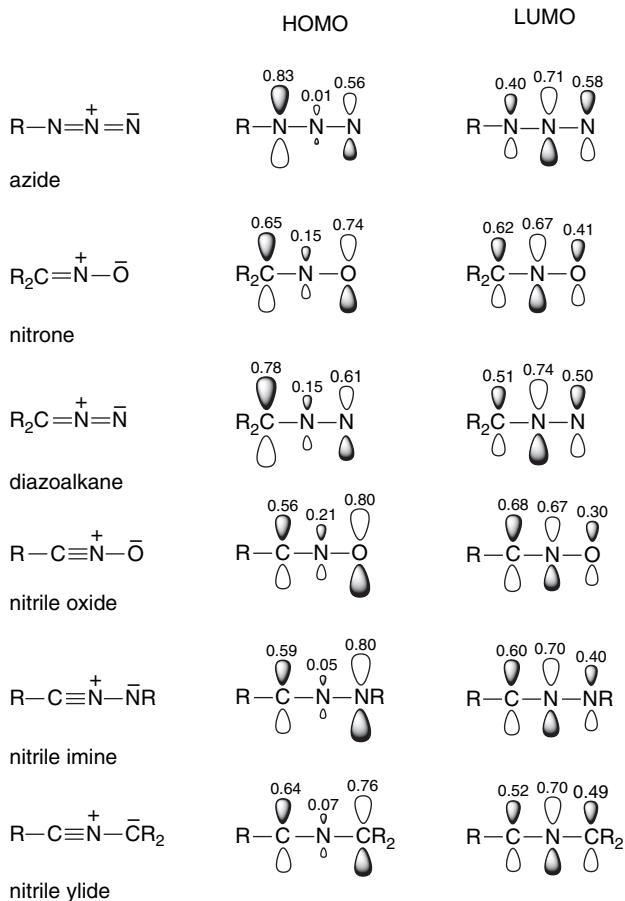


Fig. 10.15. Orbital coefficients for HOMO and LUMO of some common 1,3-dipoles. Data from *J. Am. Chem. Soc.*, **95**, 7287 (1973).

energies for the TS leading to the observed product.¹²³ The energies (MP2/6-31G*) of the four different TSs are shown in Figure 10.17.

To dissect the factors involved, the TSs were approached in stepwise fashion and the energies associated with each step were assessed. The steps were: (a) deformation of the reactants to their TS geometry; (b) approach of the reactants to the TS geometry; and (c) bond formation. The picture that emerged was that the *earliest* TS had the lowest E_a . Although the total binding energy was less in this looser TS, there was a smaller cost in terms of deformations and repulsions for bringing the reactants together. The favored TS was also characterized by the lowest dipole moment and reflects a favorable alignment of the electrostatic features of the reactants. Finally, bond formation was favored in this TS by a relatively strong donor-acceptor interaction between the HOMO of the electron-rich vinyl ether and the LUMO of the dipolarophile, in agreement with the qualitative FMO analysis.

¹²³ Y. L. Pascal, J. Chanet-Ray, R. Vessiere, and A. Zeroual, *Tetrahedron*, **48**, 7197 (1992); A. Rastelli, M. Bagatti, R. Gandolfi, and M. Burdisso, *J. Chem. Soc., Faraday Trans.*, **90**, 1077 (1994).

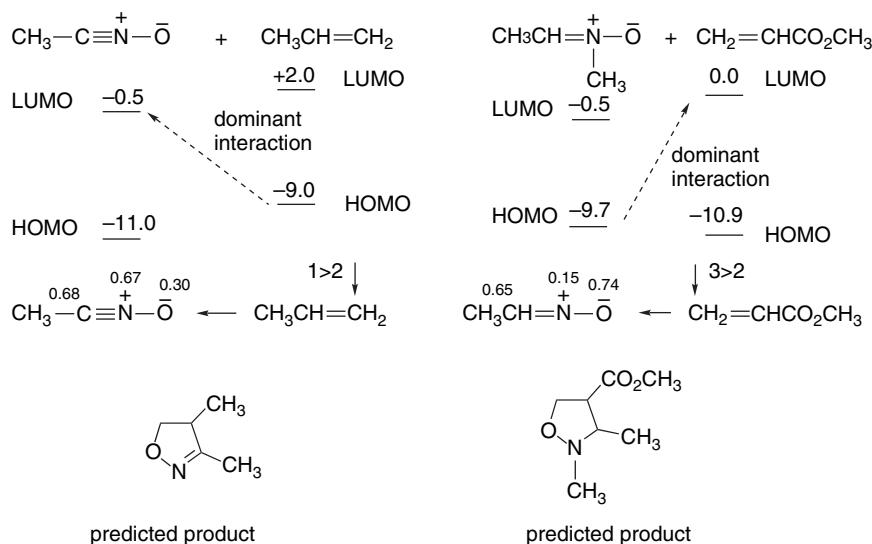


Fig. 10.16. Prediction of the regioselectivity of 1,3-dipolar cycloaddition reactions on the basis of FMO interactions. The orbital energies of the reactants (in eV) are indicated.

In another study, the role of dipolarophile substituents on reactivity was assessed using disubstituted ethenes with the nitrile ylide 1,3-dipole. A DFT (B3LYP/6-31G*) study examined E_a and the degree of synchronicity as a function of substituent electronic character. The reaction had successively smaller E_a and less synchronicity as the substituent became more electron attracting in the order $\text{CH}_3 < \text{Cl} < \text{OH} < \text{C}\equiv\text{N} < \text{N}=\text{O}$.¹²⁴

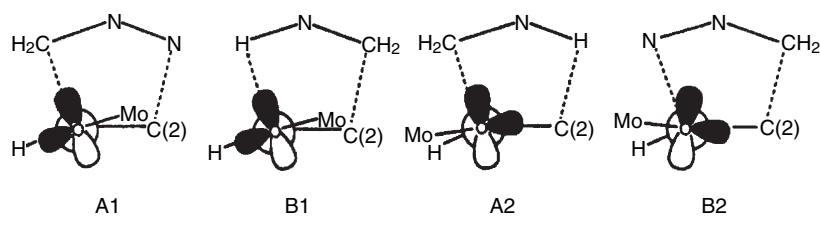
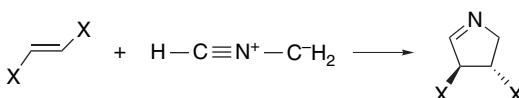


Fig. 10.17. Transition structures for 1,3-dipolar addition of methoxyethene and diazomethane. Structures **A1** and **B1** correspond to the *syn* conformation of methoxyethene, whereas **A2** and **B2** correspond to the *anti* conformation. The TS with the lowest energy corresponds to the observed product. From *J. Chem. Soc., Faraday Trans.*, **90**, 1077 (1994).

¹²⁴ H. Liao, M. D. Su, W.-S. Chung, and S.-Y. Chu, *Int. J. Quantum Chem.*, **83**, 318 (2001).

SECTION 10.3

1,3-Dipolar Cycloaddition Reactions

X	E_a	Degree of Asynchronicity
N = O	-1.4	0.309
C≡N	+1.4	0.198
Cl	+10.1	0.107
OH	+13.2	0.154
CH ₃	+14.3	0.025

Note that there is no barrier for the (hypothetical) reaction with dinitrosoethene. For X = N=O and C≡N, shallow energy minima for prereaction complexes were identified. The conclusion that can be drawn from this study is that stronger EWGs in the dipolarophile lead to greater electrophile/nucleophile character and higher reactivity. This is the same qualitative trend noted for D-A reactions (see p. 847). The nitrile ylide is clearly an electron donor in these reactions, which is consistent with the relatively high energy of the HOMO, as indicated in Figure 10.14.

Computations were also applied to representative 1,3-dipoles in reaction with ethene.¹²⁵ The E_a and ΔE for the reactions were calculated using CCSD(T)/6-311G** energies at B3LYP/6-31G* structural minima.

1,3-Dipole	E_a	ΔE	Leading bond (Å)
H-C≡N ⁺ -CH ₂ ⁻	+6.9	-72.1	2.443
H-C≡N ⁺ -NH ⁻	+6.9	-62.6	2.326
H-C≡N ⁺ -O ⁻	+11.4	-45.9	2.235
N≡N ⁺ -CH ₂ ⁻	+14.3	-37.0	2.225
N≡N ⁺ -NH ⁻	+17.2	-26.2	2.143
N≡N ⁺ -O ⁻	+23.5	-10.7	2.036

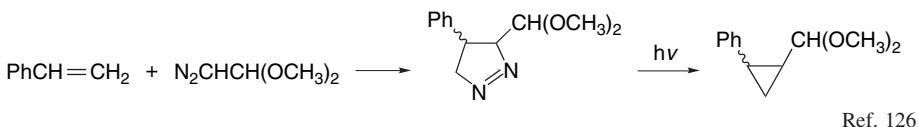
A number of factors appear to be involved here. There is an Bell-Evans-Polyani type correlation with the most stable products (most negative ΔE) having the lowest E_a . There is also a trend toward a later TS with the slower reactions, as indicated by the length of the leading bond in the TS. This is consistent with the Hammond postulate, with the smaller E_a correlating with an early TS. Within the 1,3-dipoles, there is a negative correlation with electronegativity. The most electrophilic 1,3-dipoles are the least reactive in this case. This trend suggests a dominant HOMO_{dipole}-LUMO_{dipolarophile} interaction, but it also may reflect the strength of the bonds being formed, which decreases in the same direction.

In broad terms, there is similarity in the reactivity and regiochemistry relationships for 1,3-DPCA and those of the D-A reaction. The most favorable reactions are those with the most complementary electronic character, that is, high nucleophilicity in one reactant with high electrophilicity in the other. Such reactions have high charge transfer character, early TS, and lower TS energy. Bond formation is more advanced in the TS between the most complementary pair of reaction centers and asynchronicity is high. The best match between HOMO and LUMO predicts the preferred regiochemistry. Relative reactivity trends should also be governed by these criteria, but as yet no broad quantitative analyses of relative reactivity have been developed.

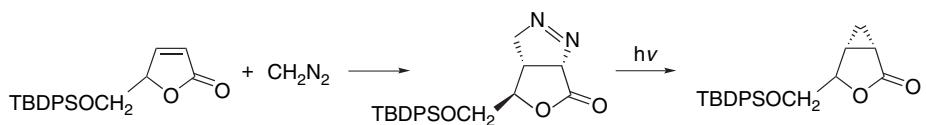
¹²⁵ M.-D. Su, H.-L. Liao, W.-S. Chung, and S.-Y. Chu, *J. Org. Chem.*, **64**, 6710 (1999).

10.3.2. Scope and Applications of 1,3-Dipolar Cycloadditions

As can be judged from Scheme 10.6, a wide variety of five-membered heterocyclic compounds can be made by the 1,3-DPCA reaction. Sometimes, these products are not the final target but rather intermediates for preparation of other compounds. Pyrazolines, which are formed from alkenes and diazo compounds, for example, can be pyrolyzed or photolyzed to give cyclopropanes.

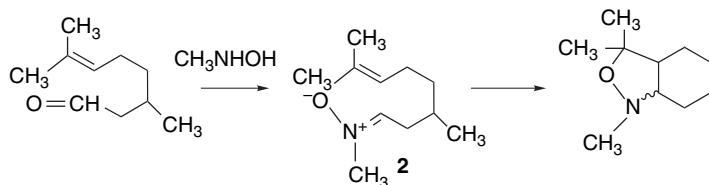


Ref. 126



Ref. 127

The addition of nitrones to alkenes serves both to form a carbon-carbon bond and to introduce oxygen and nitrogen functionality.¹²⁸ The products are isoxazolines and the oxygen-nitrogen bond can be cleaved by reduction, leaving both an amino and a hydroxy function in place. A number of imaginative syntheses have employed this strategy. Intramolecular 1,3-dipolar cycloaddition has proven to be especially useful in synthesis. The nitrone **2** is generated by condensation of the aldehyde group with *N*-methylhydroxylamine and then goes on to product by intramolecular cycloaddition.



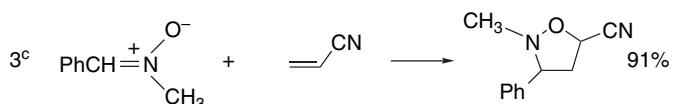
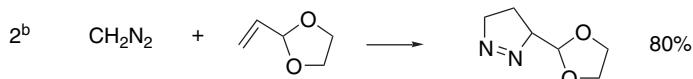
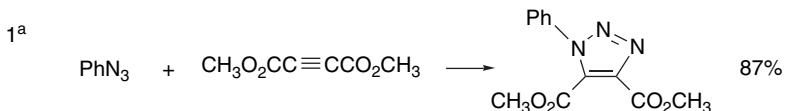
Ref. 129

Scheme 10.7 gives some other examples of 1,3-DPCA reactions. Entries 1 to 3 are typical intermolecular 1,3-DPCA. The 1,3-dipoles in each instance are isolatable compounds. Entries 4 and 5 are intramolecular nitrone cycloadditions. The product from Entry 5 was used in the synthesis of the alkaloid pseudotropine. The proper stereochemical orientation of the hydroxyl group is ensured by the structure of the isoxazoline from which it is formed.

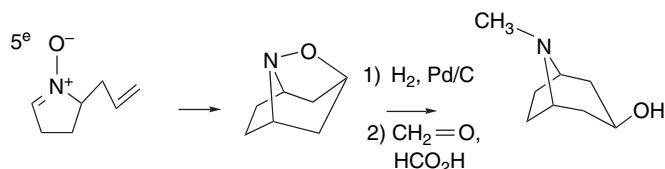
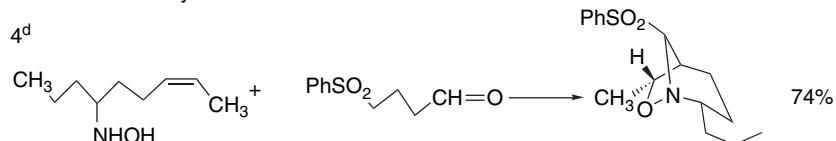
An interesting variation of the 1,3-DPCA involves generation of 1,3-dipoles from three-membered rings. As an example, aziridines **3** and **4** give adducts derived from apparent formation of 1,3-dipoles **5** and **6**, respectively.¹³⁰

- ¹²⁶ P. Carrie, *Heterocycles*, **14**, 1529 (1980).
- ¹²⁷ M. Martin-Vila, N. Hanafi, J. M. Jimenez, A. Alvarez-Larena, J. F. Piniella, V. Branchadell, A. Oliva, and R. M. Ortuno, *J. Org. Chem.*, **63**, 3581 (1998).
- ¹²⁸ For reviews of nitrone cycloadditions, see D. St. C. Black, R. F. Crozier, and V. C. Davis, *Synthesis*, 205 (1975); J. J. Tufariello, *Acc. Chem. Res.*, **12**, 396 (1979); P. N. Confalone and E. M. Huie, *Org. React.*, **36**, 1 (1988).
- ¹²⁹ N. LeBel and D. Hwang, *Org. Synth.*, **58**, 106 (1978).
- ¹³⁰ R. Huisgen and H. Maeder, *J. Am. Chem. Soc.*, **93**, 1777 (1971).

A. Intermolecular Cycloadditions



B. Intramolecular Cycloadditions



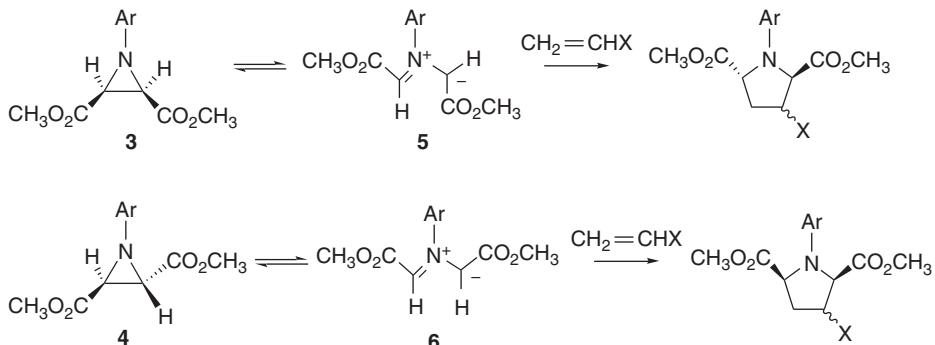
a. R. Huisgen, R. Knorr, L. Möbius, and G. Szejmies, *Chem. Ber.*, **98**, 4014 (1965).

b. J. M. Stewart, C. Carlisle, K. Kem, and G. Lee, *J. Org. Chem.*, **35**, 2040 (1970).

c. R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.*, **101**, 2568 (1968).

d. N. A. LeBel and N. Balasubramanian, *J. Am. Chem. Soc.*, **111**, 3363 (1989).

e. J. J. Tufariello, G. B. Mullen, J. J. Tegler, E. J. Trybulski, S. C. Wong, and S. A. Ali, *J. Am. Chem. Soc.*, **101**, 2435 (1979).

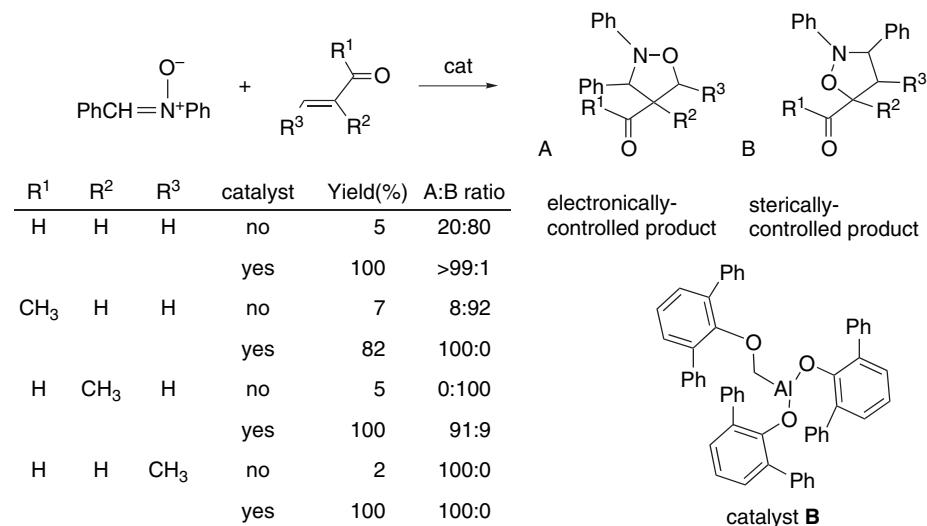


Ring opening is most facile for aziridines that have an EWG to stabilize the carbanion center in the dipole. The evidence for the involvement of 1,3-dipoles as discrete intermediates includes the observation that the reaction rates are independent of dipolarophile concentration. This fact indicates that the ring opening is the

rate-determining step in the reaction. Note that the ring opening is a stereospecific electrocyclic process. (The stereochemistry of electrocyclic ring opening is discussed in Section 10.5).

10.3.3. Catalysis of 1,3-Dipolar Cycloaddition Reactions

The role of catalysts in 1,3-DPCA reactions is similar to that in D-A reactions. Most catalysts are Lewis acids. Effective catalysts include $\text{Yb}(\text{O}_3\text{SCF}_3)_3$ with BINOL,¹³¹ Mg^{2+} -bis-oxazolines,¹³² and oxazaborolidines.¹³³ Intramolecular nitrone cycloadditions can be facilitated by Lewis acids such as ZnCl_2 .¹³⁴ The catalysts function by enhancing the reactivity of *the more electrophilic component of the reaction*. Although the diene is often nonpolar and inert to Lewis acids in D-A reactions, that is not the case for 1,3-DPCA. Consideration of catalysts must include the potential interaction with both the dipole and dipolarophile. Catalyst interaction with the 1,3-dipole is likely to be detrimental if the dipole is the more nucleophilic component of the reaction. For example, with nitrones and enones, formation of a Lewis acid adduct with the nitrone in competition with the enone is detrimental. One approach to this problem is to use highly substituted catalysts that are selective for the less substituted reactant. Bulky aryloxylaluminum compounds are excellent catalysts for nitrone cycloaddition and also enhance regioselectivity.¹³⁵ The reaction of diphenylnitron with enones is usually subject to steric regiochemical control. With the catalyst **B** high *electronic regiochemical control* is achieved and reactivity is greatly enhanced, but the catalyst does not strongly influence the *exo:endo* selectivity, which is 23:77 for propenal.



¹³¹ M. Kawamura and S. Kobayashi, *Tetrahedron Lett.*, **40**, 3213 (1999).

¹³² G. Desimoni, G. Faita, A. Mortoni, and P. Righetti, *Tetrahedron Lett.*, **40**, 2001 (1999); K. V. Gothelf, R. G. Hazell, and K. A. Jorgensen, *J. Org. Chem.*, **63**, 5483 (1998).

¹³³ J. P. G. Seerden, M. M. M. Boeren, and H. W. Scheeren, *Tetrahedron*, **53**, 11843 (1997).

¹³⁴ J. Marcus, J. Brussee, and A. van der Gen, *Eur. J. Org. Chem.*, 2513 (1998).

¹³⁵ S. Kanemasa, N. Ueno, and M. Shirahase, *Tetrahedron Lett.*, **43**, 657 (2002).

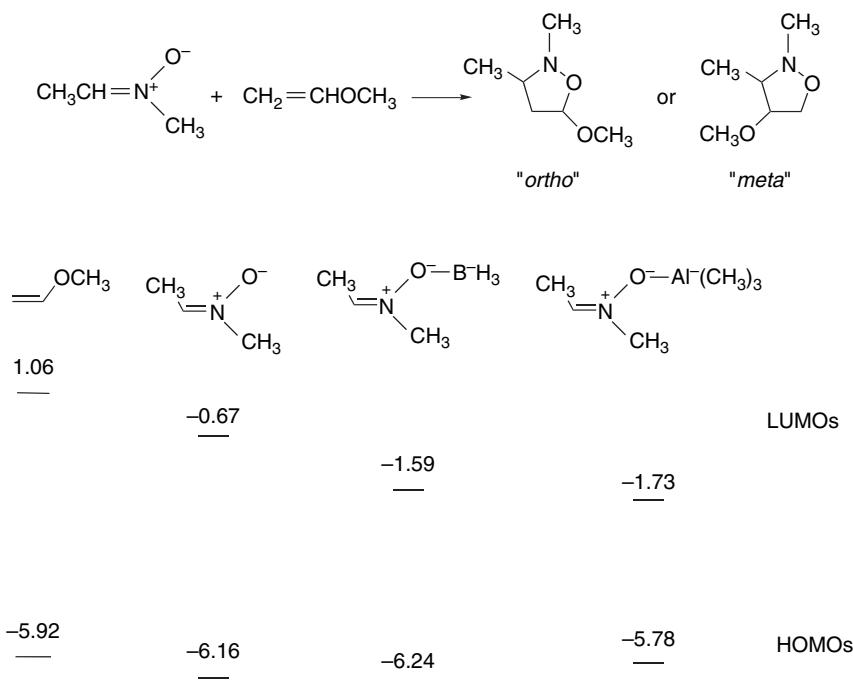


Fig. 10.18. Shift in FMO energy levels (in eV) (B3LYP/6-31G*) on complexation with BH_3 or $(\text{CH}_3)_3\text{Al}$ with nitrone reactant. Data from *Eur. J. Org. Chem.*, 2265 (2000).

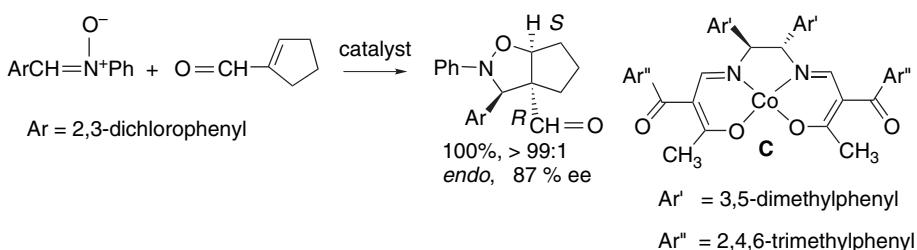
Domingo examined computationally the effect of Lewis acid catalysis in the reaction of a nitrone with a vinyl ether, a combination in which the nitrone is the electrophilic reagent.¹³⁶ The results are summarized in Figure 10.18. The Lewis acid, modeled by BH_3 or $\text{Al}(\text{CH}_3)_3$, is attached at the nitrone oxygen. The Lewis acid decreases the E_a for "ortho" addition, while increasing it for "meta" addition. The catalyst also increases the selectivity for the *exo* TS. These results are consistent with the energy changes of the FMO of the reactants. The catalyst lowers the energy of the nitrone LUMO, enhancing its interaction with the vinyl ether HOMO. The reaction takes on enhanced charge transfer character in the presence of the catalyst. These overall effects are similar to those found in D-A reactions catalyzed by Lewis acids.

As with D-A reactions, it is possible to achieve enantioselective cycloaddition in the presence of chiral catalysts.¹³⁷ Many of the catalysts are similar to those used in enantioselective D-A reactions. The catalysis usually results from a lowering of the LUMO energy of the dipolarophile, which is analogous to the Lewis acid catalysis of D-A reactions. The more organized TS, incorporating a metal ion and associated ligands, then enforces a preferred orientation of the reagents. For example, the bulky aryl groups in the catalyst C favor one direction of approach of the nitrone reactant.¹³⁸

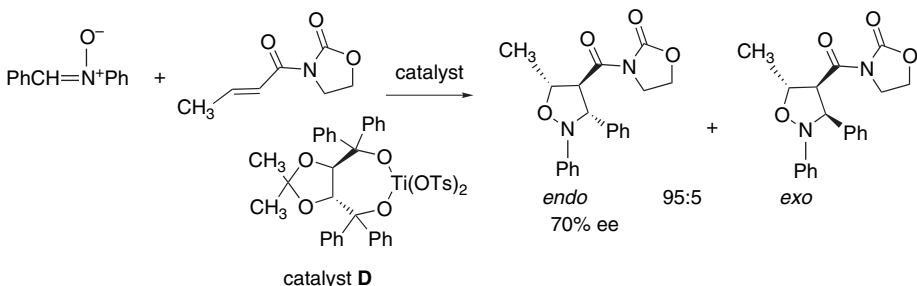
¹³⁶ L. R. Domingo, *Eur. J. Org. Chem.*, 2265 (2000).

¹³⁷ K. V. Gothelf and K. A. Jorgensen, *Chem. Rev.*, **98**, 863 (1998); M. Frederickson, *Tetrahedron*, **53**, 403 (1997).

¹³⁸ T. Mita, N. Ohtsuki, T. Ikeno, and T. Yamada, *Org. Lett.*, **4**, 2457 (2002).



The Ti(IV) TADDOL catalyst **D** leads to moderate to high enantioselectivity in nitrone cycloaddition with *N*-acyloxazolidinones.¹³⁹



10.4. [2 + 2] Cycloaddition Reactions

As indicated in the Introduction, [2 + 2] cycloadditions are forbidden for the $[\pi_{2_s} + \pi_{2_s}]$ topology but allowed for the $[\pi_{2_a} + \pi_{2_s}]$ topology.¹⁴⁰ One example of $[2\pi_s + 2\pi_a]$ cycloaddition involves ketenes.¹⁴¹ An alternative description of the orbital array for this reaction is a $[\pi_{2_s} + (\pi_{2_s} + \pi_{2_s})]$ addition.¹⁴² The basis set orbital arrays for both arrangements are shown in Figure 10.19. The $[\pi_{2_a} + \pi_{2_s}]$ system has Möbius topology, whereas the $[\pi_{2_s} + (\pi_{2_s} + \pi_{2_s})]$ system has Hückel topology with six π electrons involved and is an allowed process.

The TS found for addition is very asynchronous with a strong initial interaction of the ketene *sp* carbon with both carbons of the alkene and considerable polar character.¹⁴³ Analysis of the electronic interactions at the TS by NPA shows substantial charge transfer from ethene to ketene, as would be expected on the basis

¹³⁹ K. V. Gothelf and K. A. Jorgensen, *Acta Chem. Scand.*, **50**, 652 (1996); K. B. Jensen, K. V. Gothelf, R. G. Hazell, and K. A. Jorgensen, *J. Org. Chem.*, **62**, 2471 (1997); K. B. Jensen, K. V. Gothelf, and K. A. Jorgensen, *Helv. Chim. Acta*, **80**, 2039 (1997).

¹⁴⁰ R. B. Woodward and R. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **8**, 781 (1969).

¹⁴¹ W. T. Brady and R. Roe, *J. Am. Chem. Soc.*, **93**, 1662 (1971); W. T. Brady, in *The Chemistry of Ketenes, Allenes and Related Compounds*, S. Patai, ed., John Wiley, Chichester, 1980, Chap. 8.

¹⁴² E. Valenti, M. A. Pericas, and A. Moyano, *J. Org. Chem.*, **55**, 3582 (1990).

¹⁴³ L. A. Burke, *J. Org. Chem.*, **50**, 3149 (1985); X. Wang and K. N. Houk, *J. Am. Chem. Soc.*, **112**, 1754 (1990); S. Yamabe, T. Minato, and Y. Osamura, *J. Chem. Soc., Chem. Commun.*, 53 (1993); S. Yamabe, K. Kuwata, and T. Minato, *Theo. Chem. Acc.*, **102**, 139 (1999).

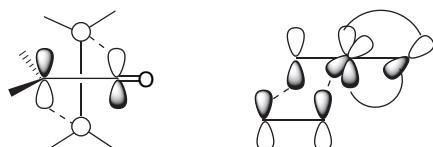


Fig. 10.19. $[\pi 2_a + \pi 2_s]$ and $[\pi 2_s + (\pi 2_s + \pi 2_s)]$ orbital arrays for alkene-ketene $[2 + 2]$ cycloaddition.

of relative electrophilicity.¹⁴⁴ Figure 10.20 gives the bond distances and NPA charges as determined by DFT (BP86/III) computations.

Predictions of stereoselectivity and reactivity based on the $[\pi 2_s + (\pi 2_s + \pi 2_s)]$ TS are in better accord with experimental results than predictions derived from the $[\pi 2_s + \pi 2_a]$ TS.¹⁴⁵ Minimization of interaction between the substituents leads to a cyclobutanone in which the substituents at C(2) and C(3) are *cis*, which is the stereochemistry usually observed in these reactions. For example, *E*- and *Z*-2-butene give stereoisomeric products with ethoxyketene.¹⁴⁶

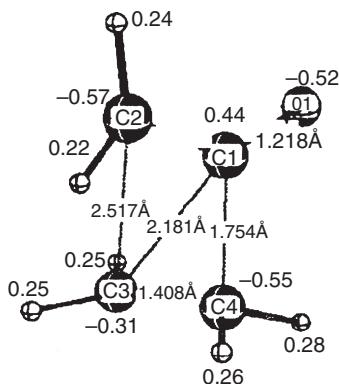
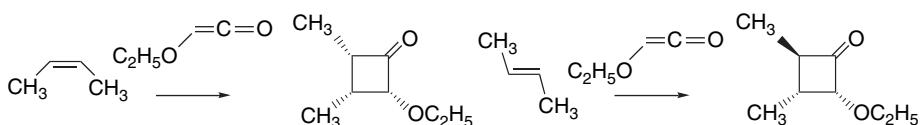


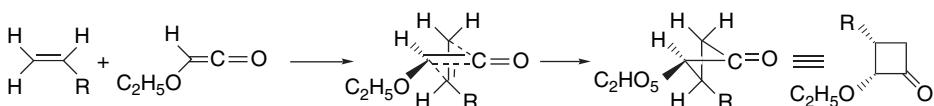
Fig. 10.20. Bond distances and NPA charges for the DFT (BP86/III) transition structure for addition between ketene and ethene. Reproduced from *J. Phys. Chem. A*, **106**, 431 (2002), by permission of the American Chemical Society.

¹⁴⁴ D. V. Deubel, *J. Phys. Chem., A*, **106**, 431 (2002).

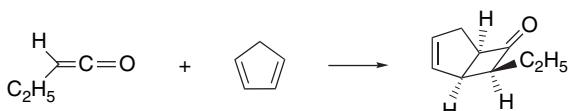
¹⁴⁵ D. J. Pasto, *J. Am. Chem. Soc.*, **101**, 37 (1979).

¹⁴⁶ T. DoMinh and O. P. Strausz, *J. Am. Chem. Soc.*, **92**, 1766 (1970).

For monosubstituted alkenes, the substituent is vicinal and *cis* to the ethoxy group in the cyclobutanone product, a structure that maximizes the separation of the alkyl and ethoxy substituents in the TS.



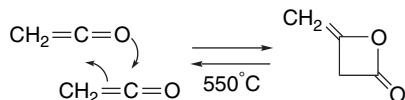
Similarly, ethyl ketene reacts with cyclopentadiene to give the ethyl group in the *endo* position.



Ref. 147

Note also the preference for [2 + 2] rather than [2 + 4] cycloaddition with cyclopentadiene. A computational comparison of the [2 + 2] and [2 + 4] modes of reaction between cyclopentadiene and ketene found the former to have a lower E_a (by about 10 kcal/mol).¹⁴⁸

The best yields are obtained when the ketene has an electronegative substituent, such as halogen. Simple ketenes are not very stable and are usually generated *in situ*. The most common method for generating ketenes for synthesis is by dehydrohalogenation of acyl chlorides, which is usually done with an amine such as triethylamine.¹⁴⁹ Ketene itself and certain alkyl derivatives can be generated by pyrolysis of carboxylic anhydrides.¹⁵⁰ Ketene can also be generated by pyrolysis of acetone.¹⁵¹ Ketene forms a dimer, from which it can be regenerated at 550°C.¹⁵²



Intramolecular ketene cycloadditions are possible if the ketene and alkene functionalities can achieve an appropriate orientation.¹⁵³

^{147.} M. Rey, S. M. Roberts, A. S. Dreiding, A. Roussel, H. Vanlierde, S. Toppet, and L. Ghosez, *Helv. Chim. Acta*, **65**, 703 (1982).

^{148.} U. Salzner and S. M. Bachrach, *J. Org. Chem.*, **61**, 237 (1996).

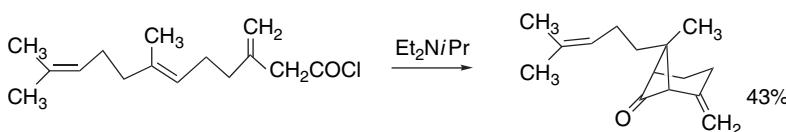
^{149.} K. Shishido, T. Azuma, and M. Shibuya, *Tetrahedron Lett.*, **31**, 219 (1990).

^{150.} G. J. Fisher, A. F. MacLean, and A. W. Schnizer, *J. Org. Chem.*, **18**, 1055 (1953).

^{151.} C. D. Hurd, *Org. Synth.*, **I**, 330 (1941).

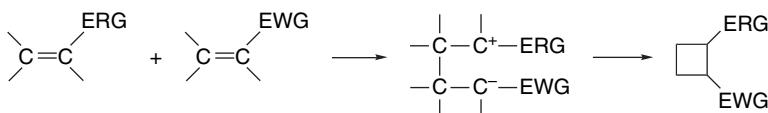
^{152.} S. Andreades and H. D. Carlson, *Org. Synth.*, **V**, 679 (1973).

^{153.} B. B. Snider, R. A. H. F. Hui, and Y. S. Kulkarni, *J. Am. Chem. Soc.*, **107**, 2194 (1985); B. B. Snider and R. A. H. F. Hui, *J. Org. Chem.*, **50**, 5167 (1985); W. T. Brady and Y. F. Giang, *J. Org. Chem.*, **50**, 5177 (1985).

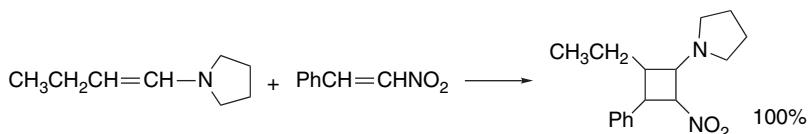


Ref. 154

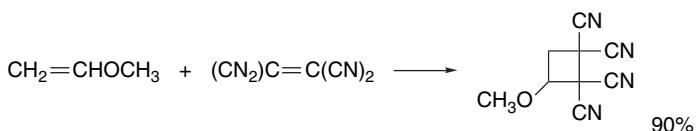
Cyclobutanes can also be formed by nonconcerted processes involving zwitterionic intermediates. The combination of an electron-rich alkene (enamine, vinyl ether) and an electrophilic one (nitro- or policyanoalkene) is required for such processes.



Below are two examples of this reaction type.



Ref. 155



Ref. 156

The stereochemistry of these reactions depends on the lifetime of the dipolar intermediate, which, in turn, is influenced by the polarity of the solvent. In the reactions of enol ethers with tetracyanoethylene, the stereochemistry of the vinyl ether portion is retained in nonpolar solvents. In polar solvents, cycloaddition is nonstereospecific as a result of a longer lifetime for the zwitterionic intermediate.¹⁵⁷

The [2 + 2] cycloaddition of ketenes and imines is an important route to the β -lactam ring (azetidinone),¹⁵⁸ which is a crucial structural feature of the penicillin class of antibiotics. A number of theoretical treatments of this reaction indicate that in solution phase this is a two-step reaction, with the second step being rate determining.¹⁵⁹ The stepwise nature of the reaction is accommodated by the relative stability of both charged moieties, an iminium cation and an enolate anion.

¹⁵⁴ E. J. Corey and M. C. Desai, *Tetrahedron Lett.*, **26**, 3535 (1985).

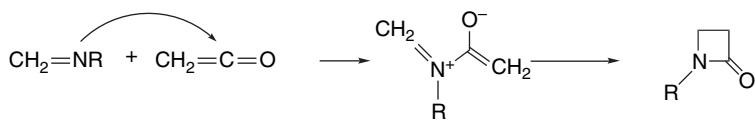
¹⁵⁵ M. E. Kuehne and L. Foley, *J. Org. Chem.*, **30**, 4280 (1965).

¹⁵⁶ J. K. Williams, D. W. Wiley, and B. C. McKusick, *J. Am. Chem. Soc.*, **84**, 2210 (1962).

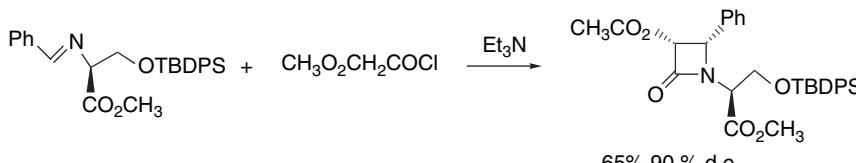
¹⁵⁷ R. Huisgen, *Acc. Chem. Res.*, **10**, 117, 199 (1977).

¹⁵⁸ C. Palomo, J. M. Aizpurua, I. Ganboa, and M. Ojima and F. Dalaloge, *Chem. Soc. Rev.*, **26**, 377 (1997).

¹⁵⁹ X. Assfeld, J. A. Sordo, J. Gonzalez, M. F. Ruiz-Lopez, and T. L. Sordo, *Theochem*, **106**, 193 (1993); X. Assfeld, M. F. Ruiz-Lopez, J. Gonzalez, R. Lopez, J. A. Sordo, and T. L. Sordo, *J. Comput. Chem.*, **15**, 479 (1994); T. N. Truong, *J. Phys. Chem. B*, **102**, 7877 (1998).



In addition to its application in the synthesis of β -lactams, this reaction has been used for stereoselective synthesis of the side chain of the taxol class of antitumor agents.

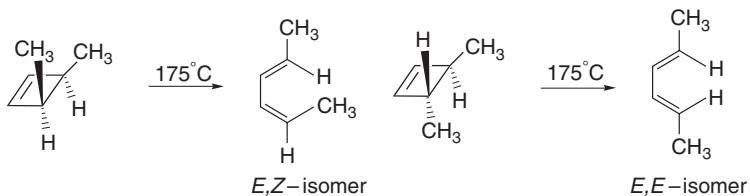


Ref. 160

10.5. Electrocyclic Reactions

10.5.1. Overview of Electrocyclic Reactions

An electrocyclic reaction is defined as the formation of a single bond between the terminal atoms of a linear conjugated system of π electrons and the reverse process. One example is the thermal ring opening of cyclobutenes to butadienes.



Ref. 161

It is not surprising that thermolysis of cyclobutenes leads to ring opening because the strain in the four-membered ring is relieved. The ring opening of cyclobutene to 1,3-butadiene is exothermic by 11 kcal/mol. The E_a for simple alkyl-substituted cyclobutene is in the range of 30–35 kcal/mol.¹⁶² What is particularly significant about these reactions is that they are stereospecific. *cis*-3,4-Dimethylcyclobutene is converted to *E,Z*-2,4-hexadiene, whereas *trans*-3,4-dimethylcyclobutene yields the *E,E*-isomer. The level of stereospecificity is very high. In the ring opening of *cis*-3,4-dimethylcyclobutene, for example, only 0.005% of the minor product *E,E*-2,4-hexadiene is formed, even though it is more stable than the *E,Z*-isomer.¹⁶³

The reason for the stereospecificity is that the groups bonded to the breaking bond rotate in the same sense during the ring-opening process. Such motion, in which all

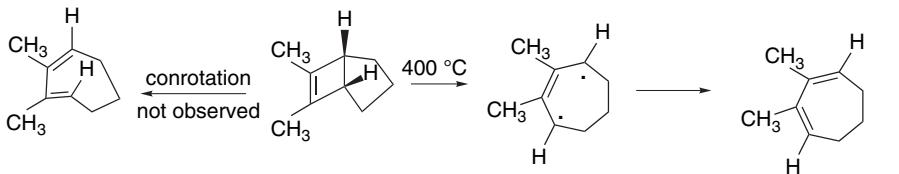
¹⁶⁰ V. Farina, S. I. Hauck, and D. G. Walker, *Synlett*, 761 (1992).

¹⁶¹ R. F. K. Winter, *Tetrahedron Lett.*, 1207 (1965).

¹⁶² W. Kirmse, N. G. Rondan, and K. N. Houk, *J. Am. Chem. Soc.*, **106**, 7989 (1984).

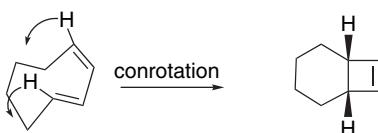
¹⁶³ J. I. Brauman and W. C. Archie, Jr., *J. Am. Chem. Soc.*, **94**, 4262 (1972).

the substituents rotate either clockwise or counterclockwise, is called the *conrotatory* mode. When the conrotatory motion is precluded by some structural feature, ring opening requires a much higher temperature. In the bicyclo[3.2.0]hept-6-ene example shown below, the five-membered ring prevents a conrotatory ring opening because it would lead to the very strained *Z,E*-cycloheptadiene. The reaction takes place only at very high temperature, 400°C, and probably involves the diradical shown as an intermediate.



Ref. 164

The *principle of microscopic reversibility* (see p. 275) requires that the reverse process, ring closure of a butadiene to a cyclobutene, also be conrotatory. Usually this is thermodynamically unfavorable, but a case in which the ring closure is energetically favorable is conversion of *E,Z*-1,3-cyclooctadiene to *cis*-bicyclo[4.2.0]oct-7-ene. The ring closure is favorable in this case because of the strain associated with the *E*-double bond. The ring closure occurs by a conrotatory process.



Ref. 165

Electrocyclic reactions of 1,3,5-trienes lead to 1,3-cyclohexadienes. Note that only the 3-*Z*-isomer can attain a conformation suitable for cyclization. The ring closure is normally the favored direction of reaction for conjugated trienes because of the greater thermodynamic stability of the cyclic compound, which has six σ bonds and two π bonds, whereas the triene has five σ and three π bonds. The closure of *Z*-1,3,5-hexatriene to cyclohexa-1,3-diene is exothermic by 16.4 kcal/mol.¹⁶⁶ The E_a is about 30 kcal/mol.¹⁶⁷ These ring closure reactions also exhibit a high degree of stereospecificity, illustrated with octatrienes **7** and **8**. *E,Z,E*-2,4,6-Octatriene (**7**) cyclizes only to *cis*-5,6-dimethyl-1,3-cyclohexadiene, whereas the *E,Z,Z*-2,4,6-octatriene (**8**) leads exclusively to the *trans* cyclohexadiene isomer.¹⁶⁸ A point of particular importance regarding the stereochemistry of this reaction is that the groups at the termini of the triene system rotate in the opposite sense during the cyclization process, a mode of electrocyclic reaction known as *disrotatory*.

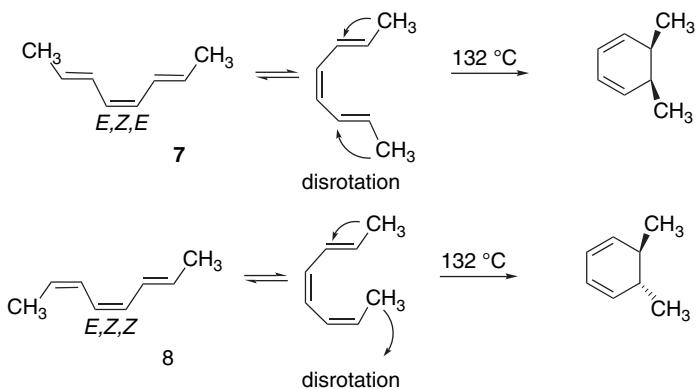
¹⁶⁴ R. Criegee and H. Furr, *Chem. Ber.*, **97**, 2949 (1964).

¹⁶⁵ K. M. Schumate, P. N. Neuman, and G. J. Fonken, *J. Am. Chem. Soc.*, **87**, 3996 (1965); R. S. H. Liu, *J. Am. Chem. Soc.*, **89**, 112 (1967).

¹⁶⁶ R. B. Turner, B. J. Mallon, M. Tichy, W. von E. Doering, W. R. Roth, and G. Schroeder, *J. Am. Chem. Soc.*, **95**, 8605 (1973); W. R. Roth, O. Adamczak, R. Breuckmann, H.-W. Lennartz, and R. Boese, *Chem. Ber.*, **124**, 2499 (1991).

¹⁶⁷ K. E. Lewis and H. Steiner, *J. Chem. Soc.*, 3080 (1964).

¹⁶⁸ E. N. Marvell, G. Caple, and B. Schatz, *Tetrahedron Lett.*, 385 (1965); E. Vogel, W. Grimme, and E. Dinne, *Tetrahedron Lett.*, 391 (1965); J. E. Baldwin and V. P. Reddy, *J. Org. Chem.*, **53**, 1129 (1988).



10.5.2. Orbital Symmetry Basis for the Stereospecificity of Electrocyclic Reactions

A mechanistic description of electrocyclic reactions must explain not only the high degree of stereospecificity, but also why four π -electron systems undergo conrotatory reactions, whereas six π -electron systems undergo disrotatory reactions. Woodward and Hoffmann proposed that the stereochemistry of the reactions is controlled by the symmetry properties of the highest occupied molecular orbital (HOMO) of the reacting system.¹⁶⁹ The idea that the HOMO should control the course of the reaction is another example of *frontier molecular orbital theory* (FMO), which holds that it is the electrons of highest energy, i.e., those in the HOMO, that are of prime importance in determining the course of the reaction (see p. 43).¹⁷⁰

Why do the symmetry properties of the HOMO determine the stereochemistry of the electrocyclic reaction? For convenience, let us examine the microscopic reverse of the ring opening. The stereochemical features of the reaction are the same in both the forward or reverse directions. For conjugated dienes, the HOMO is ψ_2 . For bonding to occur between C(1) and C(4), the positive lobe on C(1) must overlap with the positive lobe on C(4) (or negative with negative, since the signs are interchangeable). This overlap of lobes of the same sign can be accomplished only by a conrotatory motion. Disrotatory motion causes overlap of orbitals of opposite sign, leading to an antibonding overlap that would preclude bond formation. Other conjugated dienes have identical orbital symmetries, so the conrotatory mode is preferred for all thermal electrocyclic processes of 1,3-dienes. The conrotatory process is illustrated in Figure 10.21.

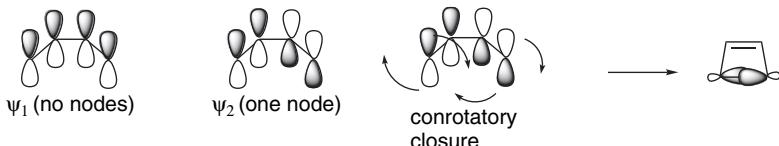


Fig. 10.21. Symmetry properties of the occupied π orbitals of a conjugated diene.

¹⁶⁹ R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395 (1965).

¹⁷⁰ K. Fukui and H. Fujimoto, in *Mechanisms of Molecular Migrations*, Vol. 2, B. S. Thyagarajan, ed., Interscience, New York, 1968, p. 117; K. Fukui, *Acc. Chem. Res.*, **4**, 57 (1971); K. Fukui, *Angew. Chem. Int. Ed. Engl.*, **21**, 801 (1982).

The analysis for the 1,3,5-triene system according to FMO theory proceeds in the same way as for a diene, but leads to the conclusion that a bonding interaction between C(1) and C(6) of the triene will require a disrotatory motion. This is because the HOMO, ψ_3 , has positive lobes on the same face of the π system and these must overlap to permit bond formation. The symmetry properties of other six π -electron conjugated triene systems are the same, so disrotatory ring closure (or opening) is general for conjugated trienes. The π orbitals for the hexatriene system are shown in Figure 10.22.

When we recall the symmetry patterns for linear polyenes that were discussed in Chapter 1 (see p. 29), we can further generalize the predictions based on the symmetry of the polyene HOMO. The HOMOs of the $4n$ systems are like those of 1,3-dienes in having opposite phases at the terminal atoms. The HOMOs of other $4n + 2$ systems are like trienes and have the same phase at the terminal atoms. Systems with $4n \pi$ electrons will undergo electrocyclic reactions by conrotatory motion, whereas systems with $4n + 2 \pi$ electrons will react by the disrotatory mode.

The analysis of electrocyclic reactions can also be done using *orbital correlation diagrams*.¹⁷¹ This approach focuses attention on the orbital symmetries of both reactants and products and considers the symmetry properties of all the orbitals. In any concerted process, the orbitals of the starting material must be smoothly transformed into orbitals of product having the same symmetry. If this process of orbital conversion leads to the ground state electronic configuration of the product, the process will have a relatively low activation energy and be an *allowed* process. If, on the other hand, the orbitals of the reactant are transformed into a set of orbitals that does not correspond to the ground state of the product, a high-energy TS occurs and the reaction is *forbidden*, since it would lead to an excited state of the product.

The cyclobutene-butadiene interconversion can serve as an example of the construction of an orbital correlation diagram. For this reaction to occur, the four π orbitals of butadiene must be converted smoothly into the two π and two σ orbitals of the ground state of cyclobutene. The π orbitals of butadiene are ψ_1 , ψ_2 , ψ_3 , and ψ_4 . For cyclobutene, the four orbitals are σ , π , σ^* , and π^* , with each of them classified with respect to the symmetry elements that are maintained in the course of the transformation. The relevant symmetry features depend on the structure of the reacting system. The most common elements of symmetry to be considered are planes of symmetry and rotation axes. An orbital is classified as symmetric, *S*, if it is unchanged by reflection in a plane of symmetry or by rotation about an axis of symmetry. If the orbital changes sign (phase) at each lobe as a result of the symmetry operation, it is called antisymmetric, *A*. Proper molecular orbitals must be either symmetric or antisymmetric. If an orbital is neither *S* nor *A*, it must be adapted by combination with other orbitals to meet this requirement.

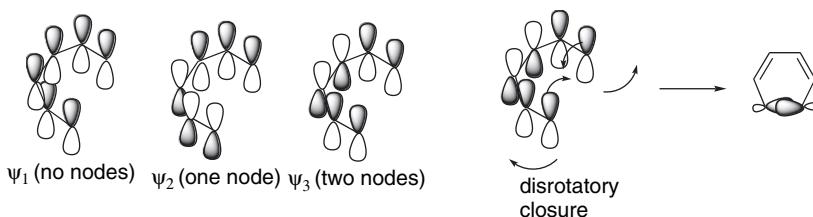
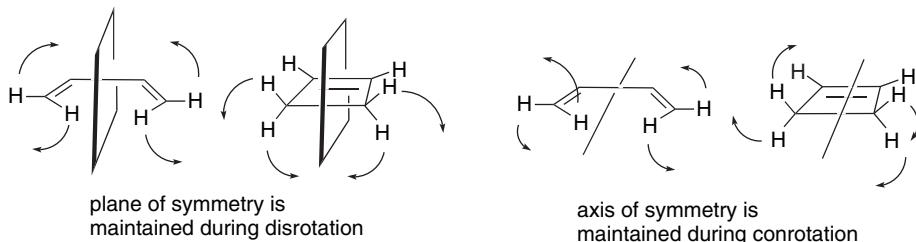


Fig. 10.22. Symmetry properties of the occupied π orbitals of a conjugated triene.

¹⁷¹ H. C. Longuet-Higgins and E. W. Abrahamson, *J. Am. Chem. Soc.*, **87**, 2045 (1965).

Figure 10.23 illustrates the classification of the MOs of butadiene and cyclobutene. There are two elements of symmetry that are common to both *s-cis*-butadiene and cyclobutene: a plane of symmetry and a twofold axis of rotation. The plane of symmetry is maintained during a disrotatory transformation of butadiene to cyclobutene. In the conrotatory transformation, the axis of rotation is maintained throughout the process. Therefore to analyze the disrotatory process, the orbitals must be classified with respect to the plane of symmetry, and to analyze the conrotatory process, they must be classified with respect to the axis of rotation.



Both the disrotatory and the conrotatory process can be analyzed by comparing the symmetry classification of reactant and product orbitals given in Figure 10.23. The orbitals are arranged according to energy in Figure 10.24, and the states of like symmetry for the disrotatory process are connected. It is seen that in the disrotatory process, not all of the ground state orbitals of cyclobutene correlate with ground state orbitals of butadiene. The bonding π orbital of cyclobutene is transformed into an antibonding orbital (ψ_3) of butadiene. In the reverse process, ψ_2 of butadiene is transformed into the antibonding π^* orbital of cyclobutene. Because of the failure of the orbitals of the ground state molecules to correlate, the transformation would lead to a high-energy TS, and the disrotatory reaction is said to be *symmetry forbidden*.

Analysis of the conrotatory process is carried out in exactly the same way. In this case the element of symmetry that is maintained throughout the reaction process is the twofold rotation axis. The resulting correlation diagram is shown in Figure 10.24. The conrotatory reaction is *symmetry allowed*, since the bonding orbitals of butadiene correlate with the bonding orbitals of cyclobutene and vice versa. Figure 10.25 is a pictorial representation of the orbital in the reactant, transition structure, and product.

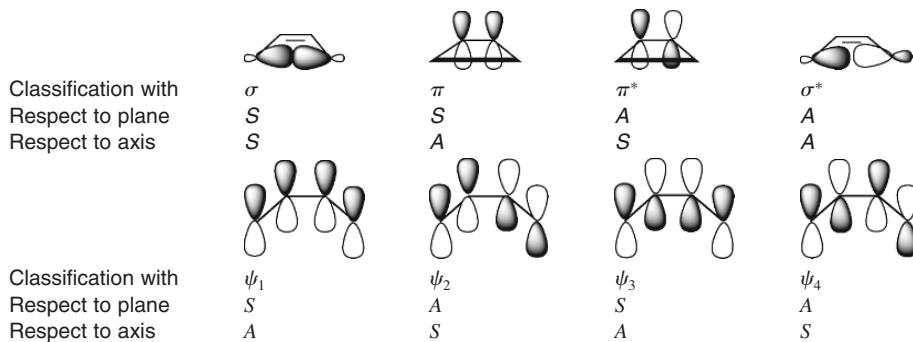


Fig. 10.23. Elements of symmetry for and classification of orbitals for disrotatory and conrotatory interconversion of 1,3-butadiene and cyclobutene.

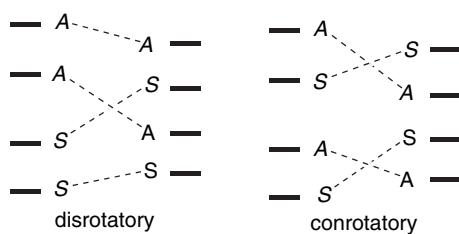


Fig. 10.24. Correlation diagrams for interconversion of cyclobutene and 1,3-butadiene: (left) symmetry forbidden disrotatory reaction; (right) symmetry allowed conrotatory reaction.

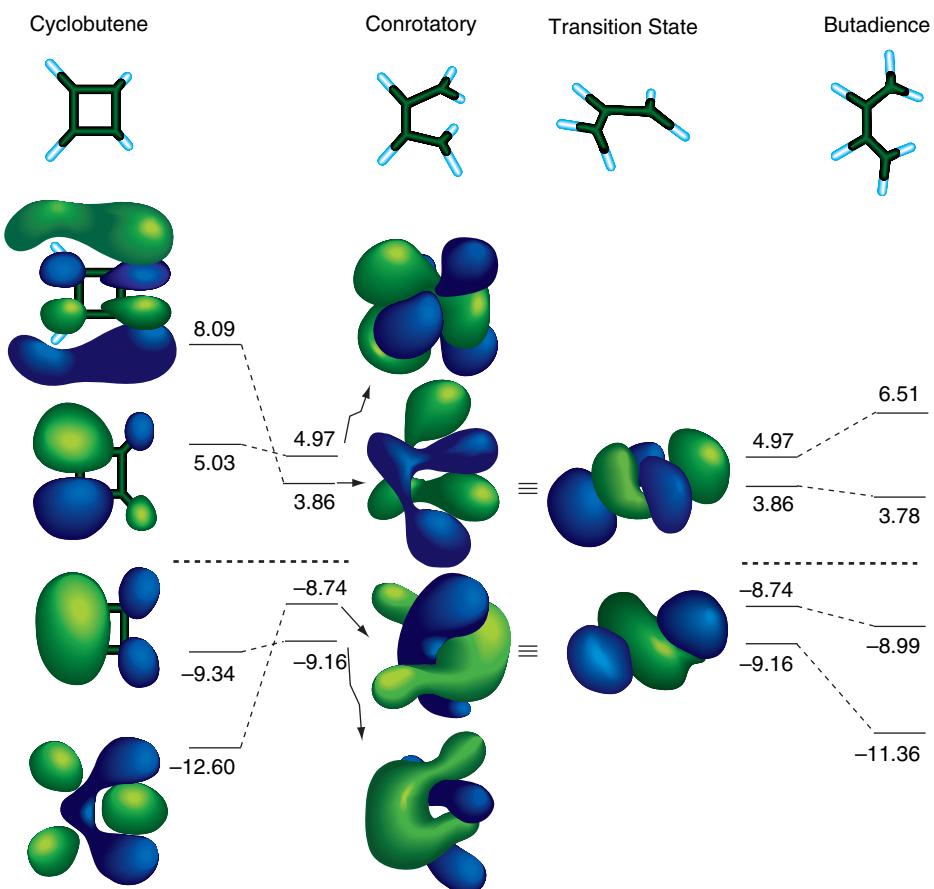
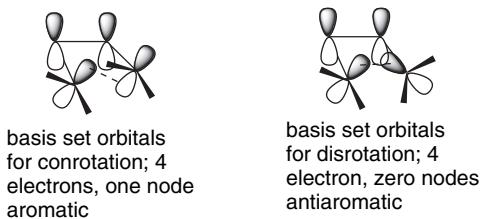


Fig. 10.25. Correlation of orbitals of cyclobutene with the conrotatory transition state and the product, 1,3-butadiene. Energies (in eV) are from HF/6-31G(d) computations. Reproduced from *J. Am. Chem. Soc.*, **125**, 5072 (2003), by permission of the American Chemical Society.

Correlation diagrams can be constructed in an analogous manner for the disrotatory and conrotatory modes for interconversion of 1,3,5-hexatriene and cyclohexadiene. They lead to the prediction that the disrotatory mode is an allowed process, whereas the conrotatory reaction is forbidden, which is in agreement with the experimental results on this reaction. Other electrocyclizations can be analyzed by the same method. Substituted derivatives of polyenes obey the orbital symmetry rules, even in cases where the substitution pattern does not correspond in symmetry to that of the orbital system. It is the symmetry of the participating orbitals, not of the molecule as a whole, that is crucial to the analysis.

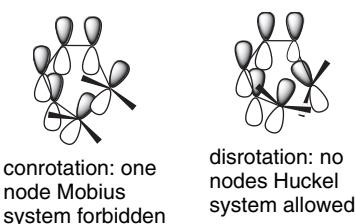
Electrocyclic reactions can also be analyzed on the basis of the idea that transition states can be classified as aromatic or antiaromatic, just as is the case for ground state molecules.¹⁷² A stabilized aromatic TS results in a low activation energy, i.e., an allowed reaction. An antiaromatic TS has a high energy barrier and corresponds to a forbidden process. The analysis of electrocyclizations by this process consists of examining the array of basis set orbitals that is present in the transition structure and classifying the system as aromatic or antiaromatic. For the butadiene-cyclobutene interconversion, the TSs for conrotatory and disrotatory interconversion are shown below. The array of orbitals represents the *basis set orbitals*, that is, the complete set of $2p$ orbitals involved in the reaction process, not the individual molecular orbitals. The tilt at C(1) and C(4) as the butadiene system rotates toward the TS is different for the disrotatory and conrotatory modes. The dashed line represents the σ bond that is being broken (or formed).



For the cyclobutene-butadiene TS, the conrotatory closure results in a Möbius system, whereas a disrotatory TS gives a Hückel system. The same rules of aromaticity apply as for ground state molecules. A Hückel system is aromatic when it has $4n + 2$ electrons. A Möbius system is aromatic when it has $4n$ electrons. In the case of the cyclobutene-butadiene interconversion, which involves four electrons, it is the conrotatory Möbius TS that is the favored aromatic transition state.

Basis set orbital analysis of the hexatriene-cyclohexadiene system leads to the conclusion that the disrotatory process will be favored. The basis set orbitals for the conrotatory and disrotatory transition states are shown below. Here, with six electrons involved, it is the disrotatory mode (Hückel system) that gives a stabilized TS.

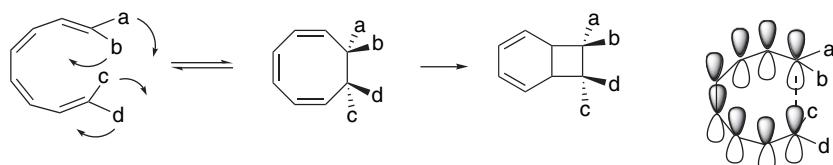
¹⁷² H. E. Zimmerman, *Acc. Chem. Res.*, **4**, 272 (1971); M. J. S. Dewar, *Angew. Chem. Int. Ed. Engl.*, **10**, 761 (1971).



There have been a number of computational studies of the 1,3-butadiene-cyclobutene electrocyclization.¹⁷³ The approaches usually involve location of the minimum energy TS (as described in Section 3.2.2.3) and evaluation of its characteristics. These computational approaches confirm the preference for the conrotatory process, and DFT and CI-MO calculations can provide good estimates of E_a .¹⁷⁴ The aromaticity of the TS structures can also be evaluated computationally. The criteria are the same as for ground state molecules, namely energy, bond lengths, and magnetic properties.¹⁷⁵

A number of theoretical analyses of the 1,3,5-hexatriene electrocyclization support the preference for the disrotatory mode. For example, MP2/CAS/6-311+G(*d,p*) calculations found the TSs for both modes of cyclization, as shown in Figure 10.26. The disrotatory mode is 11 kcal/mol lower in energy.¹⁷⁶

For conjugated tetraenes, $n = 8$, conrotation should be preferred. The expectation that cyclization of eight π -electron systems will be conrotatory has been confirmed by study of isomeric 2,4,6,8-decatetraenes. Electrocyclic reaction occurs near room temperature. The unsubstituted system, has an E_a of 17.0 kcal/mol and ΔH of -11.2 kcal/mol.¹⁷⁷ At slightly higher temperatures, the cyclooctatriene system that is formed undergoes a subsequent disrotatory cyclization, establishing equilibrium with the corresponding bicyclo[4.2.0]octa-2,4-diene.¹⁷⁸



MO calculations (MP2/6-31G*) on the TS confirmed that it is helical and conforms to the expected conrotatory mode.¹⁷⁹ This is a Möbius type TS. The NICS and magnetic properties attributed to the TS by MO calculation also indicate that it has aromatic character.¹⁸⁰

- ^{173.} N. G. Rondan and K. N. Houk, *J. Am. Chem. Soc.*, **107**, 2099 (1985); J. Breulet and H. F. Schaefer, III, *J. Am. Chem. Soc.*, **106**, 1221 (1984); O. Wiest, D. C. Montiel, and K. N. Houk, *J. Phys. Chem. A*, **101**, 8378 (1997).
- ^{174.} L. O. Deng and T. Ziegler, *J. Phys. Chem.*, **99**, 612 (1995); S. Sakai, *Theochem*, **461**, 283 (1999).
- ^{175.} H. Jiao and P. v. R. Schleyer, *J. Phys. Org. Chem.*, **11**, 655 (1998).
- ^{176.} S. Sakai and S. Takane, *J. Phys. Chem. A*, **103**, 2878 (1999).
- ^{177.} G. Desimoni, G. Faita, S. Guidetti, and P. P. Righetti, *Eur. J. Org. Chem.*, 1921 (1999).
- ^{178.} R. Huisgen, A. Dahmen, and H. Huber, *Tetrahedron Lett.*, 1461 (1969); R. Huisgen, A. Dahmen, and H. Huber, *J. Am. Chem. Soc.*, **89**, 7130 (1967); A. Dahmen and R. Huisgen, *Tetrahedron Lett.*, 1465 (1969).
- ^{179.} B. E. Thomas, IV, J. D. Evanseck, and K. N. Houk, *J. Am. Chem. Soc.*, **115**, 4165 (1993); B. E. Thomas, J. D. Evanseck, and K. N. Houk, *Isr. J. Chem.*, **33**, 287 (1993).
- ^{180.} H. Jiao and P. v. R. Schleyer, *J. Chem. Soc., Perkin Trans. 2*, 407 (1994).

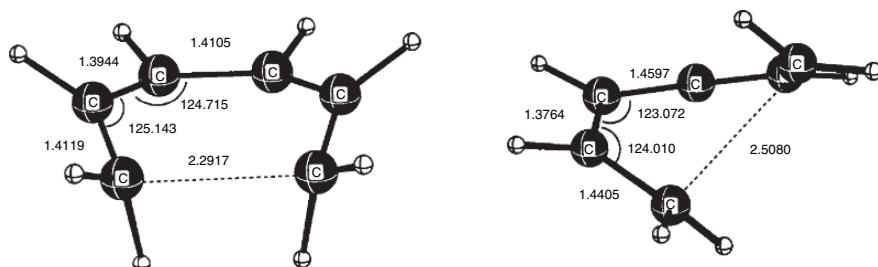


Fig. 10.26. Disrotatory (left) and conrotatory (right) transition structures for 1,3,5-hexatriene electrocyclization from MP2/CAS/6-311+G(*d,p*) calculations. Reproduced from *J. Phys. Chem. A*, **103**, 2878 (1999), by permission of the American Chemical Society.

We have considered three viewpoints from which thermal electrocyclic processes can be analyzed: symmetry characteristics of the frontier orbital, orbital correlation diagrams, and transition state aromaticity. All arrive at the same conclusions about the stereochemistry of electrocyclic reactions. *Reactions involving $4n + 2$ electrons are disrotatory and involve a Hückel-type transition structure, whereas those involving $4n$ electrons are conrotatory and the orbital array are of the Möbius type.* These general principles serve to explain and correlate many specific experimental observations. The chart that follows summarizes the relationship between transition structure topology, the number of electrons, and the feasibility of the reaction.

Orbital Symmetry Rules for Electrocyclic Reactions

Electrons	Hückel (disrotatory)	Möbius (conrotatory)
2	Aromatic	Antiaromatic
4	Antiaromatic	Aromatic
6	Aromatic	Antiaromatic
8	Antiaromatic	Aromatic

Figure 10.27 summarizes the energy relationships for the four-, six-, and eight-electron systems relative to the polyenes. We see that for cyclobutene-1,3-butadiene, ring opening is favored and the E_a is 32 kcal/mol. The E_a is similar for the 1,3,5-triene cyclization (30 kcal/mol), but ring closure is favored. The E_a drops to 17.0 kcal/mol for the *Z,Z*-1,3,5,7-octatriene to 1,3,5-cyclooctatriene cyclization, whereas the E_a for the reverse reaction is 28.2 kcal/mol.

For cyclobutenes, there is another interesting aspect to the stereochemistry of the electrocyclic reactions. There are two stereochemically distinct possibilities for the conrotatory process. A substituent group at C(3) might move away from or toward the breaking bond.

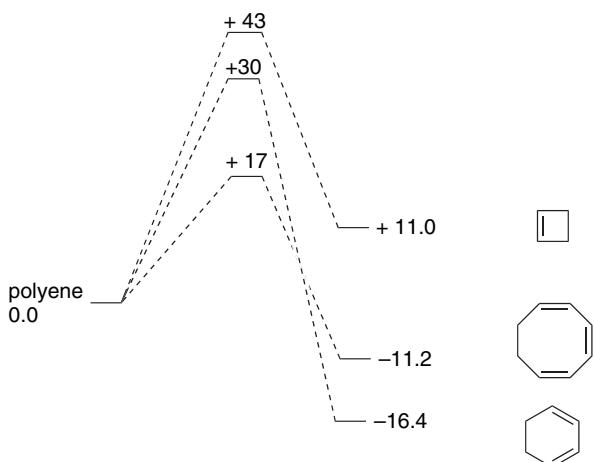
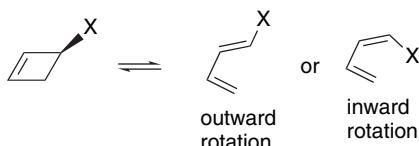
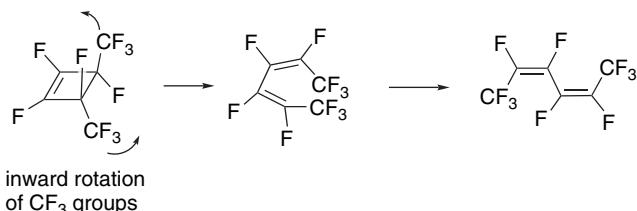


Fig. 10.27. Summary of relative E_a and ΔH relationships in kcal/mol for electrocyclic reactions of conjugated dienes, trienes, and tetraenes.



Steric factors should cause a preference for the larger group to move outward. It was observed, however, that in the case of 1,2,3,4-tetrafluoro-*trans*-3,4-bis(trifluoromethyl)cyclobutene, ring opening occurred with an inward rotation of the trifluoromethyl groups, leading to the *Z,Z*-product.¹⁸¹



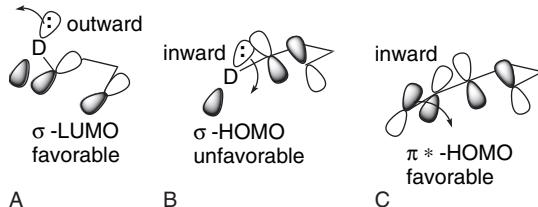
MO calculations (HF/6-21G) for the case of $Y = CH=O$ found that the formyl group preferred to rotate inward and this was confirmed experimentally.¹⁸² A general theoretical analysis indicates that the preference is for donor substituents to rotate outward, whereas acceptor substituents prefer to rotate inward.¹⁸³ A qualitative understanding of this stereoselectivity is based on analysis of the interaction of the substituents with the C(3)–C(4) σ bond that is breaking. The σ and σ^* orbitals of the reacting bond become much closer in energy in the TS, making them better donors and acceptors, respectively, in interactions with substituents. The orbital orientations

¹⁸¹ W. R. Dolbier, Jr., H. Koroniak, D. J. Burton, and P. Heinze, *Tetrahedron Lett.*, **27**, 4387 (1986).

¹⁸² K. Rudolf, D. C. Spellmeyer, and K. N. Houk, *J. Org. Chem.*, **52**, 3708 (1987).

¹⁸³ D. C. Spellmeyer and K. N. Houk, *J. Am. Chem. Soc.*, **110**, 3412 (1988); W. R. Dolbier, Jr., H. Koroniak, K. N. Houk, and C. Sheu, *Acc. Chem. Res.*, **29**, 471 (1996).

are such that donors interact with the LUMO best by outward rotation (**A**) while leading to a repulsive interaction with the HOMO by inward rotation (**B**). In contrast, acceptor substituents stabilize the HOMO in the TS best by inward rotation because a π^* -substituent orbital can provide a stabilizing interaction with the C(3)–C(4) HOMO (**C**). The largest outward preferences are for strong donor groups such as O^- and NH_2 , whereas $\text{CH}=\text{O}$ and $\text{CH}=\text{NH}_2^+$ favor inward rotation.



The rotational preferences for a number of groups have been analyzed by HF/6-31G* computation of TS energies. The trends agree with the rotational preference that is observed experimentally.¹⁸⁴ Some of the substituents have also been examined by DFT [B3LYP/6-31G(d)] computations.¹⁸⁵ Some of the data are given in Table 10.5.

The acetyl group is calculated to have a slight preference for outward rotation. Lewis acids increase the tendency toward inward rotation by making the substituent more electrophilic.¹⁸⁶ In accordance with this expectation, a Lewis acid (ZnI_2) changes the ratio from 2:1 favoring outward rotation to 5:1 favoring inward rotation.

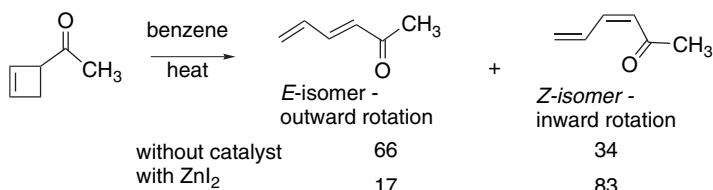


Table 10.5. Directive Effect of Substituents on Inward/Outward Conrotation in Cyclobutene Ring Opening

Donor substituent $\Delta_{\text{in-out}}^{\text{a}}$		Acceptor substituent $\Delta_{\text{in-out}}^{\text{a}}$		
	HF/6-31G* ^a	B3LYP/6-311G*	HF/6-31G* ^b	B3LYP/6-31G* ^c
O^-	24.4		$\text{CH}=\text{O}$	-4.6
NH_2	17.5	14.7	$\text{CH}=\text{NH}_2^+$	-10.1
OH	17.2		NO_2	7.3
F	16.9		$\text{N}=\text{O}$	-2.6
Cl	13.6		CF_3	2.6
CH_3	6.8	6.5	CN	2.3
				4.3

a. $\Delta_{\text{in-out}}$ is energy difference in kcal/mol between transition states for inward and outward rotation.

b. S. Niwayama, E. A. Kallel, D. C. Spellmeyer, C. M. Sheu and K. N. Houk, *J. Org. Chem.*, **61**, 2813 (1996).

c. P. S. Zhang, and K. N. Houk, *J. Am. Chem. Soc.*, **125**, 5072 (2003).

¹⁸⁴. E. A. Kallel, Y. Wang, D. C. Spellmeyer, and K. N. Houk, *J. Am. Chem. Soc.*, **112**, 6759 (1990); S. Niwayama, E. A. Kallel, D. C. Spellmeyer, C. Sheu, and K. N. Houk, *J. Org. Chem.*, **61**, 2813 (1996); W. R. Dolbier, Jr., H. Koroniak, K. N. Houk, and C. Sheu, *Acc. Chem. Res.*, **29**, 471 (1996).

¹⁸⁵. P. S. Lee, X. Zhang, and K. N. Houk, *J. Am. Chem. Soc.*, **125**, 5072 (2003).

¹⁸⁶. S. Niwayama and K. N. Houk, *Tetrahedron Lett.*, **34**, 1251 (1993); S. Niwayama, *J. Org. Chem.*, **61**, 640 (1996).

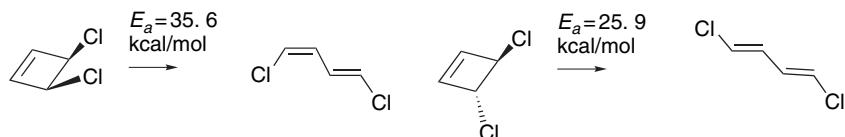
Table 10.6. Effect of Substituents on E_a for Outward or Inward Rotation.

	Strong outward	Moderate outward	Inward		Deactivating (both)	SECTION 10.5
O ⁻ Li ⁺	-17.2	NO ₂	-3.3	BH ₂	-24.5	CF ₃ +3.5 (out)
NH ₂	-14.6	Cl	-3.0	CH=N ⁺ H ₂	-19.5	CF ₃ +5.4(in)
OH	-9.3	CH ₃ C=O	-2.6	C ⁺ (OH) ₂	-18.3	NH ₃ ⁺ +0.5 (out)
F	-6.1	CN	-2.3	N=O	-7.1	NH ₃ ⁺ +8.2(in)
				CH=O	-6.9	

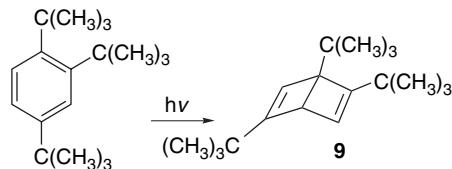
These substituents also have an effect on the reaction rate, which is indicated by the E_a , relative to the unsubstituted compound, as shown in Table 10.6. The strongly outwardly directing donor substituents decrease the E_a more for outward rotation, whereas the inward-directing groups preferentially stabilize the TS for inward rotation. A few substituents, e.g., CF₃ and NH₃⁺, are destabilizing toward both types of TS.

10.5.3. Examples of Electrocyclic Reactions

In addition to the 3,4-dimethylcyclobutene case discussed in Section 10.5.1, there are many other examples of electrocyclic ring opening of cyclobutanes, and *cis*- and *trans*-3,4-dichlorocyclobutene have been examined carefully. The products are those expected for conrotation.¹⁸⁷ In the case of the *trans*-isomer, the product results from outward rotation of both chlorine atoms, in agreement with the calculated substituent effect. The *cis*-isomer, in which one of the chlorines must rotate inward, has a substantially higher E_a .



A particularly interesting case involves the bicyclo[2.2.0]hexa-2,5-diene system. This ring system is a valence isomer of the benzene ring and is often referred to as *Dewar benzene*. Attempts prior to 1960 to prepare Dewar benzene derivatives failed, and the pessimistic opinion was that such efforts would be fruitless because Dewar benzene would be so unstable as to immediately revert to benzene. Then in 1962, van Tamelen and Pappas isolated a stable Dewar benzene derivative **9** by photolysis of 1,2,4-tri-(*t*-butyl)benzene.¹⁸⁸ The compound was reasonably stable, reverting to the aromatic starting material only on heating. Part of the stability of this particular derivative can be attributed to steric factors. The *t*-butyl groups are farther apart in the Dewar benzene structure than in the aromatic structure.



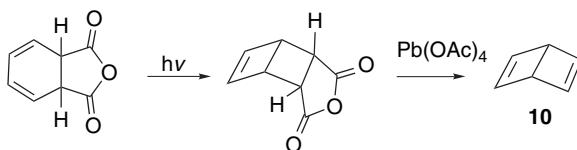
¹⁸⁷ R. Criegee, D. Seebach, R. E. Winter, B. Boerretzen, and H. Brune, *Chem. Ber.*, **98**, 2339 (1963); G. Maier and A. Bothur, *Eur. J. Org. Chem.*, 2063 (1998).

¹⁸⁸ E. E. van Tamelen, S. P. Pappas, and K. L. Kirk, *J. Am. Chem. Soc.*, **93**, 6092 (1971); this paper contains references to the initial work and describes subsequent studies.

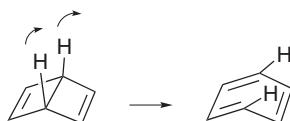
The unsubstituted Dewar benzene **10** was successfully prepared in 1963.

CHAPTER 10

Concerted Pericyclic Reactions



This compound is less stable than **9** and reverts to benzene with a half-life of about 2 days at 25°C, with $\Delta H^\ddagger = 23$ kcal/mol.¹⁸⁹ Nevertheless, the relative kinetic stability of Dewar benzene is surprisingly high when one considers that its conversion to benzene is exothermic by 71 kcal/mol. Furthermore, the central bond is not only strained but also *bis*-allylic. The kinetic stability of Dewar benzene is related to the orbital symmetry requirements for concerted electrocyclic transformations. The concerted thermal pathway would be conrotatory, since the reaction is the ring opening of a cyclobutene and therefore leads not to benzene, but to a highly strained *Z,Z,E*-cyclohexatriene. A disrotatory process, which would lead directly to benzene, is forbidden.



There have been several computational studies of the process.¹⁹⁰ CAS-SCF/6-311G++ calculations found a TS that leads from Dewar benzene to benzene without the intermediacy of the *Z,Z,E*-isomer. Both a conrotatory and a disrotatory TS were found, as shown in Figure 10.28. The conrotatory TS is calculated to be about 22.9 kcal/mol above Dewar benzene and 99.3 kcal/mol less stable than benzene.¹⁹¹ Thus, although a route for ring opening exists, the energy barrier is sufficient to permit the isolation of Dewar benzene.

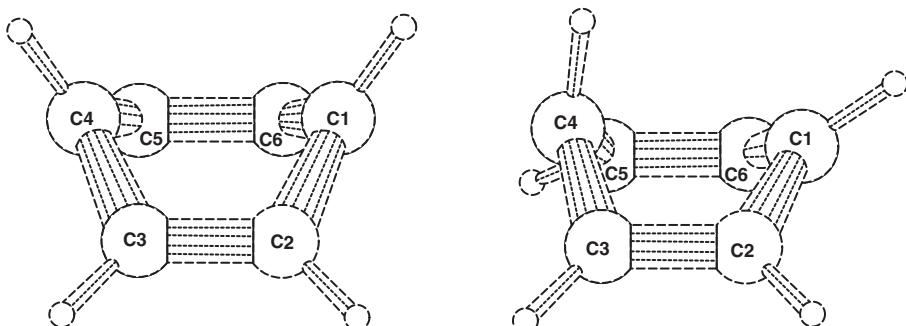
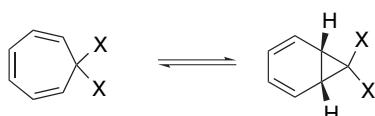


Fig. 10.28. Disrotatory (left) and conrotatory (right) transition structures for conversion of *cis*-bicyclo[2.2.0]hexa-2,5-diene (Dewar benzene) to benzene. The conrotatory TS is 6.6 kcal/mol lower in energy than the disrotatory TS. Reproduced from *Theochem*, **492**, 217 (1999), by permission of Elsevier.

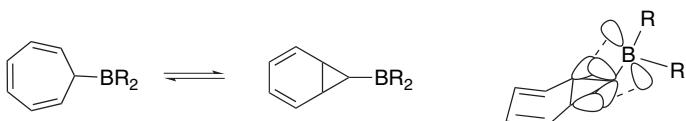
¹⁸⁹ M. J. Goldstein and R. S. Leight, *J. Am. Chem. Soc.*, **99**, 8112 (1977).

¹⁹⁰ R. P. Johnson and K. J. Daoust, *J. Am. Chem. Soc.*, **118**, 7381 (1996).

¹⁹¹ R. W. A. Havenith, L. W. Jenneskens, and J. H. van Lenthe, *Theochem*, **492**, 217 (1999).



There are numerous examples of interconversion of 1,3,5-trienes and 1,3-cyclohexadiene systems by the electrocyclic mechanism.¹⁹² An especially interesting case of hexatriene-cyclohexadiene interconversion is the equilibrium between cycloheptatrienes and bicyclo[4.1.0]hepta-2,4-dienes.¹⁹³



Synthetic applications of electrocyclic reactions are normally designed to take advantage of their stereospecificity, especially for the construction of Z-double bonds. Scheme 10.8. shows some examples. Entries 1 and 2 illustrate the inward rotation of formyl groups in cyclobutenes to generate Z-enals. The product in Entry 3 results from outward rotation of the substituents. Although they are EWGs, their reduced electrophilicity and enhanced steric demands favor outward rotation. Entries 4 to 6 illustrate the formation of cyclohexadienes by triene electrocyclization. Note that in Entry 6, there has also been a hydrogen migration, presumably by a 1,5-hydrogen shift (see Section 10.6).

^{192.} V. A. Bakulev, *Russ. Chem. Rev.*, **64**, 99 (1995).

^{193.} G. Maier, *Angew. Chem. Int. Ed. Engl.*, **6**, 402 (1967).

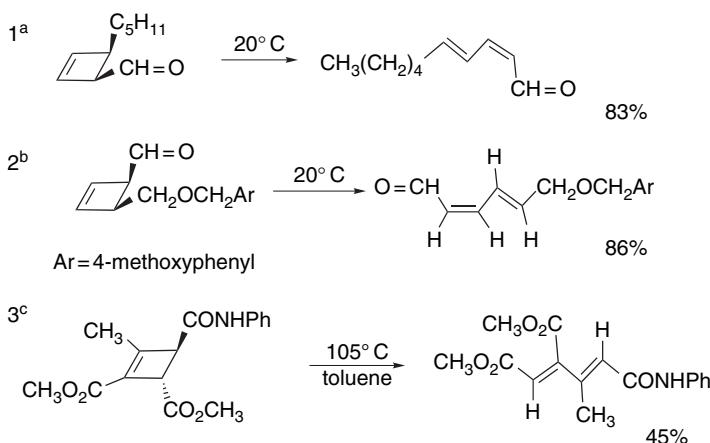
^{194.} M. Gorlitz and H. Gunther, *Tetrahedron*, **25**, 4467 (1969).

^{195.} P. Warner and S.-L. Lu, *J. Am. Chem. Soc.*, **95**, 5099 (1973); P. M. Warner and S.-L. Lu, *J. Am. Chem. Soc.*, **102**, 331 (1980); K. Takeuchi, H. Fujimoto, and K. Okamoto, *Tetrahedron Lett.*, **22**, 4981 (1981); T.-H. Tang, C. S. Q. Lew, Y.-P. Cui, B. Capon, and I. G. Csizmadia, *Theochem*, **305**, 49 (1994); Y. Guzel, E. Saripinar, and L. Yildirim, *Monatsh. Chem.*, **123**, 513 (1996).

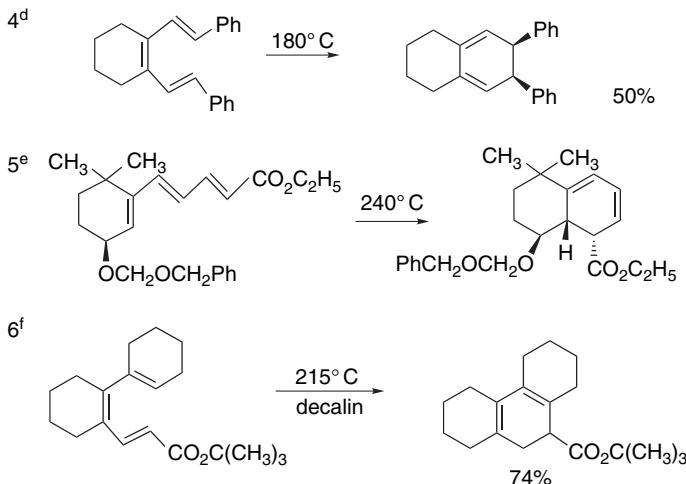
^{196.} I. D. Gridnev, O. L. Tok, N. A. Gridneva, Y. N. Bubnov, and P. R. Schreiner, *J. Am. Chem. Soc.*, **120**, 1034 (1998).

Scheme 10.8. Electrocyclic Reactions

A. Electrocyclic Ring-Opening of Cyclobutenes



B. Electrocyclization of Substituted 1,3,5-hexatrienes.

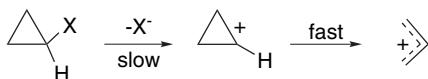


- a. K. J. Hodgetts, S. T. Saengchantara, C. J. Wallis, and T. W. Wallace, *Tetrahedron Lett.*, **34**, 6321 (1993).
- b. F. Binns, R. Hayes, S. Ingham, S. T. Saengchantara, R. W. Turner, and T. W. Wallace, *Tetrahedron*, **48**, 515 (1992).
- c. I. Yavari and S. Asghari, *Tetrahedron*, **55**, 11853 (1999).
- d. K. Voigt, P. von Zezschwitz, K. Rosauer, A. Lansky, A. Adams, O. Reiser, and A. de Meijere, *Eur. J. Org. Chem.*, 1521 (2001).
- e. H. Venkataraman and J. K. Cha, *J. Org. Chem.*, **54**, 2505 (1989).
- f. P. von Zezschwitz, F. Petry, and A. de Meijere, *Chem. Eur. J.*, **7**, 4035 (2001).

10.5.4. Electrocyclic Reactions of Charged Species

The Woodward-Hoffmann orbital symmetry rules are not limited in application to the neutral polyene systems that have been discussed up to this point. They also apply to charged systems, just as the Hückel aromaticity rule can be applied to charged ring systems. The conversion of a cyclopropyl cation to an allyl cation is the simplest

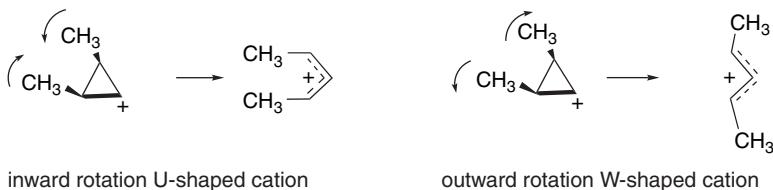
possible case of an electrocyclic process because it involves only two π electrons.¹⁹⁷ Owing to the strain imposed by the cyclopropyl ring, cyclopropyl cations do not form easily, and cyclopropyl halides and sulfonates are quite unreactive under ordinary solvolytic conditions. For example, solvolysis of cyclopropyl tosylate in acetic acid requires a temperature of 180°C. The product is allyl acetate rather than cyclopropyl acetate.¹⁹⁸ This transformation might occur by formation of the cyclopropyl cation, followed by ring opening to the allyl cation or (see below) the reaction might occur in a single step.



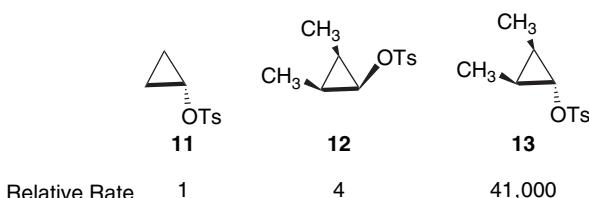
Formation of allylic products is characteristic of solvolytic reaction of other cyclopropyl halides and sulfonates. Similarly, diazotization of cyclopropylamine in aqueous solution gives allyl alcohol.¹⁹⁹

The ring opening of a cyclopropyl cation is an electrocyclic process of the $4n + 2$ type, where n equals zero, and should therefore be a disrotatory process. CCSD(T)/6-311G(2d) and B3LYP/6-31G(2d) computations on the reaction indicate that the cyclopropyl cation is not a stable intermediate and that there is no barrier to electrocyclic ring opening.²⁰⁰ This result implies that the ring opening occurs as a concerted process in conjunction with rupture of the bond to the leaving group.

As with cyclobutenes, there are two possible directions for the allowed disrotation in substituted cyclopropyl cations. For a *cis*-2,3-dimethylcyclopropyl cation, for example, two different disrotatory modes are possible, leading to structurally distinct allyl cations.



The W-shaped allylic cation should be formed in preference to the sterically less favorable U-shaped cation. This issue was investigated by comparing the rates of solvolysis of the cyclopropyl tosylates **11** to **13**.



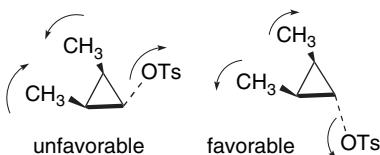
¹⁹⁷ P. v. R. Schleyer, W. F. Sliwinski, G. W. Van Dine, U. Schollkopf, J. Paust, and K. Fellenberger, *J. Am. Chem. Soc.*, **94**, 125 (1972); W. F. Sliwinski, T. M. Su, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **94**, 133 (1972).

¹⁹⁸ J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951).

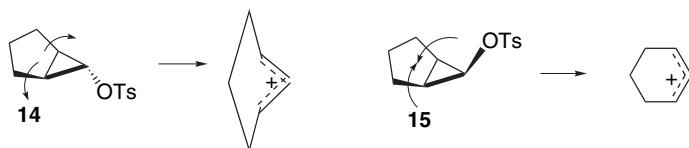
¹⁹⁹ P. Lipp, J. Buchkremer, and H. Seeles, *Justus Liebigs Ann. Chem.*, **499**, 1 (1932); E. J. Corey and R. F. Atkinson, *J. Org. Chem.*, **29**, 3703 (1964).

²⁰⁰ P. A. Arnold and B. K. Carpenter, *Chem. Phys. Lett.*, **328**, 90 (2000).

Some very significant conclusions can be drawn from the data. If formation of the cyclopropyl cation were the rate-determining step, **12** would be more reactive than **13** because the steric interaction between the tosylate leaving group and the methyl substituents in **12** is relieved as ionization occurs. Since **12** is 10,000 times less reactive than **13**, some other factor must be determining the relative rates of reaction and it is doubtful that rate-limiting ionization to a cyclopropyl cation is occurring. The results can be explained, as proposed by DePuy,²⁰¹ if the ionization and ring opening are part of a single, concerted process. In such a process, the ionization is assisted by the electrons in the breaking C(2)–C(3) bond, which provide maximum assistance when positioned toward the back side of the leaving group. This, in turn, requires that the substituents *anti* to the leaving group rotate outward as the ionization proceeds. This concerted process explains why **12** reacts more slowly than **13**. In **12** such a rotation moves the methyl groups together, resulting in increased steric interaction and the formation of the U-shaped allylic anion. In **13**, the methyl groups move away from one another and form the W-shaped allylic ion.



This interpretation is supported by results on the acetolysis of the bicyclic tosylates **14** and **15**. With **14**, after 3 months in acetic acid at 150°C, 90% of the starting material is recovered. This means that both ionization to a cyclopropyl cation and a concerted ring opening are extremely slow. The preferred disrotatory ring-opening process would lead to an impossibly strained structure, the *trans*-cyclohexenyl cation. In contrast, the stereoisomer **15** reacts at least 2×10^6 more rapidly, since it can proceed to a stable *cis*-cyclohexenyl cation.¹⁹⁷



Pentadienyl cations can undergo electrocyclization to cyclopentenyl cations. As this is a four π -electron system, it should occur by conrotation. Based on gas phase ion stability data, the reaction is exothermic by 18 kcal/mol.²⁰²



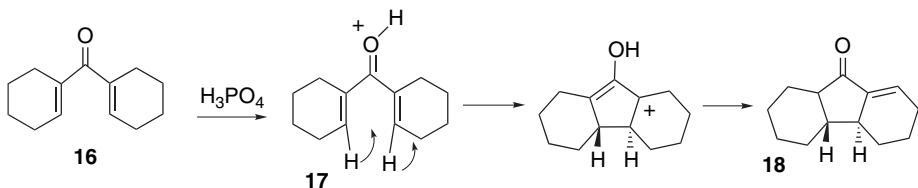
This cyclization has been employed synthetically and is known as the *Nazarov reaction*.²⁰³ An example of preferred conrotatory cyclization of four π -electron cation systems can be found in the acid-catalyzed cyclization of the dienone **16**, which

²⁰¹ C. H. DePuy, *Acc. Chem. Res.*, **1**, 33 (1968).

²⁰² F. P. Lossing and J. L. Holmes, *J. Am. Chem. Soc.*, **106**, 6917 (1984).

²⁰³ K. L. Habermas, S. E. Denmark, and T. K. Jones, *Org. React.*, **45**, 1 (1994).

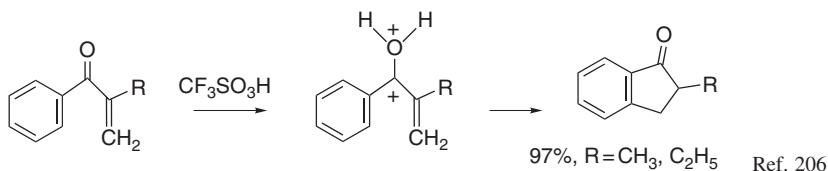
proceeds through the 3-hydroxypentadienyl cation **17**. The final product **18** arises from ketonization and deprotonation, and the stereochemistry is that expected for a conrotatory process.²⁰⁴



Although most synthetic examples of this cyclization have involved protonation of divinyl ketones to give 3-hydroxy-1,4-pentadienyl cations, computational studies suggest that the cyclization would occur even more readily with alternative substituents at C(3).²⁰⁵ For example, the parent ($X = H$) and the boron derivative ($X = BH_2$) are calculated to be more reactive.



Experimental support for this idea comes from the study of cyclization of 1-arylprop-2-en-1-ones to 1-indanones by strong acid.



The acidity dependence of this reaction suggests that it passes through the *diprotonated intermediate* shown. B3LYP/6-31G* and MP2/6-31G* calculations find the E_a to be considerably smaller for the dication than for the corresponding monocation.

E_a (kcal/mol) (B3LYP)					
5.3					
19.9					
6.2					
14.6					
24.6					
12.7					

There are also examples of electrocyclic processes involving anionic species. Since the pentadienyl anion is a six π -electron system, thermal cyclization to a cyclopentenyl anion should be disrotatory. Examples of this electrocyclic reaction are rare. NMR studies of pentadienyl anions indicate that they are stable and do not tend to cyclize.²⁰⁷ Cyclooctadienyllithium provides an example where cyclization does occur,

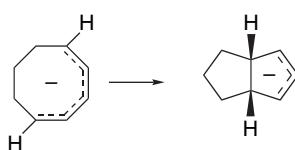
²⁰⁴ R. B. Woodward, in *Aromaticity*, Chemical Society Special Publication No. 21, 217 (1969).

²⁰⁵ D. A. Smith and C. W. Ulmen, *J. Org. Chem.*, **62**, 5110 (1997).

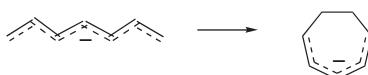
²⁰⁶ T. Suzuki, T. Ohwada, and K. Shudo, *J. Am. Chem. Soc.*, **119**, 6774 (1997).

²⁰⁷ R. B. Bates, D. W. Gosselink, and J. A. Kaczynski, *Tetrahedron Lett.*, 199, 205 (1967); R. B. Bates and D. A. McCombs, *Tetrahedron Lett.*, 977 (1969); R. B. Bates, S. Brenner, C. M. Cole, E. W. Davidson, G. D. Forsythe, D. A. McCombs, and A. S. Roth, *J. Am. Chem. Soc.*, **95**, 926 (1973).

with the first-order rate constant being $8.7 \times 10^{-3} \text{ min}^{-1}$. The stereochemistry of the ring closure is consistent with the expected disrotatory nature of the reaction.

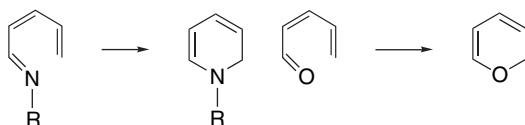


In contrast to pentadienyl anions, heptatrienyl anions cyclize readily to cyclohepta-1,3-dienyl anions.²⁰⁸ The transformation of heptatrienyl anion to cyclohepta-1,3-dienyl anion proceeds with a half-life of 13 min at -13°C . The Woodward-Hoffmann rules predict that this would be a conrotatory closure.²⁰⁹



10.5.5. Electrocyclization of Heteroatomic Trienes

Electrocyclization can also occur when heteroatoms are incorporated into diene, triene, or polyene systems. Most attention has focused on 1-azatriene and 1-oxatrienes, which lead to dihydropyridines and pyrans, respectively.



Comparison of the energy requirements of these reactions with the all-carbon system indicates reduced barriers for the aza and oxa systems, but because of the loss of the C=O bond, the 1-oxahexatriene electrocyclization is slightly endothermic.²¹⁰ Marvell and co-workers estimated the acceleration as being a factor of 10^5 to 10^6 .²¹¹ This result suggests a change in mechanism for the heteroatom cases.

A computational study has examined these effects.²¹² The reaction energy comparisons are given in Figure 10.29 and the transition structure for 1-aza-1,3,5-hexatriene is shown in Figure 10.30. NPA analysis indicates that an unshared pair of the heteroatom participates in the reaction, which leads to a strong preference for outward rotation of the N–H or N–R group in the azatrienes. There is also a change of the TS geometry, relative to 1,3,5-hexatriene. Whereas the C(2)X(1)C(6)C(5) dihedral angle is nearly 0° for X=C, it increases to 30° – 40° for X=O or N. It is the involvement of unshared electrons on oxygen and nitrogen that lowers the energy barrier.

²⁰⁸ E. A. Zuech, D. L. Crain, and R. F. Kleinschmidt, *J. Org. Chem.*, **33**, 771 (1968); R. B. Bates, W. H. Deines, D. A. McCombs, and D. E. Potter, *J. Am. Chem. Soc.*, **91**, 4608 (1969).

²⁰⁹ S. W. Staley, in *Pericyclic Reactions*, Vol. 1, A. P. Marchand and R. E. Lehr, eds., Academic Press, New York, 1977, Chap. 4.

²¹⁰ J. Rodriguez-Otero, *J. Org. Chem.*, **64**, 6842 (1999).

²¹¹ E. N. Marvell, G. Caple, T. A. Gosink, and G. Zimmer, *J. Am. Chem. Soc.*, **88**, 619 (1966).

²¹² M. J. Walker, B. N. Hietbrink, B. E. Thomas, IV, K. Nakamura, E. A. Kallel, and K. N. Houk, *J. Org. Chem.*, **66**, 6669 (2001).

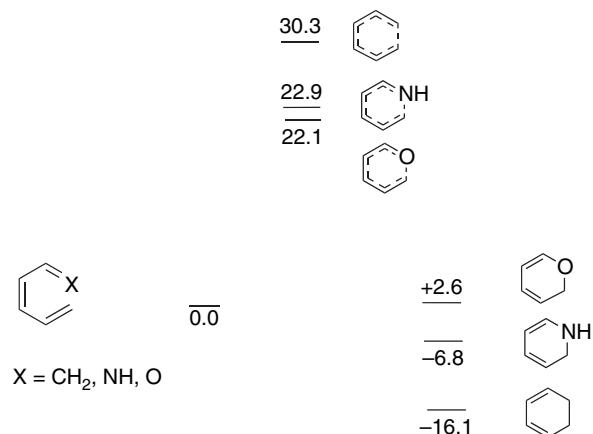


Fig. 10.29. Energy comparisons for electrocyclization of 1-aza- and 1-oxa-1,3,5-hexatriene to 1,3,5-hexatriene in kcal/mol.

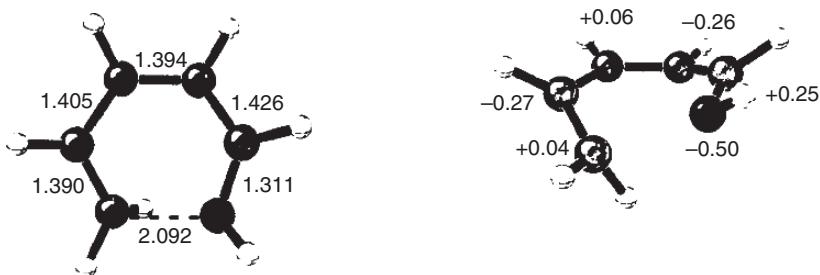


Fig. 10.30. Bond lengths and CHELPG charges of transition structure for electrocyclization of 1-aza-1,3,5-hexatriene. Reproduced from *J. Org. Chem.*, **66**, 6669 (2001) by permission of the American Chemical Society.

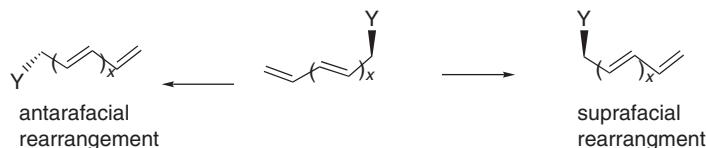
10.6. Sigmatropic Rearrangements

10.6.1. Overview of Sigmatropic Rearrangements

Sigmatropic rearrangements constitute another important class of concerted pericyclic reactions governed by orbital symmetry.²¹³ They involve a reorganization of electrons during which a group attached by a σ bond migrates to the other terminus of a conjugated π -electron system, with a simultaneous shift of the π electrons. Sigmatropic rearrangements are described by stating the relationship between the reacting centers in the migrating fragment and the π system. The order $[i, j]$ specifies the number of atoms in the migrating fragment and in the π system, respectively. As with other concerted reactions, the topology of the interacting orbitals determines the facility and the stereochemistry of each sigmatropic rearrangement. There are two topologically distinct processes by which a sigmatropic migration can occur. If the migrating group remains associated with the same face of the conjugated π system throughout the reaction, the migration is termed *suprafacial*. In the alternative

²¹³ R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 2511 (1965).

mode, called *antarafacial*, the migrating group moves to the opposite face of the π system during the course of the migration. There is another important element of stereochemistry for the migration of alkyl groups. The migrating group can retain its original configuration (retention) or undergo inversion. The stereochemical features and the number of electrons involved determine whether a reaction is allowed or forbidden.



The generalized orbital symmetry selection rules²¹³ are given below. The bases of these rules are discussed for each of the major classes of sigmatropic rearrangements.

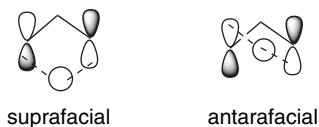
Generalized Orbital Symmetry Rules for Sigmatropic Processes

	Supra/ Retention	Supra/ Inversion	Antara/ Retention	Antara/ Inversion
Order $[1, j]$ $1 + j$				
$4n$	Forbidden	Allowed	Allowed	Forbidden
$4n + 2$	Allowed	Forbidden	Forbidden	Allowed
	Supra/Supra	Supra/Antara	Antara/Antara	
Order $[i, j]$ $i + j$				
$4n$	Forbidden	Allowed	Forbidden	
$4n + 2$	Allowed	Forbidden	Allowed	

Several important types of sigmatropic reactions are listed in Scheme 10.9. We first discuss shifts of hydrogen and alkyl groups, concentrating on [1,3]-, [1,5]-, and [1,7]-shifts. There is also a large and synthetically important group of [3,3]-sigmatropic shifts, which include the Cope and Claisen rearrangements that are dealt with in Section 10.6.3. Finally, [2,3]-sigmatropic shifts are considered in Section 10.6.4.

10.6.2. [1,3]-, [1,5]-, and [1,7]-Sigmatropic Shifts of Hydrogen and Alkyl Groups

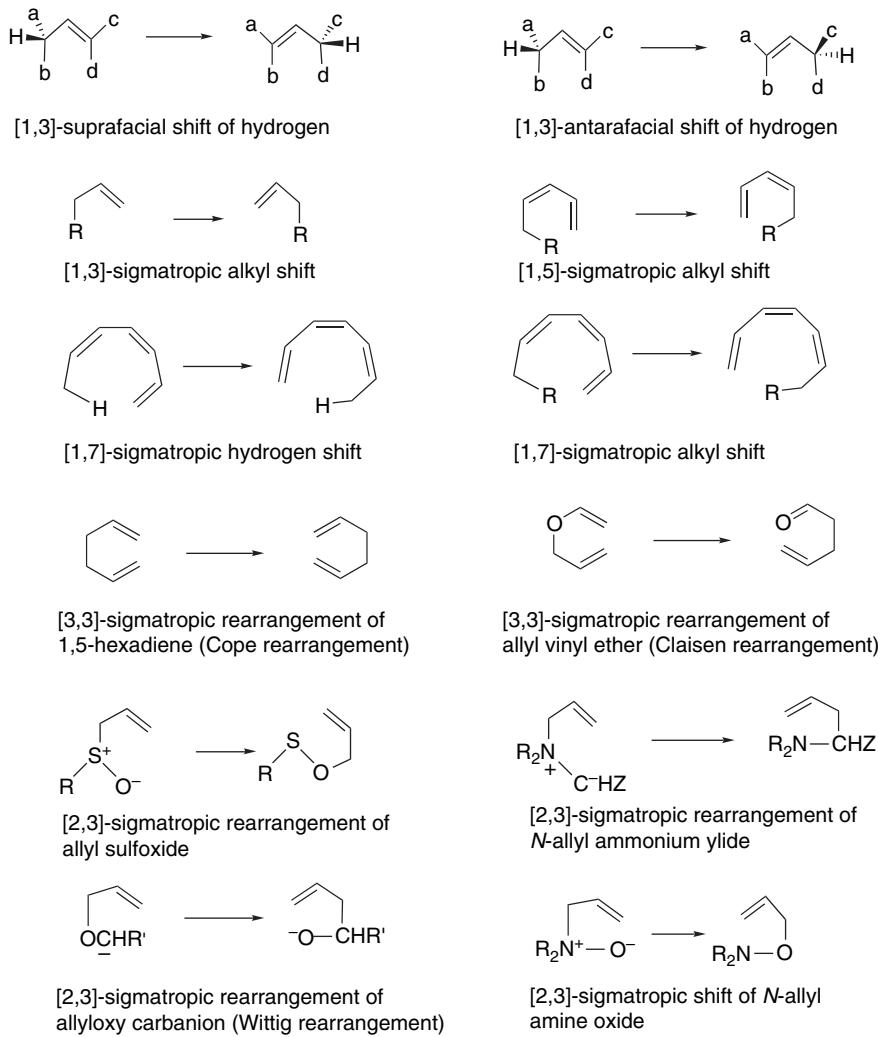
The orbital symmetry requirements of sigmatropic reactions can be analyzed by considering the interactions between the frontier orbitals of the π system and those of the migrating fragment. The simplest case, 1,3-sigmatropic shift of a hydrogen is illustrated in the first entry in Scheme 10.9. An FMO analysis of this process treats the system as a hydrogen atom interacting with an allyl radical. The frontier orbitals are the hydrogen 1s and the allyl ψ_2 orbitals. These interactions are depicted below for both the suprafacial and antarafacial modes.



Scheme 10.9. Examples of Sigmatropic Rearrangements

913

SECTION 10.6

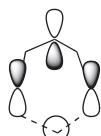
Sigmatropic
Rearrangements

A bonding interaction can be maintained only in the antarafacial mode. The 1,3-suprafacial shift of hydrogen is therefore forbidden by orbital symmetry considerations. The antarafacial process is symmetry allowed, but it involves such a contorted geometry that this shift, too, would be expected to be energetically difficult. As a result, orbital symmetry considerations indicate that concerted [1,3]-shifts of hydrogen are unlikely processes. Computational studies also find that the 1,3-shift of hydrogen should be antarafacial, but in agreement with expectations based on molecular geometry, the TS that is found is so energetic that it is close to a stepwise bond dissociation process.^{214,215}

²¹⁴. B. A. Hess, Jr., L. J. Schaad, and J. Pancir, *J. Am. Chem. Soc.*, **107**, 149 (1985).

²¹⁵. F. Bernardi, M. A. Robb, H. B. Schlegel, and G. Tonachini, *J. Am. Chem. Soc.*, **106**, 1198 (1984).

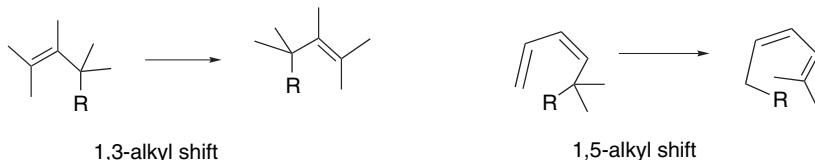
Orbital symmetry analysis of the 1,5-sigmatropic shift of hydrogen leads to the opposite conclusion. The relevant frontier orbitals in this case are the hydrogen 1s and ψ_3 of the pentadienyl radical. The suprafacial mode is allowed, whereas the antarafacial mode is forbidden. The suprafacial shift corresponds to a geometrically favorable six-membered ring.



allowed [1,5]-suprafacial
hydrogen shift in 1,3-pentadiene

An alternative analysis of sigmatropic reactions involves drawing the basis set atomic orbitals and classifying the resulting system as Hückel or Möbius in character. When this classification has been done, the electrons involved in the process are counted to determine if the TS is aromatic or antiaromatic. The conclusions reached are the same as for the frontier orbital approach. The suprafacial 1,3-shift of hydrogen is forbidden but the suprafacial 1,5-shift is allowed. Analysis of a 1,7-shift of hydrogen shows that the antarafacial shift is allowed. This analysis is illustrated in Figure 10.31. These conclusions based on orbital symmetry considerations are supported by HF/6-31G* calculations, which conclude that 1,5-shifts should be suprafacial, whereas 1,7-shifts should be antarafacial.²¹⁴

Sigmatropic migration involving alkyl group shifts can also occur.



When an alkyl group migrates, there is an additional stereochemical feature to consider. The shift can occur with retention or inversion at the migrating center. The analysis of sigmatropic shifts of alkyl groups is illustrated in Figure 10.32. The allowed processes include the suprafacial 1,3-shift with inversion and the suprafacial 1,5-shift with retention.

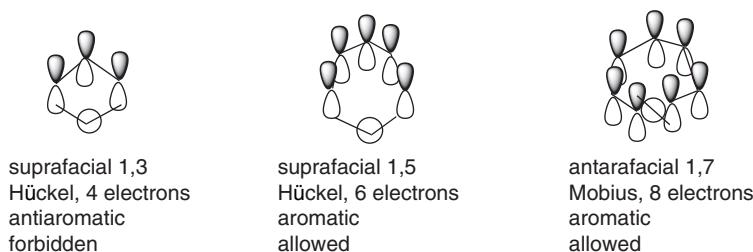


Fig. 10.31. Classification of sigmatropic hydrogen shifts with respect to basis set orbitals.

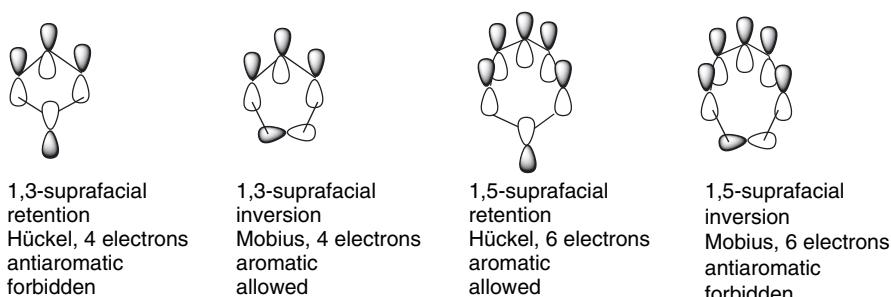


Fig. 10.32. Classification of sigmatropic shifts of alkyl groups with respect to basis set orbitals.

10.6.2.1. Computational Characterization of Transition Structures for [1,3]-, [1,5]-, and [1,7]-Sigmatropic Shifts There have been a number of computational studies aimed at providing information about the TSs of the sigmatropic rearrangements. Chamorro and co-workers characterized the TS for prototypical [1,3]-sigmatropic shifts of hydrogen and methyl.²¹⁶ The 1,3-hydrogen shift is an antarafacial process, whereas the methyl migration is a suprafacial process that occurs with inversion at the alkyl group. The corresponding nuclear positions are depicted in Figure 10.33.

Computational studies on [1,5]-sigmatropic hydrogen shifts are also in agreement with the qualitative predictions based on orbital symmetry relationships. The TS shows aromatic character. Activation energies are calculated²¹⁷ to be in the range 35–37 kcal/mol, in good agreement with the experimental value of 36.3.²¹⁸

Lee and co-workers compared the activation barrier and TS structure for suprafacial migration of BH_2 , CH_3 , and NH_2 at several levels of theory.²¹⁹

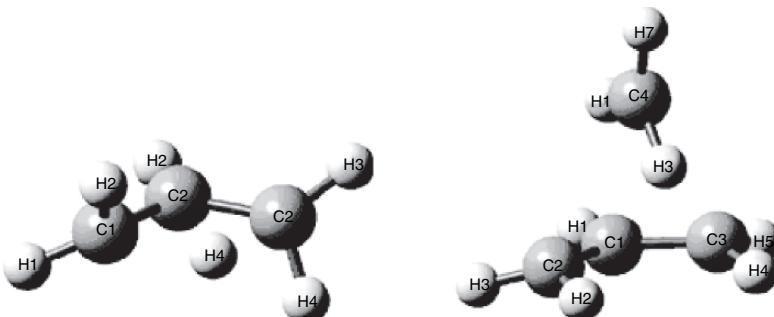


Fig. 10.33. Nuclear positions and for antarafacial [1,3]-sigmatropic migration of hydrogen and for suprafacial [1,3]-sigmatropic migration of methyl with inversion (B3LYP/6-311++G(*d,p*)), Reproduced from *J. Phys. Chem. A*, **106**, 11533 (2002), by permission of the American Chemical Society.

²¹⁶ E. Chamorro, J. C. Santos, B. Gomez, R. Contreras, and P. Fuentealba, *J. Phys. Chem. A*, **106**, 11533 (2002).

²¹⁷ I. Alkorta and J. Elguero, *J. Chem. Soc., Perkin Trans.*, **2**, 2497 (1998); B. S. Jursic, *Theochem*, **423**, 189 (1998); N. J. Saettel and O. Wiest, *J. Org. Chem.*, **65**, 2331 (2000).

²¹⁸ W. R. Roth and J. Konig, *Liebigs Ann. Chem.*, **699**, 24 (1966).

²¹⁹ J. Y. Choi, C. K. Kim, C. K. Kim, and I. Lee, *J. Phys. Chem. A*, **106**, 5709 (2002).



X	BH ₂	CH ₃	NH ₂
B3LYP/6-311++G**	3.72	81.12	69.20
G3	1.52	73.93	67.80
CBS-APNO	0.46	75.82	68.90

The barrier for boron migration is very low, but for $X = \text{CH}_3$ and NH_2 , the barriers are close to the bond dissociation energies, indicating that the reaction would be stepwise. No antarafacial pathways were found. The suprafacial migration is facile for BH_2 because the empty p orbital is available. Figure 10.34 shows the lowest-energy (QCISD/6-311G**) TS and the NPA bond orders associated with them. We see that the vacant p orbital allows for continuous bonding during the migration of BH_2 , whereas the absence of such an orbital for CH_3 and NH_2 results in electronic repulsion and a much higher-energy TS. Note the much greater bond lengths of the allyl fragment. In the case of $X = \text{CH}_3$ and NH_2 , these bonds are close to single-bond lengths, indicating substantial loss of the π bond. It is also worth noting that the allylborane system is isoelectronic with the nonclassical C_4H_7^+ carbocation (see p. 453). The computed TS for BH_2 migration corresponds in structure to the bicyclobutyl carbocation.

10.6.2.2. Examples of Sigmatropic Shifts of Hydrogen and Alkyl Groups With the generalized selection rules as a unifying theoretical framework (see p. 912), we can consider specific examples of sigmatropic rearrangements. In accordance with the orbital symmetry concepts, there are many examples of sigmatropic [1,5]-hydrogen migrations in molecules that incorporate a pentadienyl fragment. The activation energies for such reactions are usually in the vicinity of 35 kcal/mol, so the reactions require moderately elevated temperatures.²²⁰ Two examples are given below. The first rearrangement is detected by migration of the isotopic label. The second results in transformation to a more stable diene.

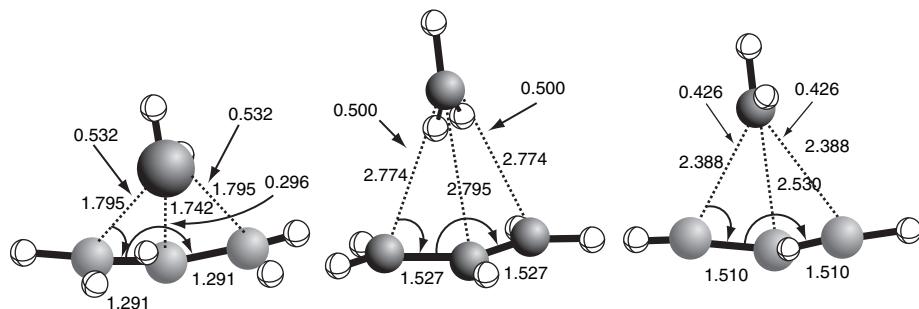
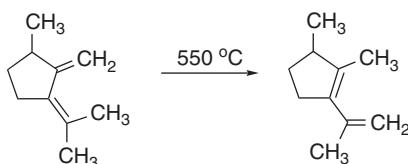
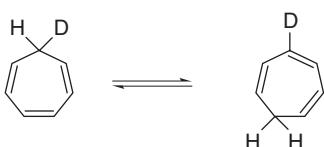


Fig. 10.34. Transition structures for suprafacial 1,3-migrations of BH_2 (left), CH_3 (center), and NH_2 (right) at the QCISD/6-311+G** level. Bond distances and NPA bond orders are shown. Adapted from *J. Phys. Chem. A*, **106**, 5709 (2002), by permission of the American Chemical Society.

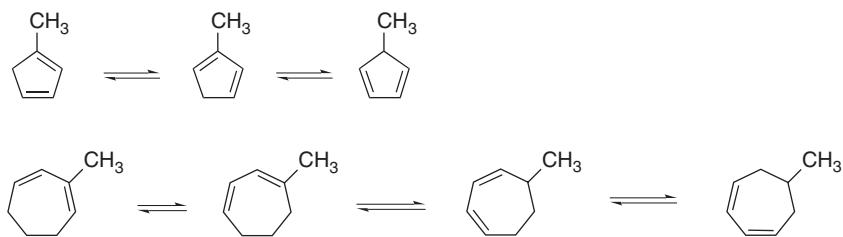
²²⁰ W. R. Roth and J. Koenig, *Liebigs Ann. Chem.*, **699**, 24 (1966).

Ref. 221



Ref. 222

Sigmatropic shifts of hydrogens have been systematically examined in cyclic systems. Early studies demonstrated equilibration among the methylcyclopentadienes²²³ and methylcycloheptadienes by 1,5-hydrogen shift.²²⁴



Computational studies (B3LYP/6-31G*) have been carried out on cyclopentadiene ($E_a = 27$ kcal/mol),²²⁵ 1,3-cyclohexadiene ($E_a = 41.9$ kcal/mol),²²⁶ 1,3-cycloheptatriene ($E_a = 32.7\text{--}35.3$ kcal/mol),²²⁷ and 1,3-cyclooctadiene ($E_a = 32.2$ kcal/mol).²²⁶ In each case, there is reasonable agreement with experimental data. The energy requirement depends on the structure of the TS, which is influenced by the ring geometry. For example, in methyl-substituted 1,3-cycloheptadienes, there are seven minima and seven TS for [1,5]-sigmatropic shifts. The E_a range from 29.6 (4 → TS34) to 35.3 (2 → TS34) kcal/mol. These energy relationships are depicted in Figure 10.35.

Like the thermal 1,3-hydrogen shift, a 1,7-hydrogen shift is allowed when antarafacial but forbidden when suprafacial. Because a π system involving seven carbon atoms is more flexible than one involving only three carbon atoms, the geometrical restrictions on the antarafacial TS are not as severe as in the 1,3-case. For the conversion of Z,Z-1,3,5-octatriene to Z,Z,E-2,4,6-octatriene, the E_a is 20.2 kcal/mol.

- ^{221.} A. P. ter Borg, H Kloosterziel, and N. Van Meurs, *Proc. Chem. Soc.*, 359 (1962).
- ^{222.} J. Wolinsky, B. Chollar, and M. D. Baird, *J. Am. Chem. Soc.*, **84**, 2775 (1962).
- ^{223.} V. A. Mironov, E. V. Sobolev, and A. N. Elizarova, *Tetrahedron*, **19**, 1939 (1963).
- ^{224.} V. A. Mironov, O. S. Chizhov, I. M. Kimelfeld, and A. A. Akhrem, *Tetrahedron Lett.*, 499 (1969).
- ^{225.} I. Alkorta and J. Elguero, *J. Chem. Soc., Perkin Trans. 2*, 2497 (1998).
- ^{226.} B. A. Hess, Jr., and J. E. Baldwin, *J. Org. Chem.*, **67**, 6025 (2002).
- ^{227.} B. A. Hess, Jr., *Int. J. Quantum Chem.*, **90**, 1064 (2002).

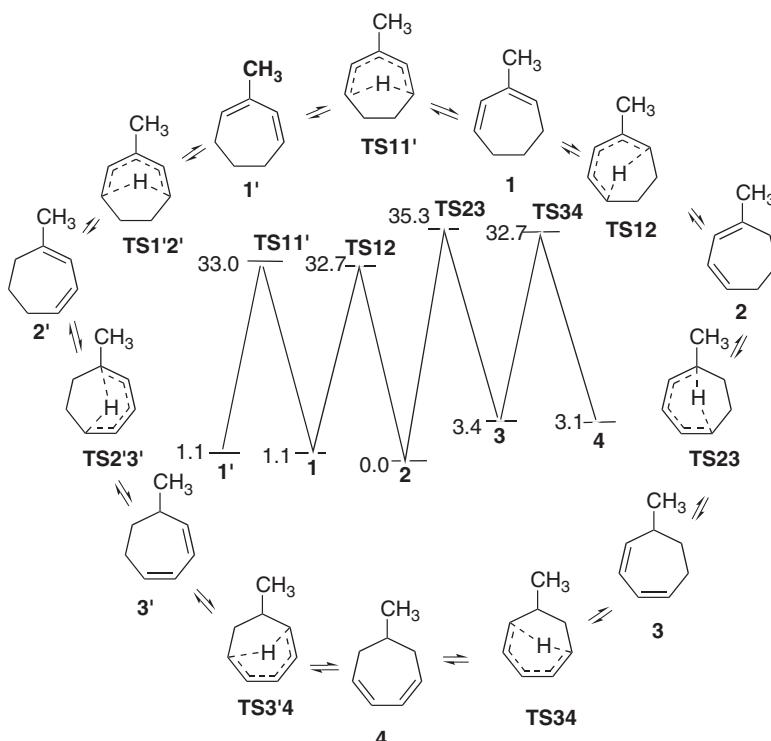
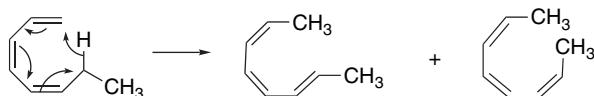


Fig. 10.35. Structures and relative energies of isomeric methyl-1,3-cycloheptatrienes and TS for [1,5]-sigmatropic hydrogen shift between them. Data from *Int. J. Quantum Chem.*, **90**, 1064 (2002).

The *Z,Z,Z*-isomer is also formed, but with a slightly higher activation energy. The kinetic isotope for the transferred hydrogen is around 7, consistent with C–H bond-breaking being involved in the rate-determining step.²²⁸ A similar E_a has been measured for the unsubstituted *Z,Z*-1,3,5-heptatriene.²²⁹

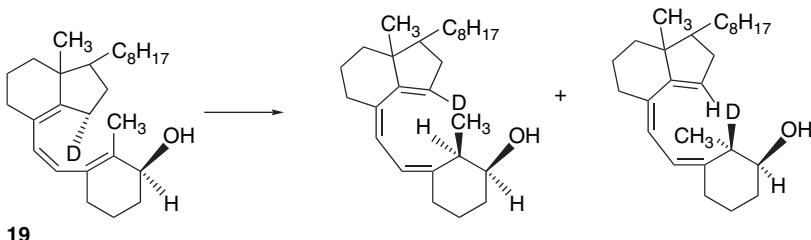


More complex structures such as **19** exhibit similar activation energies. This compound was used to demonstrate that the stereochemistry is *antarafacial*, as predicted by the general selection rules.²³⁰

²²⁸ J. E. Baldwin and V. P. Reddy, *J. Am. Chem. Soc.*, **109**, 8051 (1987).

²²⁹ M. Gurski, I. D. Gridnev, Y. V. Il'ichev, A. V. Ignatenko, and Y. N. Bubnov, *Angew. Chem. Int. Ed. Engl.*, **31**, 781 (1992).

²³⁰ C. A. Hoeger, A. D. Johnston, and W. H. Okamura, *J. Am. Chem. Soc.*, **109**, 4690 (1987); W. H. Okamura, C. A. Hoeger, K. J. Miller, and W. Reischl, *J. Am. Chem. Soc.*, **110**, 973 (1988).



An especially important case of 1,7-hydrogen shift is the thermal equilibrium between precalciferol (previtamin D₃, **20**) and calciferol (vitamin D₃, **21**).^{231,232} This reaction has an E_a of 19.2 kcal/mol.

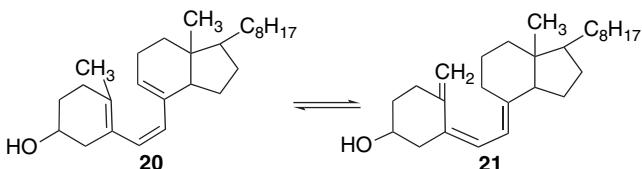


Figure 10.36 summarizes the comparative E_a for [1,3]-, [1,5]-, and [1,7]-hydrogen shifts.

10.6.3. Overview of [3,3]-Sigmatropic Rearrangements

[3,3]-Sigmatropic rearrangements are very important and useful reactions. The most important [3,3]-sigmatropic rearrangement from the synthetic point of view are those that form new carbon-carbon bonds. The [3,3]-sigmatropic rearrangement of 1,5-hexadienes is called the *Cope rearrangement*.

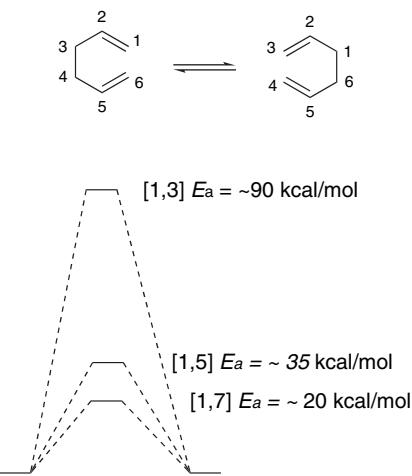
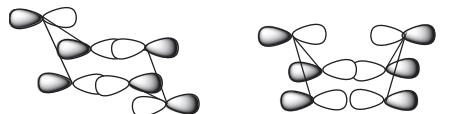


Fig. 10.36. Schematic comparison of E_a for 1,3-, 1,5-, and 1,7-sigmatropic hydrogen shifts.

²³¹ J. L. M. A. Schlatmann, J. Pot, and E. Havinga, *Rec. Trav. Chim.*, **83**, 1173 (1964).

²³² For a historical review of this reaction, see L. Fieser and M. Fieser, *Steroids*, Reinhold, New York, 1959, Chap. 4.

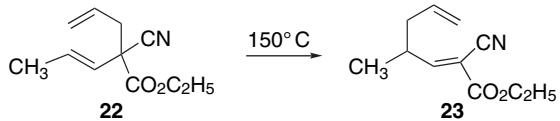
The TS for [3,3]-sigmatropic rearrangements can be considered to be two interacting allyl fragments. When the process is suprafacial in both groups, an aromatic orbital array results and the process is thermally allowed. Usually a chairlike TS is involved but a boatlike conformation is also possible.²³³



chair transition structure boat transition structure
Basis set orbitals for chair and boat transition structures
for [3,3]-sigmatropic shifts. 6 π electrons, Hückel, aromatic

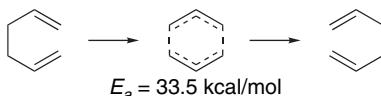
Heteroatoms can be present in the conjugated system or as substituents. From a synthetic point of view, the most important cases have oxygen or nitrogen at position 3. The oxygen case is known as the *Claisen rearrangement*. Oxygen and nitrogen substituents at C(2) or C(3) also provide important variations of [3,3]-sigmatropic rearrangements. Scheme 10.10 gives the structural pattern and names of some of the most important [3,3]-sigmatropic rearrangements. We discuss these variations in the sections that follow.

10.6.3.1. Cope Rearrangements The thermal [3,3]-sigmatropic rearrangement of 1,5-dienes is called the *Cope rearrangement*. Cope rearrangements are reversible reactions and as there is no change in the number or in the types of bonds, to a first approximation the total bond energy is unchanged. The reaction is under thermodynamic control and establishes equilibrium between the two 1,5-dienes. The position of the final equilibrium is governed by the relative stability of the starting material and product. The conversion of **22** to **23** is an example. The equilibrium in this case is controlled by the conjugation with the carbonyl and cyano groups in the product.



Ref. 234

The rearrangement of the simplest possible case, 1,5-hexadiene, has been studied using deuterium labeling. The E_a is 33.5 kcal/mol and the entropy of activation is -13.8 eu.²³⁵ The substantially negative entropy reflects the formation of the cyclic TS.



The Cope rearrangement usually proceeds through a chairlike TS. The stereochemistry of the reaction can be predicted and analyzed on the basis of a chair TS that minimizes steric interactions between the substituents. The reaction is both

²³³ K. J. Shea, G. J. Stoddard, W. P. England, and C. D. Haffner, *J. Am. Chem. Soc.*, **114**, 2635 (1992).

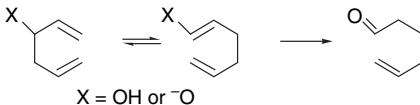
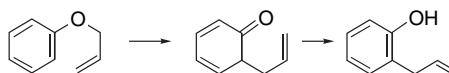
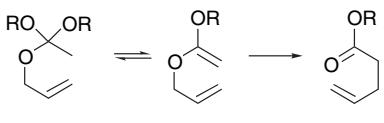
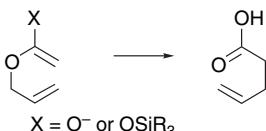
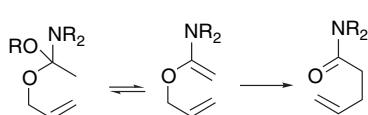
²³⁴ A. C. Cope and E. M. Hardy, *J. Am. Chem. Soc.*, **62**, 441 (1940).

²³⁵ W. v. E. Doering, V. G. Tascano, and G. H. Beasley, *Tetrahedron*, **27**, 5299 (1971); K. A. Black, S. Wilsey, and K. N. Houk, *J. Am. Chem. Soc.*, **120**, 5622 (1998).

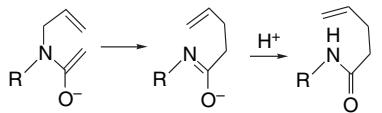
Scheme 10.10. Examples of [3,3]-Sigmatropic Rearrangements

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SECTION 10.6

Sigmatropic
Rearrangements1. Cope Rearrangement^a2. Oxy-Cope and Anionic Oxy-Cope Rearrangement^b3. Claisen Rearrangement of Vinyl Ethers^c4. Claisen Rearrangement of Aryl Ethers^d5. Orthoester Claisen Rearrangement^e6. Ester enolate and Ireland-Claisen Rearrangement^f7. N,N-Dialkyl Ketene Aminal Rearrangement^g8. O-Allyl Imidate Rearrangement^h

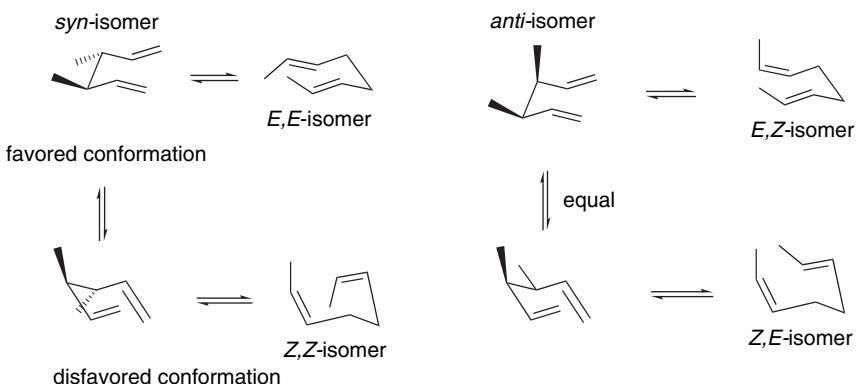
9. N-Allyl Amide Enolate Rearrangement

10. Azonia-Cope Rearrangementⁱa. S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975).b. J. A. Berson and M. Jones, Jr., *J. Am. Chem. Soc.*, **86**, 5019 (1964); D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975).c. A. M. M. Castro, *Chem. Rev.*, **104**, 2939 (2004).d. D. S. Tarbel, *Org. React.*, **2**, 1 (1944).e. W. S. Johnson, L. Wethermann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Am. Chem. Soc.*, **92**, 741 (1970).f. R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, **94**, 5898 (1972); R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).g. D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, **52**, 1030 (1969).h. L. E. Overman, *Acc. Chem. Res.*, **13**, 218 (1980).i. U. Nubbemeyer, *Synthesis*, 961 (2003).j. L. E. Overman, *Acc. Chem. Res.*, **13**, 218 (1980).

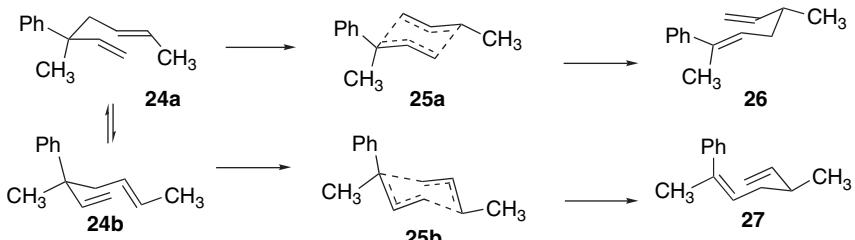
stereospecific and stereoselective. It is stereospecific in that a *Z*- or *E*-configurational relationship at either double bond is maintained in the TS and governs the stereochemical relationship at the newly formed single bond in the product.²³⁶ However, the relationship depends upon the conformation of the TS. When a chair TS is favored the *E,E*- and *Z,Z*-dienes lead to *anti*-3,4-diastereomers, whereas the *E,Z*- and *Z,E*-isomers give the 3,4-*syn* product. The reaction is stereoselective with respect to the configuration of the newly formed double bond. If both *E*- and *Z*- stereoisomers

236. W. v. E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

are possible for the product, the product ratio reflects product (and TS) stability. Thus an *E*-arrangement is normally favored for the newly formed double bonds. The stereochemical aspects of the Cope rearrangements for relatively simple reactants are consistent with a chairlike TS in which the larger substituent at C(3) or C(4) adopts an equatorial-like conformation.



Because of the concerted mechanism, chirality at C(3) or C(4) leads to enantiospecific formation of the new stereocenters at C(1) or C(6).²³⁷ These relationships are illustrated in the example below. Both the configuration of the new stereocenter and the new double bond are those expected on the basis of a chairlike TS. Since there are two stereogenic centers, the double bond and the asymmetric carbon, there are four possible stereomers of the product. Only two are formed. The *E*-isomer has the *S*-configuration at C(4), whereas the *Z*-isomer has the *R* configuration. The stereochemistry of the new double bond is determined by the relative stability of the two chair TSs. TS **25b** is less favorable than **25a** because of the axial placement of the larger phenyl substituent. Thus compound **24** reacts primarily through TS **25a** to give **26** as the major product. Minor product **27** is formed through the less sterically favorable TS **25b**.



When enantiomerically pure **24** is used, the product has an e.e. > 95% and the configuration shown above. This result establishes that chirality is maintained throughout the course of the reaction. This stereospecificity is a general feature of [3,3]-sigmatropic shifts and has made them valuable reactions in enantiospecific syntheses.²³⁸

There is a second possible TS for the Cope rearrangement having a boatlike geometry. The products corresponding to a boatlike TS are usually not observed for

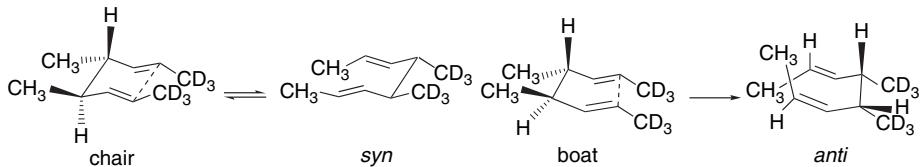
²³⁷ R. K. Hill and N. W. Gilman, *Chem. Commun.*, 619 (1967).

²³⁸ R. K. Hill, in *Asymmetric Synthesis*, Vol. 3, J. D. Morrison, ed., 1984, Chap. 8; D. Enders, M. Knopp and R. Schiffers, *Tetrahedron: Asymmetry*, **7**, 1847 (1996).

acyclic dienes. However, this TS is allowed by orbital symmetry rules and if steric factors make a boat TS preferable to a chair, reaction proceeds through a boat.

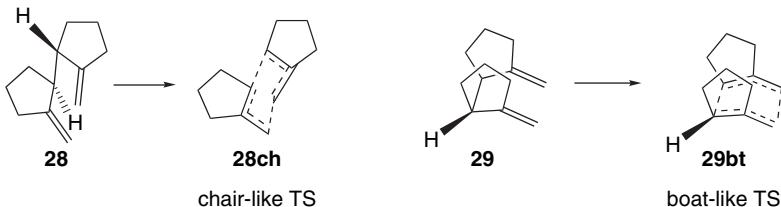


It is generally agreed that the boat TS is higher in energy than the chair TS. There have been several studies aimed at determining the energy difference between the two. One study involved 1,1,1,8,8,8-deutero-4,5-dimethyloctadienes. The chair and boat TSs predict different stereoisomeric products.



Although the process is further complicated by *cis-trans* isomerizations not considered in the above structures, by analysis of the product ratio it was possible to determine that the boat TS is about 6 kcal/mol less stable than the chair.²³⁹ Related experiments on deuterated 1,5-hexadiene itself indicated a difference of 5.8 kcal in ΔG^\ddagger for the chair and boat TSs.²⁴⁰

Another approach to determining the energy difference between the chair and boat TSs is based on measurement of the activation parameters for the isomeric alkenes **28** and **29**.²⁴¹ These two compounds are diastereomeric. Whereas **28** can attain a chairlike TS **28ch**, **29** can achieve bonding between the 1,6-carbons only in a boatlike TS, **29bt**.



Comparison of the rate of rearrangement of **28** and **29** showed **28** to react faster by a factor of 18,000. This corresponds to a difference of about 14 kcal/mol in the measured ΔH^\ddagger , but is partially compensated for by a more favorable ΔS^\ddagger for **29**. In the corresponding methylenecyclohexane analogs, the ΔH^\ddagger favors the chairlike TS by 16 kcal/mol.

The TS involves six partially delocalized electrons being transformed from one 1,5-diene system to another. Theoretical calculations on reactions with delocalized TSs, such as [3,3]-sigmatropic rearrangements, require special care. Correlation effects are especially important and either CI or DFT calculations are required.²⁴² The most

²³⁹ J. J. Gajewski, C. W. Benner, and C. M. Hawkins, *J. Org. Chem.*, **52**, 5198 (1987).

²⁴⁰ M. J. Goldstein and M. S. Benzon, *J. Am. Chem. Soc.*, **94**, 7147 (1972).

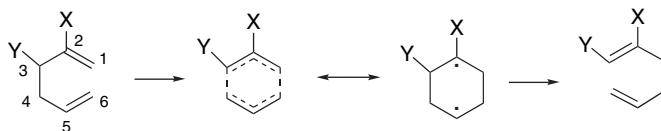
²⁴¹ K. J. Shea and R. B. Phillips, *J. Am. Chem. Soc.*, **102**, 3156 (1980).

²⁴² O. Wiest, D. C. Montiel, and K. N. Houk, *J. Phys. Chem.*, **101**, 8378 (1997).

advanced MO and DFT calculations support the idea of an aromatic TS.²⁴³ The TS can range in character from a 1,4-cyclohexadiyl diradical to two nearly independent allyl radicals, depending on whether bond making or bond breaking is more advanced.²⁴⁴ The *electrons remain paired* in either case, however, and the two representations are best considered to be resonance structures. The energy surface in the transition region seems to be quite flat; that is, there does not seem to be a strong difference in the energy over the range from 1.64 to 2.19 Å.²⁴⁵

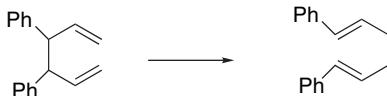


Substituent effects provide other insights into the nature of the TS for the Cope rearrangement. Conjugated substituents at C(2), C(3), C(4), or C(5) accelerate the reaction.²⁴⁶ Donor substituents at C(2) and C(3) have an accelerating effect.²⁴⁷ The net effect on the reaction rate of any substituent is determined by the relative stabilization of the TS and ground state.²⁴⁸ The effect of substituents on the stabilization of the TS can be analyzed by considering their effect on two interacting allyl systems. We consider the case of phenyl substituents in detail.



As shown in Table 10.7, phenyl substituents at positions 2 and 3 reduce the ΔH^\ddagger . On the other hand, a 1-substituent, which is conjugated in the reactant but not the product, increases the ΔH^\ddagger .

The first step in interpreting these substituent effects is to recognize how they affect the reactant and product energy. Substituents that are conjugated, such as cyano and phenyl, are more stabilizing on a double bond than at a saturated carbon. For example, the rearrangement of 3,4-diphenyl-1,5-hexadiene to 1,6-diphenyl-1,5-hexadiene is exothermic by 10.2 kcal/mol, indicating about 5 kcal/mol of stabilization at each conjugated double bond.



- ²⁴³ D. A. Hrovat, W. T. Borden, R. L. Vance, N. G. Rondan, K. N. Houk, and K. Morokuma, *J. Am. Chem. Soc.*, **112**, 2018 (1990); D. A. Hrovat, K. Morokuma, and W. T. Borden, *J. Am. Chem. Soc.*, **116**, 1072 (1994); O. Wiest, K. A. Black and K. N. Houk, *J. Am. Chem. Soc.*, **116**, 10336 (1994); M. D. Davidson, I. H. Hillier, and M. A. Vincent, *Chem. Phys. Lett.*, **246**, 536 (1995); S. Yamada, S. Okumoto, and T. Hayashi, *J. Org. Chem.*, **61**, 6218 (1996); W. T. Borden and E. R. Davidson, *Acc. Chem. Res.*, **29**, 57 (1995); P. M. Kozlowski, M. Dupuis, and E. R. Davidson, *J. Am. Chem. Soc.*, **117**, 774 (1995); K. N. Houk, B. R. Beno, M. Nendel, K. Block, H.-Y. Yoo, S. Wilsey, and J. K. Lee, *Theochem*, **398**, 169 (1997); E. R. Davidson, *Chem. Phys. Lett.*, **284**, 301 (1998).
- ²⁴⁴ J. J. Gajewski and N. D. Conrad, *J. Am. Chem. Soc.*, **100**, 6268, 6269 (1978); J. J. Gajewski and K. E. Gilbert, *J. Org. Chem.*, **49**, 11 (1984).
- ²⁴⁵ P. M. Kozlowski, M. Dupuis, and E. R. Davidson, *J. Am. Chem. Soc.*, **117**, 774 (1995); E. R. Davidson, *J. Phys. Chem.*, **100**, 6161 (1996).
- ²⁴⁶ M. J. S. Dewar and L. E. Wade, *J. Am. Chem. Soc.*, **95**, 290 (1972); *J. Am. Chem. Soc.*, **99**, 4417 (1977); R. Wehrli, H. Schmid, D. E. Bellus, and H. J. Hansen, *Helv. Chim. Acta*, **60**, 1325 (1977).
- ²⁴⁷ M. Dollinger, W. Henning, and W. Kirmse, *Chem. Ber.*, **115**, 2309 (1982).
- ²⁴⁸ For analysis of substituent effects in molecular orbital terminology, see B. K. Carpenter, *Tetrahedron*, **34**, 1877 (1978); F. Delbecq and N. T. Anh, *Nouv. J. Chim.*, **7**, 505 (1983).

Table 10.7. Effect of Phenyl Substituents on Activation Enthalpy of Cope Rearrangements

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	$\Delta H^\ddagger(\text{calc.})^{\text{a}}$	$\Delta H^\ddagger(\text{exp})$
H	H	H	H	H	H	33.2	33.5 ^b
Ph	H	H	H	H	H	36.2	—
H	Ph	H	H	H	H	29.4	29.3 ^c
H	H	Ph	H	H	H	28.4	28.1 ^c
Ph	H	Ph	H	H	H	30.2	30.5 ^d
Ph	H	H	Ph	H	H	29.2	29.9 ^c
H	Ph	H	Ph	H	H	24.6	26.7 ^c
H	Ph	H	H	Ph	H	21.3	21.3 ^f
H	H	Ph	Ph	H	H	—	24.0 ^g
Ph	H	Ph	H	Ph	H	29.2	27.8 ^d
Ph	H	Ph	Ph	H	Ph	19.1	21.3 ^g

SECTION 10.6

Sigmatropic
Rearrangements

a. Calculated from D. A. Hrovat, J. Chen, K. N. Houk, and W. T. Borden, *J. Am. Chem. Soc.*, **122**, 7456 (2000).

b. W. v. E. Doering, V. G. Toscano, and G. H. Beasley, *Tetrahedron*, **27**, 5299 (1971).

c. M. J. S. Dewar and L. E. Wade, Jr., *J. Am. Chem. Soc.*, **99**, 4417 (1977).

c. E. G. Foster, A. C. Cope, and F. Daniels, *J. Am. Chem. Soc.*, **69**, 1893 (1947).

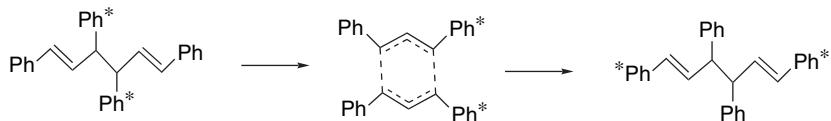
d. W. von E. Doering and Y. Wang, *J. Am. Chem. Soc.*, **121**, 10112 (1999).

e. W. von E. Doering, L. Birlandeanu, K. Sarma, J. H. Teles, F.-G. Klaerner, and J.-S. Gehrke, *J. Am. Chem. Soc.*, **110**, 4289 (1994).

f. W. R. Roth, H.-W. Lennartz, W. v. E. Doering, L. Birlandeanu, C. A. Guyton, and T. Kitagawa, *J. Am. Chem. Soc.*, **112**, 1722 (1990).

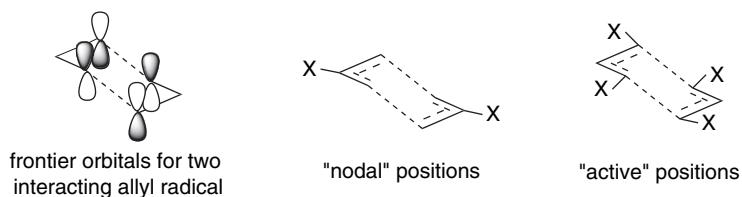
g. W. von E. Doering, L. Birlandeanu, K. Sarma, G. Blaschke, U. Scheidemantel, R. Boese, J. Benet-Buchholz, F.-G. Klarner, J. S. Zimny, R. Sustmann, and H.-G. Korth, *J. Am. Chem. Soc.*, **122**, 193 (2000).

On the other hand, the degenerate rearrangement of *syn*-1,3,4,6-tetraphenyl-1,6-hexadiene is equi-energetic.



The next step is to understand how the *position* of the substitution influences the direction and magnitude of the rate effect and TS structure. If the TS is best represented by two loosely interacting allyl radicals, substituents at the 1, 3, 4, and 6 positions should have the strongest influence. This is because the 2 and 5 positions are at nodes of the frontier orbitals in allyl radicals and should not strongly influence radical stability. On the other hand, a cyclohexadiyl diradical intermediate should be affected most strongly by 2- and 5-substituents. The 1, 3, 4, and 6 positions have been called “active” and the 2 and 5 positions “nodal” to distinguish their relationship to the allyl HOMO orbitals.²⁴⁹ It was suggested that substituents at the “active” positions would move the TS toward the diallyl radical structure (by preferentially stabilizing that structure), whereas substituents at the “nodal” positions would favor the 1,4-cyclohexadiyl structure.

²⁴⁹. (a) W. v. E. Doering and Y. Wang, *J. Am. Chem. Soc.*, **121**, 10112 (1999); (b) W. von E. Doering, L. Birlandeanu, K. Sarma, G. Blaschke, U. Scheidemantel, R. Boese, J. Benet-Buchholz, F.-G. Klaerner, J. S. Gehrke, B. U. Zimny, R. Sustmann, and H.-G. Korth, *J. Am. Chem. Soc.*, **122**, 193 (2000).



Borden, Houk, and co-workers evaluated the various phenyl-substituted cases using B3LYP/6-31G* calculations.²⁵⁰ They found that the TS structure did indeed respond to the placement of phenyl substituents. Phenyl groups at the 2 and 5 positions resulted in a tighter, more 1,4-cyclohexadiyl TS, whereas 1- and 4-phenyl substituents resulted in a looser, more diallylic TS. When several substituents of the same type (matched) were present, the effects were reinforced. On the other hand, 1,5-diphenyl-1,3,5-hexatriene, where the substituents are of different types (unmatched) led to little change from the unsubstituted system. The bond lengths for some of the relevant systems are shown in Figure 10.37. The C–C bond length in the TS for 1,3,4,6-tetraphenyl-1,3,5-hexatriene corresponds to a bond order of only 0.06.

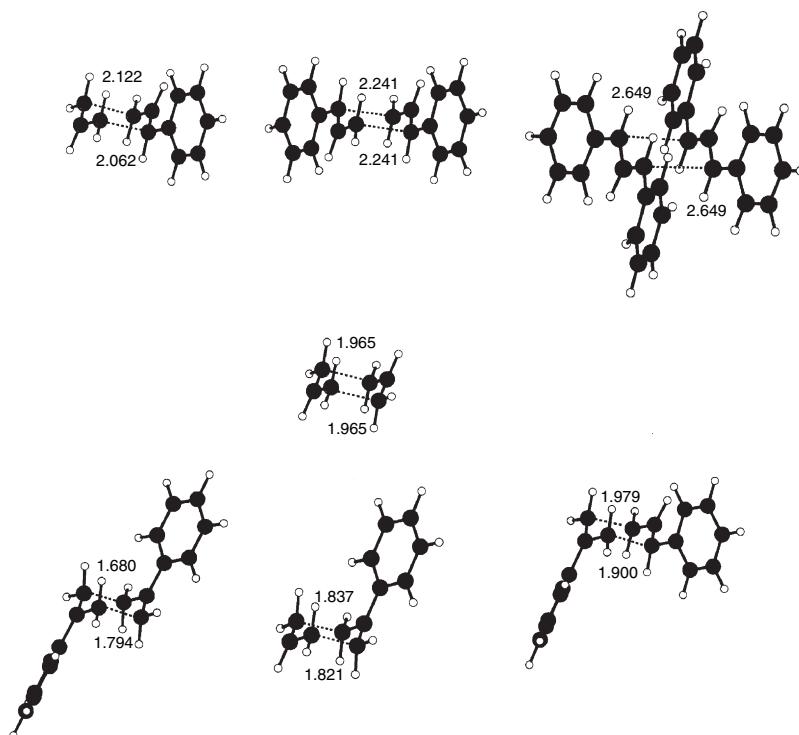


Fig. 10.37. Changes in bond length at the TS for [3,3]-sigmatropic rearrangement of phenyl-substituted 1,3,5-hexatrienes. (a) Top: cumulative loosening of the TS with one, two, and four phenyl groups in “active” positions. (b) Center: unsubstituted system. (c) Lower Left: cumulative tightening of TS by 2- and 2,5-phenyl substitution. (d) Lower Right. “unmatched” 2- and 4-substituents are competitive, leading to little structural change. Reproduced from *J. Am. Chem. Soc.*, **122**, 7456 (2000), by permission of the American Chemical Society.

²⁵⁰ D. A. Hrovat, J. Chen, K. N. Houk, and W. T. Borden, *J. Am. Chem. Soc.*, **122**, 7456 (2000).

In the case of the 2,5-diphenyl derivative, the bond distance corresponds to a bond order of 0.94. Thus these TS structures span a range from nearly “diallylic” to nearly “cyclohexadiyl” character. The substituent effects are also reflected in TS energies. An additional “matched” phenyl substituent lowers TS energy more than an addition “unmatched” substituent.

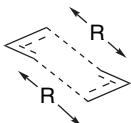
Effect of Phenyl Substitution on E_a (kcal/mol) for Rearrangement of 1,3,5-Hexatrienes

Unsubstituted	1-Phenyl	1,4-Diphenyl	1,3,4,6-Tetraphenyl
33.2	36.2	29.2	19.1 (matched)
	2-Phenyl	2,5-Diphenyl	
	29.4	21.3 (matched)	
	2-Phenyl	2,4-Diphenyl	
	29.4	27.1 (unmatched)	

The role of cyano substituents has also been explored in detail. The symmetrical “matched” 2,5- and 1,3,4,6-systems and the unmatched (but still symmetrical) 1,3,5-cyano system were investigated.²⁵¹ The effect of the substituents on TS energy was examined, as were the 1–6 and 3–4 bond distances. The energies of the TSs were evaluated relative to two allyl radicals by an isodesmic reaction.



Several levels of calculations were performed with the 6-31* basis set using a type of CAS-SCF computation. Cyano substituents at both positions were stabilizing, but more so at 2,5 than at 1,3,4,6. The energetic and geometric effects are similar to those in the phenyl-substituted compounds. The TS is tightened (cyclohexadiyl-like) by 2,5-substituents, but loosened (diallyl-like) by 1,3,4,6-substitution. The 2,5-cyano substituents provide the highest TS stabilization. The distribution of unpaired electron density was used to assess radical character. In contrast to the significant energy and geometry differences, there was little change in the radical character of the TS with substitution.



Effect of Cyano Substituents on Transition State Energy and Structure

Substitution	$R(1, 6) = (3, 4) \text{\AA}$	$\Delta E(\text{isodesmic}) \text{kcal/mol}$
None	1.9661	-22.7
2,5-	1.7524	-41.0
1,3,5-	2.1062	-32.1
1,3,4,6-	2.4670	-29.4

²⁵¹ V. N. Staroverov and E. R. Davidson, *J. Am. Chem. Soc.*, **122**, 7377 (2000).

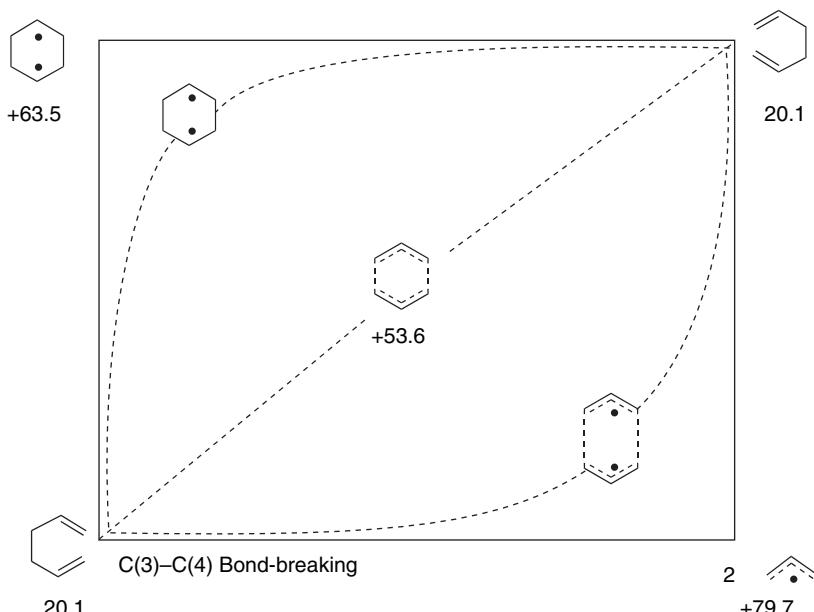
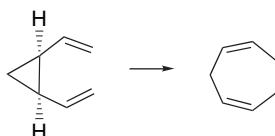


Fig. 10.38. More-O'Ferrall-Jencks diagram representing the variable transition structure for the Cope rearrangement. Energies (in kcal/mol) are from thermodynamic data, as quoted by D. A. Hrovat, J. Chen, K. N. Houk, and W. T. Borden, *J. Am. Chem. Soc.*, **122**, 7456 (2000).

The idea that the nature of the Cope rearrangement TS is variable can be expressed in terms of a More-O'Ferrall-Jencks energy diagram, as in Figure 10.38.²⁵² The 1,4-cyclohexadiyl diradical is believed to have a ΔH_f of 63.5 kcal/mol, which is 43.4 kcal/mol above 1,5-hexadiene. Two separate allyl radicals are at 79.7 kcal/mol, which is 59.6 kcal/mol above the reactant.^{249a} The unsubstituted TS is at 53.6 kcal/mol, which is well below either the 1,4-diyloxy radicals or two allyl radicals, and the reaction proceeds by a concerted process. For the unsubstituted compound, there is a nearly equal amount of bond making and bond breaking at the TS, with a C(1)–C(6) and C(3)–C(4) bond order of 0.49.²⁵⁰ The substituent effects can be interpreted by analyzing how they affect reactant and product energies and how they change TS character.

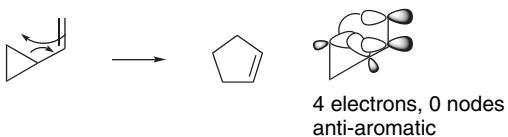
When strain is relieved, Cope rearrangements can occur at much lower temperatures and with complete conversion to ring-opened products. Some particularly striking examples of Cope rearrangement can be found in the rearrangement of *cis*-divinylcyclopropanes. An example is the conversion of *cis*-divinylcyclopropane to 1,4-cycloheptadiene, a reaction that occurs readily at temperatures below -40°C .²⁵³



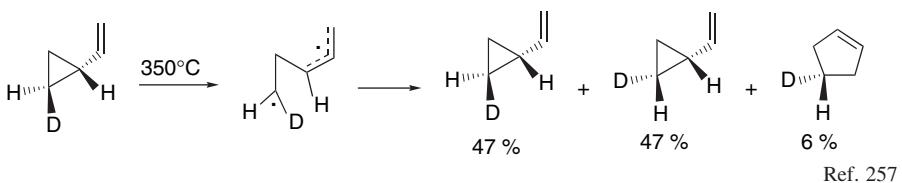
²⁵² J. J. Gajewski, *Acc. Chem. Res.*, **13**, 142 (1980); K. N. Houk, S. M. Gustafson, and K. A. Black, *J. Am. Chem. Soc.*, **114**, 8565 (1992); J. J. Gajewski, *Acc. Chem. Res.*, **30**, 219 (1997).

²⁵³ W. v. E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).

Before we go into these reactions in detail, let us examine vinylcyclopropane itself, which rearranges at high temperature to cyclopentene.²⁵⁴

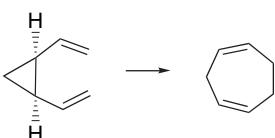


The most geometrically accessible TS corresponds to a forbidden 1,3-suprafacial alkyl shift with retention of configuration. The rearrangement requires a temperature of at least 200°–300° C.²⁵⁵ The measured E_a is about 50 kcal/mol, which is consistent with a stepwise reaction beginning with rupture of a cyclopropane bond and formation of an allylic fragment.²⁵⁶ Support for a nonconcerted mechanism comes from the observation that *cis-trans* isomerization occurs faster than the rearrangement. This isomerization presumably occurs by reversible cleavage of the C(1)–C(2) cyclopropane bond.



When this prior stereoisomerization is accounted for, the rearrangement is found to have resulted from a mixture of all possible suprafacial, antarafacial, inversion, and retention combinations in roughly equal amounts, indicating lack of stereoselectivity.²⁵⁸ Thus, the rearrangement of vinylcyclopropane occurs with nearly complete bond rupture. Computational modeling of the reaction finds no intermediate, and the TS is diradical in character.²⁵⁹

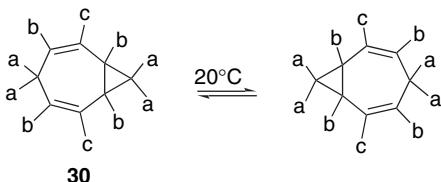
A dramatic difference in reactivity is evident when *cis*-divinylcyclopropane is compared with vinylcyclopropane.²⁶⁰ *cis*-Divinylcyclopropane can only be isolated at low temperature because it very rapidly undergoes Cope rearrangement to 1,4-cycloheptatriene.²⁶¹ At 0°C ΔH^\ddagger is 18.8 kcal/mol and ΔS^\ddagger is –9.4 eu.



- ²⁵⁴. C. G. Overberger and A. E. Borchert, *J. Am. Chem. Soc.*, **82**, 1007 (1960).
- ²⁵⁵. T. Hudlicky, T. M. Kutchan, and S. M. Naqui, *Org. React.*, **33**, 247 (1984); T. Hudlicky and J. D. Price, *Chem. Rev.*, **89**, 1467 (1989); J. E. Baldwin, in *Chemistry of the Cyclopropyl Group*, Vol. 2, Z. Rapoport, ed., Wiley, 1995, pp. 469–494.
- ²⁵⁶. D. K. Lewis, D. J. Charney, B. L. Kalra, A. M. Plate, M. H. Woodard, S. J. Cianciosi, and J. E. Baldwin, *J. Phys. Chem.*, **101**, 4097 (1997).
- ²⁵⁷. M. R. Willcott and V. H. Cargle, *J. Am. Chem. Soc.*, **89**, 723 (1967).
- ²⁵⁸. J. J. Baldwin, K. A. Villarica, D. I. Freedberg, and F. A. L. Anet, *J. Am. Chem. Soc.*, **116**, 10845 (1994).
- ²⁵⁹. E. R. Davidson and J. J. Gajewski, *J. Am. Chem. Soc.*, **119**, 10543 (1997); K. N. Houk, M. Nendal, O. Wiest, and J. W. Storer, *J. Am. Chem. Soc.*, **119**, 10545 (1997); J. E. Baldwin, *J. Comput. Chem.*, **19**, 222 (1998).
- ²⁶⁰. T. Hudlicky, R. Fan, J. W. Reed, and K. G. Gadamasetti, *Org. React.*, **41**, 1 (1992).
- ²⁶¹. J. M. Brown, B. T. Bolding, and J. F. Stofko, Jr., *Chem. Commun.*, 319 (1973); M. Schneider, *Angew. Chem. Int. Ed. Engl.*, **14**, 707 (1975); M. P. Schneider and A. Rau, *J. Am. Chem. Soc.*, **101**, 4426 (1979).

Owing to unfavorable molecular geometry, the corresponding rearrangement of *trans*-divinylcyclopropane to cycloheptatriene cannot be concerted and requires temperatures on the order of 190°C. The very low energy requirement for the Cope rearrangement of *cis*-divinylcyclopropane reflects several favorable circumstances. The *cis*-orientation facilitates interaction of the diene termini, so the loss in entropy in going to the TS is smaller than for an acyclic diene. The breaking bond is strained and this reduces the E_a . The importance of the latter factor can be appreciated by comparison with *cis*-divinylcyclobutane and *cis*-divinylcyclopentane. The former compound has $\Delta H^\ddagger = 23$ kcal/mol for rearrangement to cyclooctadiene.²⁶² *cis*-Divinylcyclopentane does not rearrange to cyclononadiene, even at 250°C.²⁶³ In the latter case, the rearrangement is presumably thermodynamically unfavorable, since there is no strain release from ring opening.

Divinylcyclopropane rearrangements can proceed with even greater ease if the ΔS^\ddagger is made less negative by incorporating both vinyl groups into a ring. An example of this is found in the degenerate homotropilidene rearrangement. A *degenerate rearrangement* is a reaction process in which no overall change in structure occurs, and the product of rearrangement is structurally identical to the starting material. Depending on the rate at which the reaction occurs, the existence of a degenerate rearrangement can be detected by use of isotopic labels or by interpretation of the temperature dependence of NMR spectra. In the case of homotropilidene, **30**, the occurrence of a dynamic equilibrium is evident from the NMR spectrum. At low temperature the rate of interconversion is slow and the spectrum indicates the presence of four vinyl protons, two allylic protons, and two pairs of cyclopropyl protons. As the temperature is raised and the rate of the rearrangement increases, it is observed that two of the vinyl protons remain essentially unchanged with respect to their chemical shift, whereas the other two coalesce with one of the pairs of cyclopropyl protons. Coalescence is also observed between the allylic protons and the other two cyclopropyl protons.²⁶⁴ The sets of protons that coalesce undergo sufficiently rapid interchange with one another to result in an averaged signal (see p. 155).



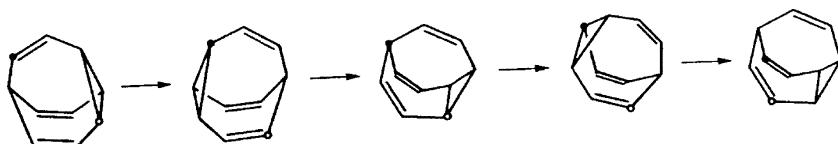
Many other examples of this type of rearrangement are known. Another interesting case is bullvalene, which is converted into itself with a first-order rate constant of 3.4×10^3 s⁻¹ at 25°C.²⁶⁵ At 10°C, the ¹H-NMR spectrum of bullvalene exhibits a single peak at 4.22 ppm, which indicates the “fluxional” nature of the molecule. Owing to the threefold axis of symmetry present in bullvalene, the degenerate rearrangement results in all of the carbons having an identical averaged environment. This is illustrated in the

²⁶² E. Vogel, *Justus Liebigs Ann. Chem.*, **615**, 1 (1958); G. S. Hammond and C. D. DeBoer, *J. Am. Chem. Soc.*, **86**, 899 (1964).

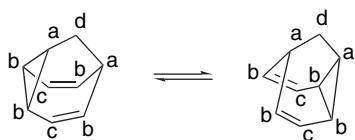
²⁶³ E. Vogel, W. Grimme, and E. Dinne, *Angew. Chem.*, **75**, 1103 (1963).

²⁶⁴ G. Schroeder, J. F. M. Oth, and R. Merenyi, *Angew. Chem. Int. Ed. Engl.*, **4**, 752 (1965); H. Gunther, J. B. Pawliczek, J. Ulmen, and W. Grimme, *Angew. Chem. Int. Ed. Engl.*, **11**, 517 (1972); W. v. E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).

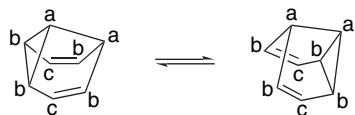
²⁶⁵ G. Schroeder and J. F. M. Oth, *Angew. Chem. Int. Ed. Engl.*, **6**, 414 (1967).



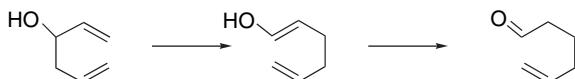
Other degenerate rearrangements have been discovered that are even faster than that of bullvalene. Barbaralane rearranges to itself with a rate constant of $1.7 \times 10^7 \text{ s}^{-1}$ at 25°C .²⁶⁸ The E_a of this rearrangement is only 7.7 kcal/mol. The lowered energy requirement is attributed to an increase in ground state energy owing to strain. Barbaralane is less symmetrical than bullvalene. There are four different kinds of carbons and protons in the averaged structure. Only the methylene group labeled "d" is unaffected by the degenerate rearrangement.



A further reduction in the barrier and increase in rate is seen with semibullvalene in which strain is increased still more. The ΔG^\ddagger for this rearrangement is 5.5 kcal/mol at -143°C .²⁶⁹



When there is a hydroxy substituent at C(3) of the diene system, the Cope rearrangement product is an enol that is subsequently converted to the corresponding carbonyl compound. This is called the *oxy-Cope* rearrangement.²⁷⁰ The formation of the carbonyl compound provides a net driving force for the reaction.²⁷¹



²⁶⁶ R. Poupko, H. Zimmerman, and Z. Luz, *J. Am. Chem. Soc.*, **106**, 5391 (1984).

²⁶⁷ R. Poupko, H. Zimmerman, K. Muller, and Z. Luz, *J. Am. Chem. Soc.*, **118**, 7995 (1996).

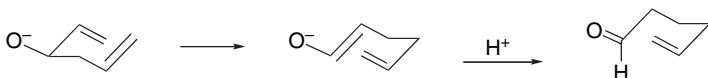
²⁶⁸ W. v. E. Doering, B. M. Ferrier, E. T. Fossel, J. H. Hartenstein, M. Jones, Jr., G. Klumpp, R. M. Rubin, and M. Saunders, *Tetrahedron*, **23**, 3943 (1967); H. Gunther, J. Runsink, H. Schmickler, and P. Schmitt, *J. Org. Chem.*, **50**, 289 (1985).

²⁶⁹ A. K. Cheng, F. A. L. Anet, J. Mioduski, and J. Meinwald, *J. Am. Chem. Soc.*, **96**, 2887 (1974); D. Moskau, R. Aydin, W. Leber, H. Gunther, H. Quast, H.-D. Martin, K. Hassenruck, L. S. Miller, and K. Grohmann, *Chem. Ber.*, **122**, 925 (1989).

²⁷⁰ S. R. Wilson, *Org. React.*, **43**, 93 (1993); L. A. Paquette, *Angew. Chem. Int. Ed. Engl.*, **29**, 609 (1990); L. A. Paquette, *Tetrahedron*, **53**, 13971 (1997).

²⁷¹ A. Viola, E. J. Iorio, K. K. N. Chen, G. M. Glover, U. Nayak, and P. J. Kocienski, *J. Am. Chem. Soc.*, **89**, 3462 (1967).

There is a very powerful substituent effect for dienes having anionic oxygen substituents at C(3), a reaction known as the *anionic oxy-Cope reaction*.²⁷² When the C(3) hydroxy group is converted to its alkoxide, the reaction is accelerated by factors of 10^{10} – 10^{17} .²⁷³



The rates of anionic oxy-Cope rearrangements depend on the degree of cation coordination at the oxy anion. The reactivity trend is $K^+ > Na^+ > Li^+$. Crown ethers catalyze reaction by promoting ion pair dissociation.²⁷⁴ Catalytic amounts of *tetra-n*-butylammonium salts lead to accelerated rates in some cases. This presumably results from the dissociation of less reactive ion pair species promoted by the *tetra-n*-butylammonium ion.²⁷⁵ As with other [3,3]-sigmatropic rearrangements, the stereochemistry of the anionic oxy-Cope rearrangement depends on TS conformation. There is no strong stereochemical preference associated with the C–O[−] bond, and in the absence of other controlling steric factors, products arising from both equatorial and axial orientations are formed.²⁷⁶

The origin of the rate acceleration has been explored by computation. The B3LYP/6-31+G* computational results give a ΔG^\ddagger of 6.3 kcal/mol, some 30 kcal/mol less than the unsubstituted system.²⁷⁷ Another study found the barrier to be only 8.3 kcal/mol in the gas phase. This is raised substantially (to 31.8 kcal/mol) by coordination of an Li⁺ cation at the oxygen.²⁷⁸ As shown in Figure 10.39, the TS for the anionic oxy-Cope reaction is much more asynchronous than for the parent system. The TS is much looser and closer to two dissociated fragments. Note that the C(3)–C(4) bond has lengthened substantially in the TS, whereas the C(1)–C(6) bond distance is still quite long. Several factors probably contribute to the large rate acceleration. The anionic oxy substituent substantially weakens the C(3)–C(4) bond.²⁷⁹ The delocalization of the negative charge in the enolate is also likely a factor, in view of the dissociative nature of the TS.

3-Amino groups also accelerate the Cope rearrangement.²⁸⁰ The products are enamines and subsequent reactions of the enamine are feasible, such as α -alkylation.

- ²⁷². L. A. Paquette, *Angew. Chem. Int. Ed. Engl.*, **29**, 609 (1990).
- ²⁷³. D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975); D. A. Evans, D. J. Baillargeon, and J. V. Nelson, *J. Am. Chem. Soc.*, **100**, 2242 (1978).
- ²⁷⁴. J. J. Gajewski and K. R. Gee, *J. Am. Chem. Soc.*, **113**, 967 (1991).
- ²⁷⁵. M. George, T.-F. Tam, and B. Fraser-Reid, *J. Org. Chem.*, **50**, 5747 (1985).
- ²⁷⁶. L. A. Paquette and G. D. Maynard, *J. Am. Chem. Soc.*, **114**, 5018 (1992); E. Lee, Y. R. Lee, B. Moon, O. Kwon, M. S. Shim, and J. S. Yun, *J. Org. Chem.*, **59**, 1444 (1994).
- ²⁷⁷. H. Bauman and P. Chen, *Helv. Chim. Acta*, **84**, 124 (2001).
- ²⁷⁸. F. Haeffner, K. N. Houk, S. M. Schulze, and J. K. Lee, *J. Org. Chem.*, **68**, 2310 (2003).
- ²⁷⁹. (a) M. L. Steigerwald, W. A. Goddard, III, and D. A. Evans, *J. Am. Chem. Soc.*, **101**, 1994 (1979); (b) H. Y. Yoo, K. N. Houk, J. K. Lee, M.A. Scialdone, and A. I. Meyers, *J. Am. Chem. Soc.*, **120**, 205 (1998).
- ²⁸⁰. R. W. Jemison, W. D. Ollis, I. O. S. Sutherland, and J. Tannock, *J. Chem. Soc., Perkin Trans. 1*, 1462 (1980); J. P. Hagen, K. D. Lewis, S. W. Lovell, P. Rossi, and A. Z. Tescan, *J. Org. Chem.*, **60**, 7471 (1995).

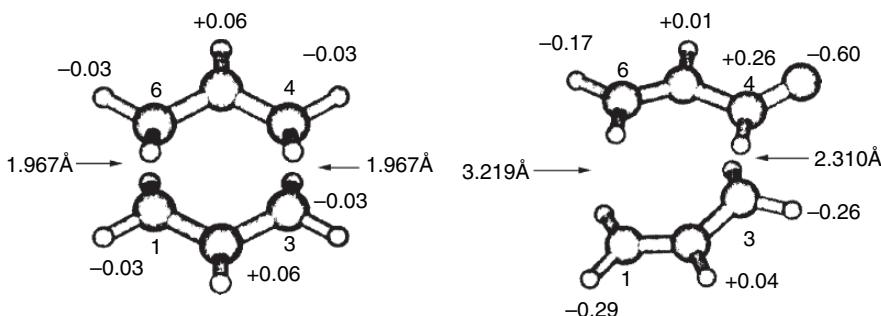
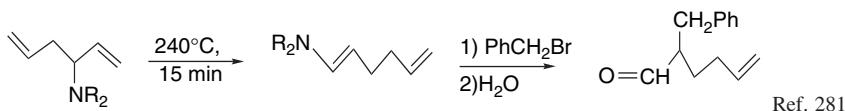
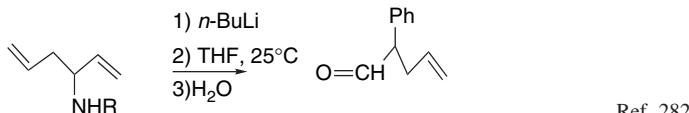


Fig. 10.39. Comparison of transition structure geometry for anionic oxy-Cope (right) rearrangement with Cope rearrangement (left) showing atom separation distances and Mulliken charges (B3LYP/6-311G*). Reproduced from *Helv. Chim. Acta*, **84**, 124 (2001), by permission of Wiley-VCH.

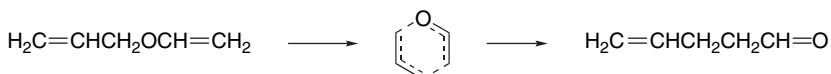


When secondary amines are used, an anionic version of the reaction occurs when the amine is deprotonated by *n*-BuLi.



However, as implied by computations on the anionic amino-Cope reaction,^{279b} a dissociative pathway is competitive and can complicate the outcome of the reaction.²⁸³

10.6.3.2. [3,3]-Sigmatropic Rearrangement in Triene Systems Containing Oxygens
 The [3,3]-sigmatropic reaction pattern is quite general for other systems that incorporate one or more heteroatoms in place of carbon in the 1,5-hexadiene unit. The most synthetically useful and widely studied of these reactions is the Claisen rearrangement, in which an oxygen atom is present at position 3.²⁸⁴ The simplest example of a Claisen rearrangement is the thermal conversion of allyl vinyl ether to 4-pentenal.



This reaction occurs with an *E_a* of 30.6 kcal/mol and an ΔS^\ddagger of -7.7 eu at 180°C.²⁸⁵ Both computational modeling of the TS and analysis of kinetic isotope effects are in accord with a concerted mechanism in which C—O bond cleavage is more advanced

^{281.} S. M. Allin, M. A. C. Button, and S. J. Shuttleworth, *Synlett*, 725 (1997).

^{282.} S. M. Allin, M. A. C. Button, and R. D. Baird, *Synlett*, 1117 (1998).

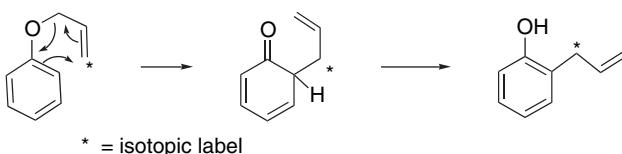
^{283.} S. M. Allin and M. A. C. Button, *Tetrahedron Lett.*, **40**, 3801 (1999).

^{284.} G. B. Bennett, *Synthesis*, 589 (1977); S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975).

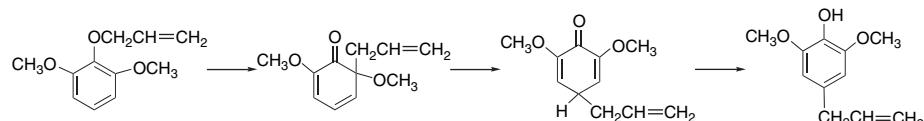
^{285.} F. W. Schuler and G. W. Murphy, *J. Am. Chem. Soc.*, **72**, 3155 (1950).

than C–C bond formation.²⁸⁶ Claisen rearrangements show a considerable sensitivity to solvent polarity, with reaction rates increasing with solvent polarity.²⁸⁷ Water is an especially favorable solvent.²⁸⁸ The solvent effect is believed to be due to differential solvation of the reactants and TS. Hydrogen bonding contributes to stabilization of the TS.²⁸⁹

Allyl ethers of phenols undergo [3,3]-sigmatropic rearrangements and some aspects of the mechanism were developed by studying these compounds.²⁹⁰ For example, an important clue as to the mechanism of the Claisen rearrangement was obtained by use of ¹⁴C-labeled allyl phenyl ether. It was found that the rearrangement was specific as to which carbon atom of the allyl group became bonded to the ring, which is consistent with a cyclic mechanism.²⁹¹



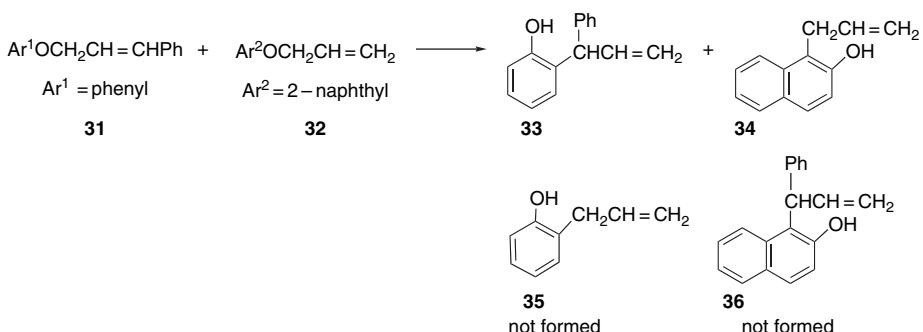
If both *ortho*-positions are substituted, the allyl group undergoes a second migration, giving the *para*-substituted phenol.



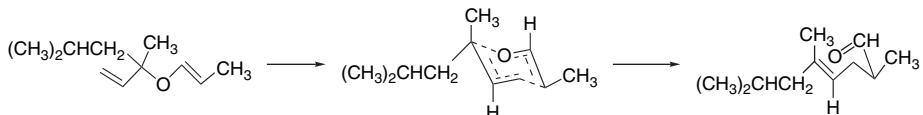
Ref. 292

The intramolecular nature of the rearrangement was established by a crossover experiment in which **31** and **32** were heated simultaneously and found to yield the same products as when they were heated separately. There was no evidence for the formation of the crossover products **35** and **36**,²⁹³ which indicates that the rearrangement must be intramolecular.

- ²⁸⁶ J. J. Gajewski and N. D. Conrad, *J. Am. Chem. Soc.*, **101**, 6693 (1979); R. L. Vance, N. G. Rondan, K. N. Houk, H. F. Jensen, W. T. Borden, A. Komornicki, and E. Winner, *J. Am. Chem. Soc.*, **110**, 2314 (1988); L. Kupczyk-Subotkowska, W. H. Saunders, Jr., H. J. Shine, and W. Subotkowski, *J. Am. Chem. Soc.*, **115**, 5957 (1993); M. P. Meyer, A. J. Del Monte, and D. A. Singleton, *J. Am. Chem. Soc.*, **121**, 10865 (1999).
- ²⁸⁷ B. Ganem, *Angew. Chem. Int. Ed. Engl.*, **35**, 937 (1996).
- ²⁸⁸ P. A. Grieco, E. B. Brandes, S. McCann, and J. D. Clark, *J. Org. Chem.*, **54**, 5849 (1989); A. Lubineau, J. Auge, N. Bellanger, and S. Caillebourdin, *J. Chem. Soc., Perkin Trans. 2*, 1631 (1992).
- ²⁸⁹ D. L. Severance and W. L. Jorgensen, *J. Am. Chem. Soc.*, **114**, 10966 (1992); M. M. Davidson and I. H. Hillier, *J. Phys. Chem.*, **99**, 6748 (1995); J. J. Gajewski, *Acc. Chem. Res.*, **30**, 219 (1997).
- ²⁹⁰ D. S. Tarbell, *Org. React.*, **2**, 1 (1944); S. J. Rhoads, in *Molecular Rearrangements*, Vol. 1, P. de Mayo, ed., Interscience, New York, 1963, pp. 655–684.
- ²⁹¹ J. P. Ryan and P. R. O'Connor, *J. Am. Chem. Soc.*, **74**, 5866 (1952).
- ²⁹² I. A. Pearl, *J. Am. Chem. Soc.*, **70**, 1746 (1948).
- ²⁹³ C. D. Hurd and L. Schmerling, *J. Am. Chem. Soc.*, **59**, 107 (1937).

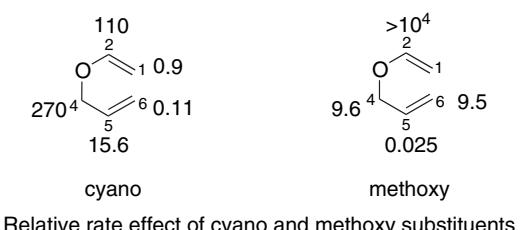


The stereochemical features of the Claisen rearrangement are very similar to those described for the Cope rearrangement, and stereochemical predictions can be made on the basis of the preference for a chairlike TS. The major product has the *E*-configuration at the newly formed double bond because of the preference for placing the larger substituent in the pseudoequatorial position in the TS.²⁹⁴



Studies of chiral substrates have also demonstrated that chirality is maintained in the reaction.²⁹⁵ Examples of the synthetic application of the Claisen rearrangement are discussed in Section 6.4.2.1 of Part B.

Like the Cope rearrangement, the Claisen rearrangement is sensitive to substituents on the reacting system. Cyano groups promote the rearrangement by a factor of 10^2 at positions 2 and 4 and have smaller effects at the other positions, as shown in the diagram below.²⁹⁶ Experimental data are also available for methoxy groups at positions 2, 4, 5, and 6.²⁹⁷ The methoxy substituent is very activating at C(2). These substituents set the pattern for π -conjugated EWG and σ -donor substituents, respectively.



As in the case of the Cope rearrangement, the interpretation of these substituent effects is best approached by considering the effect on TS stability. The effect on

²⁹⁴ R. Marbet and G. Saucy, *Helv. Chim. Acta*, **50**, 2095 (1967); A. W. Burgstahler, *J. Am. Chem. Soc.*, **82**, 4681 (1960); C. L. Perrin and D. J. Faulkner, *Tetrahedron Lett.*, 2783 (1969).

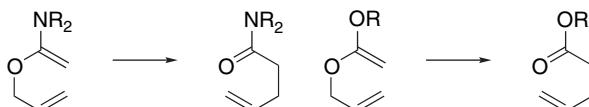
²⁹⁵ H. L. Goering and W. I. Kimoto, *J. Am. Chem. Soc.*, **87**, 1748 (1965).

²⁹⁶ C. J. Burrows and B. K. Carpenter, *J. Am. Chem. Soc.*, **103**, 6983 (1981).

²⁹⁷ R. M. Coates, B. D. Rogers, S. J. Hobbs, D. R. Peck, and D. P. Curran, *J. Am. Chem. Soc.*, **109**, 1160 (1987).

the TS for the Claisen rearrangement by hydroxy substituents has been probed using both HF/6-31G* and B3LYP/6-31G* calculations.²⁹⁸ The effect of cyano, amino, and trifluoromethyl groups has also been calculated.²⁹⁹ The effect of methoxy groups has been examined using a combination AM1-MM method. The predicted changes in E_a , as summarized in Table 10.8, are in qualitative agreement with experimental results.

These substituent effects can be analyzed by considering the effect on reactants, products, and the TS. For example, the large accelerating effect of 2-alkoxy and 2-amino substituents is due in substantial part to the amide and ester resonance stabilization that develops in the products.



The analysis can be done in terms of the Marcus theory by considering the effect on overall reaction energy ΔE_{rxn} and ΔE_0^\ddagger , the *intrinsic barrier*, using a version of the Marcus equation.³⁰⁰ (See Section 3.3.2.3 to review the Marcus equation.)

$$\Delta E^\ddagger = \Delta E_0^\ddagger + \frac{1}{2} \Delta E_{\text{rxn}} + (\Delta E_{\text{rxn}})^2 / 16(\Delta E_0^\ddagger)$$

For the HF/6-31G* calculations, the barriers were separated into effects owing to changes in reaction energy and changes in TS energy.^{299b} Changes in TS energy can be analyzed in terms of radical stabilization effects, as was done for the Cope rearrangement. (see p. 924ff). In addition, there may be variation in the extent of the polar character at the TS. The TS for the Claisen rearrangement has some ionic character, resembling an enolate for C(1), C(2), and O(3) and allyl cation for C(4), C(5), C(6). For the parent reaction, charge transfer is calculated to be 0.21e. The stabilizing effect of the 4- and 6-oxy substituents may be due to stabilization of the cationic fragment, as indicated by the charge distribution below.

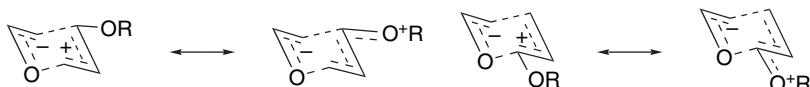


Table 10.8. Calculated Substituent Effects on E_a in kcal/mol for Claisen Rearrangement

Position	OH ^a	CN ^b	NH ₂ ^b	CF ₃ ^b	OCH ₃ ^c
1	-2.7	+0.1	-5.5	+1.1	
2	-9.1	-3.8	-6.7	-3.8	-9.1
4	-1.0	-4.8	-8.6	-1.2	-4.7
5	+5.0	-2.4	+4.5	-1.8	+4.0
6	-0.6	+2.6	-2.3	+1.6	-1.2

a. HF/6-31G*: H. Y. Yoo and K. N. Houk, *J. Am. Chem. Soc.*, **119**, 2877 (1997);

b. B3LYP/6-31G*: V. Aviyente and K. N. Houk, *J. Phys. Chem. A*, **105**, 383 (2001).

c. AM1-MM: A. Sehgal, L. Shao, and J. Gao, *J. Am. Chem. Soc.*, **117**, 11337 (1995).

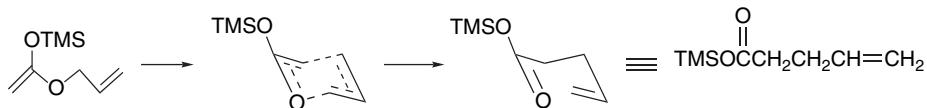
²⁹⁸ H. Y. Yoo and K. N. Houk, *J. Am. Chem. Soc.*, **119**, 2877 (1997).

²⁹⁹ (a) V. Aviyente, H. Y. Yoo, and K. N. Houk, *J. Org. Chem.*, **62**, 6121 (1997); (b) V. Aviyente and K. N. Houk, *J. Phys. Chem. A*, **105**, 383 (2001).

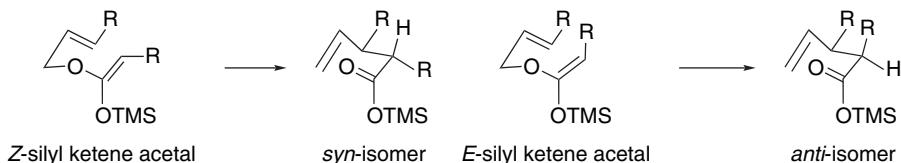
³⁰⁰ M. Y. Chen and J. R. Murdoch, *J. Am. Chem. Soc.*, **106**, 4735 (1984).

The decelerating effect of the 5-substituent is primarily on TS energy and is reflected in the intrinsic barrier. Structurally, this may be due to a repulsive interaction between the 5-oxy substituent and the ring oxygen.

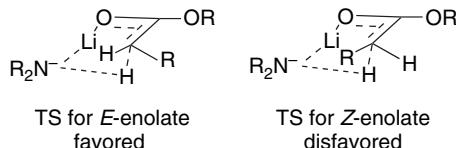
Other donor substituents, e.g., trimethylsilyloxy, at C(2) are strongly accelerating.³⁰¹ This effect is the basis of the synthetic importance of ester enolate Claisen rearrangements, in which enolates or silyl ketene acetals of allylic esters are rearranged into 4-pentenoate esters.³⁰² This reaction is known as the *Ireland-Claisen rearrangement*.



The stereoselectivity of the Ireland-Claisen rearrangement is controlled by the configuration of the double bonds in both the allylic alcohol and the silyl ketene acetal. The chair TS model predicts that the configuration at the newly formed C–C bond will be determined by the *E*- or *Z*-configuration of the silyl ketene acetal.



The stereochemistry of the silyl ketene acetal can be controlled by the conditions of preparation. The base that is usually used for enolate formation is lithium diisopropylamide (LDA). If the enolate is prepared in pure THF, the *E*-enolate is generated and this stereochemistry is maintained in the silyl derivative. The preferential formation of the *E*-enolate can be explained in terms of a cyclic TS in which the proton is abstracted from the stereoelectronically preferred orientation, more or less perpendicular to the carbonyl plane. Steric interaction between the base and the α -substituent disfavors the TS for the *Z*-enolate.



If HMPA is included in the solvent, the *Z*-enolate predominates.³⁰³ DMPU also favors the *Z*-enolate. The switch to the *Z*-enolate with HMPA or DMPU is attributed to a looser, perhaps acyclic, TS being favored as the result of strong solvation of the lithium ion by the cosolvent. The steric factors favoring the *E*-TS are therefore diminished.³⁰⁴

³⁰¹ J. J. Gajewski and J. Emrani, *J. Am. Chem. Soc.*, **106**, 5733 (1984); S. E. Denmark and M. A. Harmata, *J. Am. Chem. Soc.*, **104**, 4972 (1982).

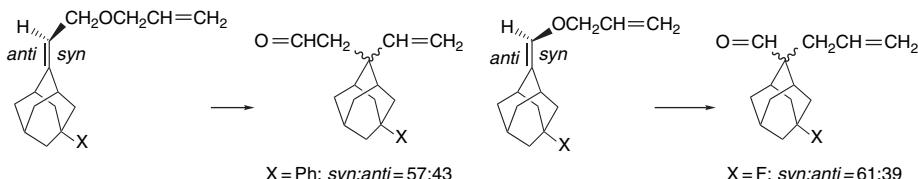
³⁰² S. Pereira and M. Srebnik, *Aldrichimica Acta*, **26**, 17 (1993).

³⁰³ R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1972); R. E. Ireland and A. K. Willard, *Tetrahedron Lett.*, 3975 (1975); R. E. Ireland, P. Wipf, and J. Armstrong, III, *J. Org. Chem.*, **56**, 650 (1991).

³⁰⁴ C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).

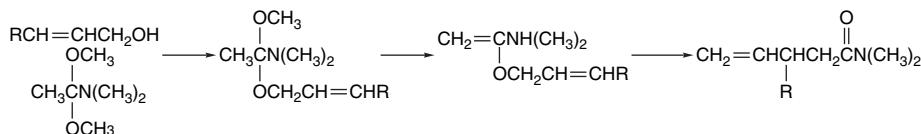
These general principles of solvent control of enolate stereochemistry are applicable to other systems.³⁰⁵

The sensitivity of the Claisen rearrangement to remote substituent effects has been examined using 2-adamantyl vinyl ethers and allyl 2-adamantylidene ethers.³⁰⁶ σ -EWG substituents favor formation of the *syn*-isomer.



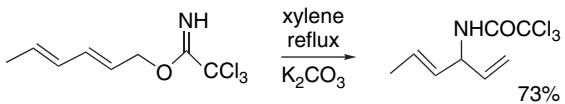
The conclusion drawn is that the TS is relatively electron deficient and is preferentially stabilized by the more electron rich (unsubstituted) of the two adamantyl bonds. A significant feature of this interpretation is that it applies to *both* the cationic and enolate fragments. Although the ionic character of both fragments is relatively small, it appears that the ability to interact with electrons from alkyl groups stabilizes both fragments. This result is consistent with the radical character of the two fragments. A similar facial selectivity was observed in the anionic oxy-Cope rearrangements.³⁰⁷ In this case, the TS bears a *negative charge*, but is still stabilized by the better donor bond.

10.6.3.3. [3,3]-Sigmatropic Rearrangement of Trienes Containing Nitrogen A reaction that is closely related to the orthoester Claisen rearrangement utilizes an amide acetal, such as dimethylacetamide dimethyl acetal, in the exchange reaction with allylic alcohols and gives amides of γ , δ -unsaturated carboxylic acids.³⁰⁸ The stereochemistry of the reaction is analogous to the other variants of the [3,3]-sigmatropic rearrangement.³⁰⁹



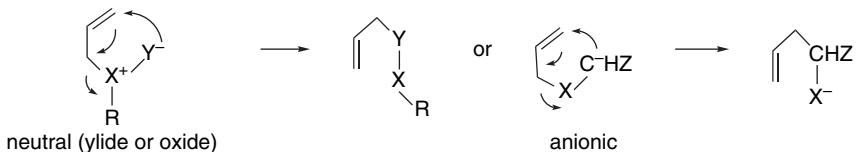
O-allyl imide esters undergo [3,3]-sigmatropic rearrangements to *N*-allyl amides. This is sometimes referred to as an *aza-Claisen rearrangement* and the resonance stabilization of the amide bond that is formed provides a thermodynamic driving force. Trichloromethyl imides can be easily made from allylic alcohols by reaction with trichloroacetonitrile. The rearrangement then provides trichloroacetamides of *N*-allylamines.³¹⁰ Yields in the reaction are sometimes improved by inclusion of K_2CO_3 in the reaction mixture.³¹¹

- ^{305.} J. Corset, F. Froment, M.-F. Lautie, N. Ratovelomanana, J. Seyden-Penne, T. Strzalko, and M. C. Roux-Schmitt, *J. Am. Chem. Soc.*, **115**, 1684 (1993).
- ^{306.} A. Mukherjee, Q. Wu, and W. J. le Noble, *J. Org. Chem.*, **59**, 3270 (1994).
- ^{307.} M.-H. Lin, W. H. Watson, R. P. Kashyap, and W. J. le Noble, *J. Org. Chem.*, **55**, 3597 (1990).
- ^{308.} A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, **47**, 2425 (1964); D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, **52**, 1030 (1969).
- ^{309.} W. Sucrow, M. Slopianka, and P. P. Calderia, *Chem. Ber.*, **108**, 1101 (1975).
- ^{310.} L. E. Overman, *J. Am. Chem. Soc.*, **98**, 2901 (1976); L. E. Overman, *Acc. Chem. Res.*, **13**, 218 (1980).
- ^{311.} T. Nishikawa, M. Asai, N. Ohyabu, and M. Isobe, *J. Org. Chem.*, **63**, 188 (1998).



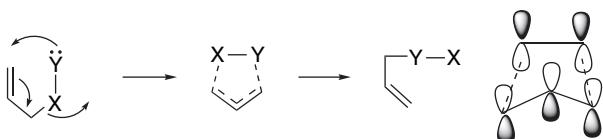
10.6.4. [2,3]-Sigmatropic Rearrangements

10.6.4.1. Mechanism of [2,3]-Sigmatropic Rearrangements There are also concerted rearrangements that exhibit a [2,3]-sigmatropic reactivity pattern. The [2,3]-sigmatropic class of rearrangements is represented by two generic charge types, one involving ylides or oxides and the other those of anions.



One requirement for a facile [2,3]-sigmatropic process is that the atom X at the allylic position be able to act as a leaving group as the adjacent atom Y begins bonding to the allyl system, so X is normally an electronegative element. The reaction is most facile in systems where the atoms X and Y bear formal charges, as in the case of ylides and oxides. The most well developed of these reactions are rearrangements of allyl sulfoxides³¹² and selenoxides³¹³ and of ammonium³¹⁴ and sulfonium³¹⁵ ylides. In the anionic variation, the group Z must be able to facilitate formation of the carbanion. The most useful examples of the anionic type are rearrangements of carbanions of allyl ethers. Scheme 10.11 outlines these kinds of [2,3]-sigmatropic rearrangements.

The TS for 2,3-sigmatropic shifts is viewed as involving an allylic system and the migrating fragment. There are six participating electrons in a Hückel-type array, so the TS is aromatic.



There have been several computational studies of [2,3]-sigmatropic rearrangements. MP3/3-21G*-level calculations of the allyl sulfoxide rearrangement reproduce the stereoselectivity and activation energies.³¹⁶ This and several related rearrangements exhibit TS aromaticity in terms of magnetic criteria (NICS and magnetic susceptibility).³¹⁷ The mechanism of the anionic [2,3]-sigmatropic Wittig rearrangement has

³¹² D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).

³¹³ K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973); D. L. J. Clive, *Tetrahedron*, **34**, 1049 (1978); Y. Nishibayashi and S. Uemura, *Top. Curr. Chem.*, **208**, 201 (2000).

³¹⁴ E. Vedejs, J. P. Hagen, B. L. Roach, and K. L. Spear, *J. Org. Chem.*, **43**, 1185 (1978).

³¹⁵ B. M. Trost and L. S. Melvin, Jr., *Sulfur Ylides*, Academic Press, New York, 1975.

³¹⁶ D. K. Jones-Hertzog and W. L. Jorgensen, *J. Am. Chem. Soc.*, **117**, 9077 (1995); D. K. Jones-Hertzog and W. L. Jorgensen, *J. Org. Chem.*, **60**, 6682 (1995); B. S. Jursic, *Theochem*, **338**, 131 (1995).

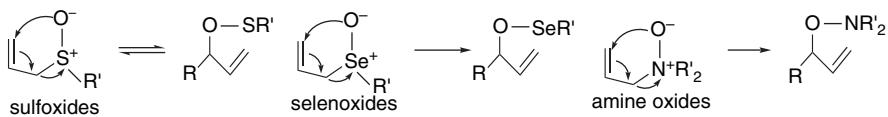
³¹⁷ F. P. Cossio, I. Morao, H. Jiao, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **121**, 6737 (1999); A. A. Fonkin, A. O. Kushko, A. V. Kirij, A. G. Yurchenko, and P. v. R. Schleyer, *J. Org. Chem.*, **65**, 2984 (2000).

Scheme 10.11. Examples of [2,3]-Sigmatropic Rearrangements

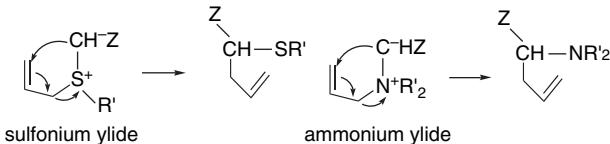
CHAPTER 10

Concerted Pericyclic Reactions

A. Allylic Sulfoxides, Selenoxides and Amine Oxides.



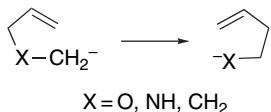
B. Sulfonium and Ammonium Ylides



C. Anions of Allyl Ethers

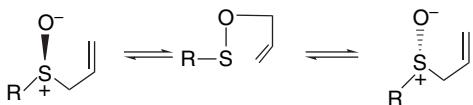


been probed by B3LYP/6-31+G* computations and comparisons made for carbon, nitrogen, and oxygen prototypes.³¹⁸



Computation in the gas phase did not locate a concerted TS, but indicated instead that the reactions proceed by dissociation-reassociation. The reassociation process has no barrier, whereas the dissociation has a very small one (2.4–2.6 kcal/mol). For the oxy anion, inclusion of a Li^+ counterion resulted in a concerted process with a barrier of about 12 kcal/mol. Since this more closely approximates solution conditions, it suggests that a concerted mechanism is feasible in solution. The dissociation mechanism is favored for both nitrogen and carbon.

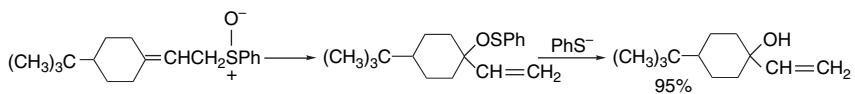
10.6.4.2. [2,3]-Sigmatropic Rearrangements of Oxides and Ylides The rearrangement of allylic sulfoxides to allylic sulfenates first received attention in connection with the mechanism of racemization of allyl aryl sulfoxides.³¹⁹ Although the allyl sulfoxide structure is strongly favored at equilibrium, rearrangement through the achiral allyl sulfenate provides a low-energy pathway for racemization.



³¹⁸. F. Haeffner, K. N. Houk, S. M. Schulze, and J. K. Lee, *J. Org. Chem.*, **68**, 2310 (2003).

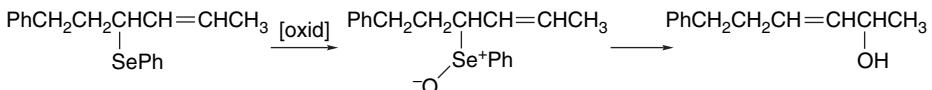
³¹⁹. R. Tang and K. Mislow, *J. Am. Chem. Soc.*, **92**, 2100 (1970).

The allyl sulfoxide–allyl sulfenate rearrangement can be used to prepare allylic alcohols. The reaction is carried out in the presence of a reagent, such as phenylthiolate or trimethyl phosphite, that traps the sulfenate by cleaving the S–O bond.

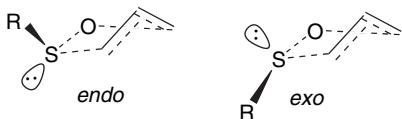


Ref. 320

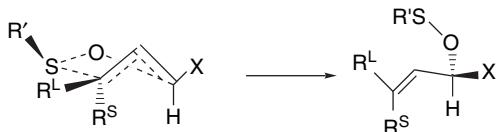
An analogous transposition occurs with allylic selenoxides, which can be generated *in situ* by oxidation of allylic seleno ethers.³²¹



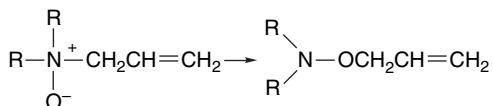
There are two possible TS structures for the rearrangement of allylic sulfoxides, known as *exo* and *endo*. For acyclic systems, the *endo* TS, that is, with the sulfur substituent pointed toward the allylic fragment, is preferred.³²²



The stereochemistry of the new double bond depends on the conformational preference of the α -substituents. The preference is not high for primary groups, but branched groups prefer a pseudoequatorial position and lead to the *E*-isomer.³²³



N-Allylamine oxides represent the pattern for [2,3]-sigmatropic rearrangement where $X = N$ and $Y = O^-$. The rearrangement provides *O*-allyl hydroxylamine derivatives.

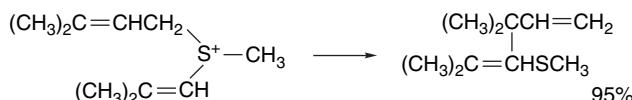


³²⁰ D. A. Evans, G. C. Andrews, and C. L. Sims, *J. Am. Chem. Soc.*, **93**, 4956 (1971).

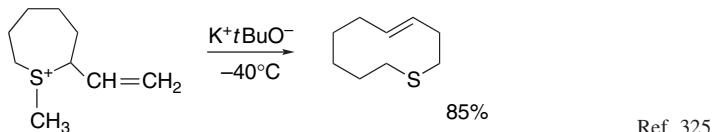
³²¹ H. J. Reich, *J. Org. Chem.*, **40**, 2570 (1975); D. L. J. Clive, G. Chittatu, N. J. Curtis, and S. M. Menchen, *Chem. Commun.*, 770 (1978).

³²² R. W. Hoffmann and N. Maak, *Tetrahedron Lett.*, 2237 (1976); H. J. Reich, K. E. Yelm, and S. Wollowitz, *J. Am. Chem. Soc.*, **105**, 2503 (1983).

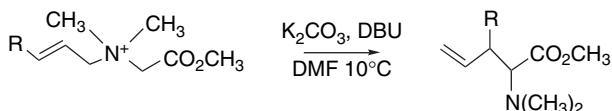
³²³ T. Sato, J. Otera, and H. Nozaki, *J. Org. Chem.*, **54**, 2779 (1989).



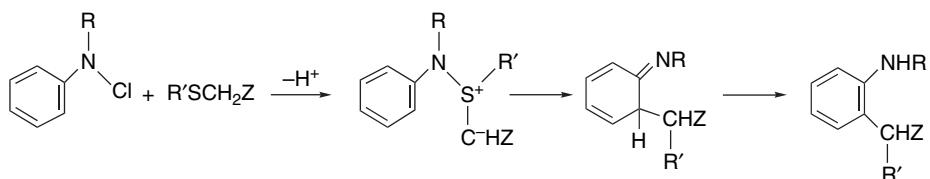
This reaction results in formation of a new carbon-carbon bond. The reaction proceeds best when the ylide has a carbanion-stabilizing substituent. It has found synthetic application in ring-expansion sequences for generation of medium-sized rings.



The corresponding ammonium ylides can also be generated when one of the nitrogen substituents has an anion-stabilizing group on the α -carbon. For example, quaternary salts of *N*-allyl α -aminoesters readily rearrange to α -allyl products.³²⁶



A useful method for *ortho*-alkylation of aromatic amines is based on [2,3]-sigmatropic rearrangement of *S*-anilinosulfonium ylides. These ylides are generated from anilinosulfonium ions, which can be prepared from *N*-chloroanilines and sulfides.³²⁷



This method is the basis for synthesis of nitrogen-containing heterocyclic compounds when Z is a carbonyl-containing group that can undergo cyclization with the amino group.³²⁸

10.6.4.3. [2,3]-Sigmatropic Rearrangements of Anions

The [2,3]-sigmatropic rearrangement pattern is also observed with anionic species. The most important case

³²⁴ J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *Chem. Commun.*, 537 (1968).

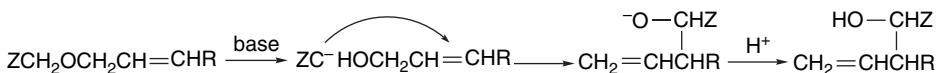
³²⁵ V. Cere, C. Paolucci, S. Pollicino, E. Sandri, and A. Fava, *J. Org. Chem.*, **43**, 4826 (1978).

³²⁶ I. Coldham, M. L. Middleton, and P. L. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2951 (1997); I. Coldham, M. L. Middleton, and P. L. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2817 (1998).

³²⁷ P. G. Gassman and G. D. Gruetzmacher, *J. Am. Chem. Soc.*, **96**, 5487 (1974); P. G. Gassman and H. R. Drewes, *J. Am. Chem. Soc.*, **100**, 7600 (1978).

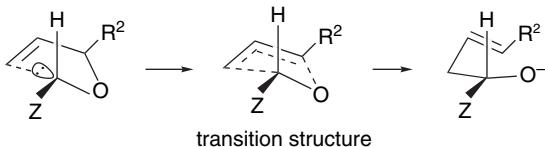
³²⁸ P. G. Gassman, T. J. van Bergen, D. P. Gilbert, and B. W. Cue, Jr., *J. Am. Chem. Soc.*, **96**, 5495 (1974); P. G. Gassman and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5508 (1974); P. G. Gassman, G. Gruetzmacher, and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5512 (1974).

for synthetic purposes is the *Wittig rearrangement*, in which a strong base converts allylic ethers to α -allyl alkoxides.³²⁹

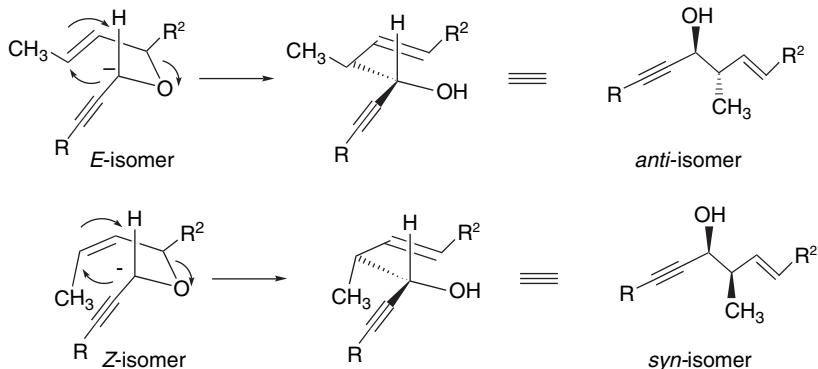


As the deprotonation at the α' -carbon must compete with deprotonation of the α -carbon in the allyl group, most examples involve a conjugated or electron-withdrawing substituent Z that can facilitate deprotonation.³³⁰ In addition to direct deprotonation, there are other means of generating the anions of allyl ethers.^{331,332}

The stereochemistry of the Wittig rearrangement can be predicted in terms of a cyclic TS in which the α -substituent R² prefers an equatorial orientation.³³³



A consistent feature of the stereochemistry is a preference for *E*-stereochemistry at the newly formed double bond, but the reaction can also show stereoselectivity at the newly formed single bond. This stereoselectivity has been carefully studied for the case where the substituent Z is an acetylenic group.



The preferred stereochemistry arises from the TS that minimizes interaction between the alkynyl and R² substituents. This stereoselectivity is exhibited in the rearrangement of **37** to **38**.

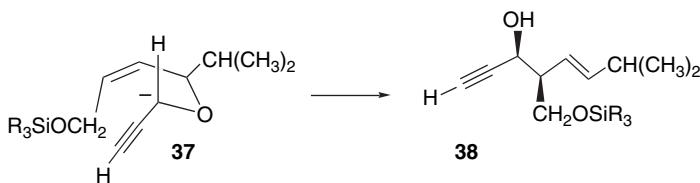
³²⁹ J. Kallmarten, in *Stereoselective Synthesis, Houben Weyl Methods in Organic Chemistry*, R. W. Hoffmann, J. Mulzer, and E. Schaumann, eds., G. Thieme Verlag, Stuttgart, 1996, pp. 3810; T. Nakai and K. Mikami, *Org. Reactions*, **46**, 105 (1994).

³³⁰ For reviews of [2,3]-sigmatropic rearrangement of allyl ethers, see T. Nakai and K. Mikami, *Chem. Rev.*, **86**, 885 (1986).

³³¹ W. C. Still and A. Mitra, *J. Am. Chem. Soc.*, **100**, 1927 (1978).

³³² K. Hioki, K. Kono, S. Tani, and M. Kunishima, *Tetrahedron Lett.*, **39**, 5229 (1998).

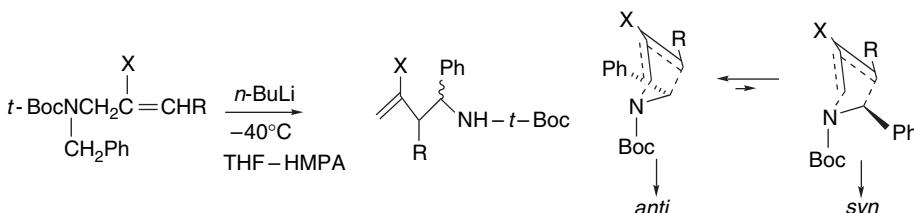
³³³ R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **18**, 563 (1979); K. Mikami, Y. Kimura, N. Kishi, and T. Nakai, *J. Org. Chem.*, **48**, 279 (1983); K. Mikami, K. Azuma, and T. Nakai, *Tetrahedron*, **40**, 2303 (1984); Y.-D. Wu, K. N. Houk, and J. A. Marshall, *J. Org. Chem.*, **55**, 1421 (1990).



Ref. 334

The effect of substituents on the TS has been explored using MP3/6-31+G* computations.³³⁵ An alkynyl group at C(5) results in a much later TS than in the unsubstituted case and the TS has greater cyclic character. This tighter TS would be expected to be more sensitive to the steric effects that lead to stereoselectivity. These computations also indicated a preference for carbonyl substituents to adopt an *s-trans-endo* conformation that leads to the observed *syn* stereoselectivity. Inclusion of a Li⁺ cation leads to a chelated TS, again in accord with observed stereochemistry. These TSs are depicted in Figure 10.40. α -Carboxy substituents also lead to reaction through chelated TSs.³³⁶

[2,3]-Sigmatropic rearrangements of anions of *N*-allyl amines have also been observed and are known as aza-Wittig rearrangements.³³⁷ The reaction requires anion-stabilizing substituents and is favored by *N*-benzyl and by silyl or sulfenyl substituents on the allyl group.³³⁸ The reaction is further facilitated by *N*-acyl groups and by EWGs on the amide nitrogen.³³⁹ These groups all facilitate the initial deprotonation and the charge redistribution that accompanies rearrangement. The steric interactions between the benzyl group and allyl substituent govern the stereoselectivity, which markedly improved in the trimethylsilyl derivatives.³⁴⁰



R	X	<i>syn:anti</i>
CH ₃	H	3:2
C ₂ H ₅	H	1:1
(CH ₃) ₂ CH	H	4:3
CH ₃	Si(CH ₃) ₃	<1:20
C ₂ H ₅	Si(CH ₃) ₃	1:18
(CH ₃) ₂ CH	Si(CH ₃) ₃	1:11

³³⁴ M. M. Midland and J. Gabriel, *J. Org. Chem.*, **50**, 1143 (1985).

³³⁵ K. Mikami, T. Uchida, T. Hirano, Y.-D. Wu, and K. N. Houk, *Tetrahedron*, **50**, 5917 (1994).

³³⁶ T. Okajima and Y. Fukazawa, *Chem. Lett.*, 81 (1997).

³³⁷ C. Vogel, *Synthesis*, 497 (1997).

³³⁸ J. C. Anderson, S. C. Smith, and M. E. Swarbrick, *J. Chem. Soc., Perkin Trans. 1*, 1517 (1997).

³³⁹ J. C. Anderson, A. Flaherty, and M. E. Swarbrick, *J. Org. Chem.*, **65**, 9152 (2000).

³⁴⁰ J. C. Anderson, D. C. Siddons, S. C. Smith, and M. E. Swarbrick, *J. Org. Chem.*, **61**, 4820 (1996).

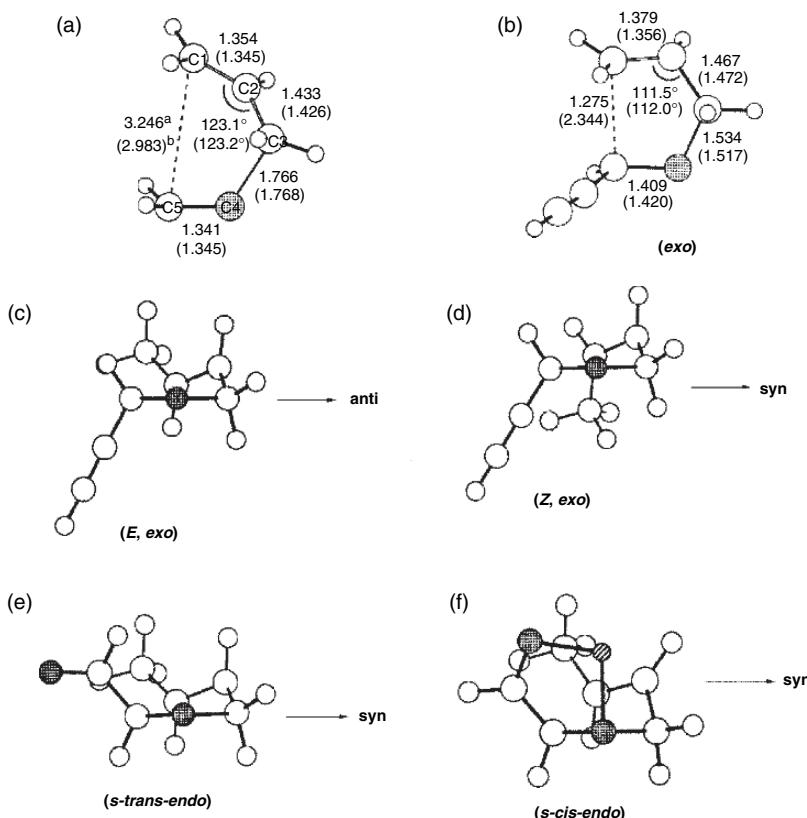


Fig. 10.40. Relationship between TS structure and stereoselectivity in [2,3]-sigmatropic rearrangement of allyloxymethyl anion: (a) early TS for unsubstituted allyloxymethyl anion; (b) tighter cyclic TS for stabilized allyloxypropargyl anion; (c,d) preferred conformation of *E*- and *Z*-crotyloxypropargyl anions leading to the *E* \rightarrow *anti* and *Z* \rightarrow *syn* stereoselectivity; (e,f) unchelated and chelated TSs for α -crotyloxy ethanal enolate leading to the *E* \rightarrow *syn* stereoselectivity. Reproduced from *Tetrahedron*, **50**, 5917 (1994), by permission of Elsevier.

Topic 10.1. Application of DFT Concepts to Reactivity and Regiochemistry of Cycloaddition Reactions

Recently, attempts have been made to understand both the relative reactivity and regioselectivity of the Diels-Alder reaction in terms of the DFT concepts of hardness and softness. Several DFT parameters have been examined as potential indicators of D-A reactivity. (See Topic 1.5 to review the DFT concepts of hardness, softness, Fukui functions, and global electrophilicity.) The D-A reaction can be thought of as having two components in the overall electronic reorganization, corresponding to initial charge transfer between the diene and dienophile, followed by electronic reconfiguration to generate the new bonds. These ideas parallel FMO theory, but DFT considers the total electron density rather than the distribution of the frontier orbitals.

Table 10.9. DFT Global Electrophilicity of Representative Dienes and Dienophiles^a

	Primarily Electrophilic	Balanced		Primarily Nucleophilic	
(NC) ₂ C=C(CN) ₂	5.96	CH ₃ CO ₂ CH = CHCH=CH ₂	1.10	CH ₃ OCH=CHCH=CH ₂	0.77
Maleic anhydride	3.24	CH ₂ =CHCH=CH ₂	1.05	CH ₂ =CH ₂	0.73
CH ₂ =CHCH=O ⁺ B ⁻ H ₃	3.20	CH ₂ =CCH=CH ₂	0.94	TMSOCH=CHCH=CH ₂	0.73
CH ₂ =C(CN) ₂	2.82	CH ₃		Furan	0.59
CH ₂ =CHNO ₂	2.61	CH ₃ CH=CHCH=CH ₂	0.93	(CH ₃) ₂ NCH=CHCH=CH ₂	0.57
CH ₃ O ₂ CC≡CCO ₂ CH ₃	2.27	H ₂ C=CCH=CH ₂	0.88	HC≡CH	0.54
CH ₂ =C(CO ₂ CH ₃) ₂	1.93	OTMS		2-Methylfuran	0.52
CH ₂ =CHCH=O	1.84	(CH ₃) ₂ C=CHCH=CH ₂	0.86		
CH ₂ =CHCN	1.74	Cyclopentadiene	0.83	CH ₃ OCH=CH	0.42
CH ₂ =CHCOCH ₃	1.65			Pyrrole	0.31
HC≡CCO ₂ CH ₃	1.52			(CH ₃) ₂ NCH=CH ₂	0.27
CH ₂ =CHCO ₂ CH ₃	1.50				

a. From L. R. Domingo, M. Aurell, P. Perez, and R. Contreras, *Tetrahedron*, **58**, 4417 (2002).

Domingo investigated the *global electrophilic parameter*, ω , as an indicator of relative reactivity.³⁴¹ Table 10.9 gives the value of this parameter calculated for a number of dienes and dienophiles.

This parameter gives an ordering that is in good qualitative agreement with the reactivity trends that would be expected on the basis of polar and resonance substituent interactions, although the parent molecules, ethene and ethyne, are somewhat more toward the nucleophilic side of the scale than might have been anticipated. The electrophilic group includes the traditional dienophiles such as acrolein and acrylonitrile. Dienes with donor substituents, such as 1-methoxy-1,3-butadiene, exhibit the anticipated nucleophilic characteristics. Note that a 1-ERG seems to have a stronger effect than a 2-ERG (compare the isomeric trimethylsiloxy-1,3-butadienes). This is consistent with the greater reactivity of 1-methoxy-1,3-butadiene than the 2-isomer (see Table 10.2). Methoxyethene and dimethylaminoethene are among the most nucleophilic dienophiles in the list. It should be noted that ω is a *global* parameter; that is, it pertains to the molecule as a whole. Thus, it gives no indication of the regioselectivity of the reaction, but is an indicator of the direction and extent of electron transfer between the reactants. The idea that increased charge transfer increases reactivity suggests that mutual reactivity will be highest for compounds that have the largest difference in ω . This is equivalent to the FMO concept that the strongest donors and strongest acceptors will have the highest mutual reactivity.

The issue of regiochemistry can be addressed by identifying sites of *local electrophilicity* and *local nucleophilicity*. This was done by calculation of a *local electrophilicity index*.³⁴² The index of nucleophilicity can be taken as f^- , the local Fukui function for electrophilic attack. The regiochemistry is then predicted by matching the highest local electrophilicity in the electrophilic component with the largest f^- for the nucleophilic component. Table 10.10 gives some values of representative dienes and dienophiles.

We see that a terminal ERG on the diene leads to $f_{(1)}^- > f_{(4)}^-$, that is, the carbon at the *end* of the conjugated system is the most nucleophilic. For example, compare the f^- values for the substituted (4) and unsubstituted (1) atoms for 1,3-pentadiene, and

³⁴¹ L. R. Domingo, M. J. Aurell, P. Perez, and R. Contreras, *Tetrahedron*, **58**, 4417 (2002).

³⁴² L. R. Domingo, M. J. Aurell, P. Perez, and R. Contreras, *J. Phys. Chem. A*, **106**, 6871 (2002).

Table 10.10. Local Electrophilicity and Fukui Functions for Some Dienes and Dienophiles^a

Dienes	C(1)	C(4)		TOPIC 10.1 <i>Application of DFT Concepts to Reactivity and Regiochemistry of Cycloaddition Reactions</i>
1 4	ω	f^-	ω	
$\text{CH}_2 = \text{CHCH} = \text{CH}_2$	0.355	0.338	0.355	0.338
$\text{CH}_2 = \text{CHCH} = \text{CHCH}_3$	0.300	0.309	0.282	0.2296
$\text{CH}_2 = \text{CCH} = \text{CH}_2$	0.316	0.380	0.354	0.289
$\begin{array}{c} \\ \text{CH}_3 \end{array}$				
$\text{CH}_2 = \text{CHC} = \text{C}(\text{CH}_3)_2$	0.277	0.273	0.234	0.277
$\text{CH}_2 = \text{CHCH} = \text{CHOCH}_3$	0.251	0.290	0.240	0.217
$\text{CH}_2 = \text{CHCH} = \text{CHOSi}(\text{CH}_3)_3$	0.232	0.264	0.217	0.218
$\text{CH}_2 = \text{CCH} = \text{CH}_2$	0.240	0.465	0.315	0.212
$\begin{array}{c} \\ \text{OSi}(\text{CH}_3)_3 \end{array}$				
$\text{CH}_2 = \text{CHCH} = \text{CHN}(\text{CH}_3)_2$	0.173	0.304	0.230	0.117
Dienophiles	C(1)	C(2)		
1 2	ω	f^+	ω	f^+
$\text{CH}_2 = \text{CH} = \text{O}^+ - \text{B}^- \text{H}_3$	1.144	0.357	0.253	0.079
$\text{CH}_2 = \text{C}(\text{CN})_2$	1.407	0.499	0.589	0.209
$\text{CH}_2 = \text{CHNO}_2$	0.726	0.279	0.200	0.077
$\text{CH}_2 = \text{CHCH} = \text{O}$	0.685	0.372	0.253	0.137
$\text{CH}_2 = \text{CHCN}$	0.816	0.469	0.461	0.265
$\text{CH}_2 = \text{CHCOCH}_3$	0.579	0.351	0.250	0.152
$\text{CH}_2 = \text{CHCO}_2\text{CH}_3$	0.617	0.409	0.300	0.199
$\text{CH}_2 = \text{CH}_2$	0.365	0.500	0.365	0.500
$\text{CH} \equiv \text{CH}$	0.268	0.500	0.268	0.500
$\text{CH}_2 = \text{CHOCH}_3$	0.183	0.435	0.194	0.463
$\text{CH}_2 = \text{CHN}(\text{CH}_3)_2$	0.108	0.399	0.119	0.442

a. From L. R. Domigo, M. J. Aurell, P. Perez, and R. Contreras, *J. Phys. Chem. A*, **106**, 6871 (2002).

for the cases substituted by methoxy, trimethylsilyloxy, and dimethylamino groups. This implies that the *unsubstituted* terminal carbon will be the most nucleophilic site of the diene, which is the same prediction that is made by resonance or FMO treatment of terminally substituted butadienes. For dienophiles having EWG substituents, the $\omega_{(\text{local})}$ or f^+ parameters can indicate relative electrophilicity. For such dienophiles, the β -(unsubstituted)carbon is more electrophilic than the α -(substituted)carbon, again consistent with resonance and FMO conclusions. The local electrophilicity of ethene (0.365) is less than for EWG-substituted derivatives, in agreement with its lower reactivity as a dienophile.

In all the cases studied by this approach so far, the diene is the nucleophile and the dienophile is the electrophile. For this combination, the dienophile $\omega_{(\text{global})}$ shows a correlation with reactivity, whereas comparison of the f^+ between C(1) and C(2) gives an indication of the regioselectivity. Dienophiles with EWG substituents have higher f^+ at the unsubstituted carbon, in agreement with observed regioselectivity. For ERG cases (methoxyethene and dimethylaminoethene) the ω value is small and the highest f^+ value shifts to the substituted carbon. For the dienes, the position with the largest f^- is predicted to be the most nucleophilic. The challenging case of dienes with 2-EWG groups (see p. 844) has not yet been addressed by DFT analysis.

Another DFT-based approach to regioselectivity focused on softness. It has been suggested, based on the DFT definitions, that maximum reactivity should occur when

the local softness of reacting positions is matched.³⁴³ This proposal has been explored in a quantitative way.³⁴⁴ Local softness values were calculated for a number of substituted dienes and dienophiles. Then the alternative regioisomers were evaluated by comparing the alternative pairs:

$$\text{Ortho regioisomer} = (s^-_1 - s^+_{1'})^2 + (s^-_4 - s^+_{2'})^2 \quad (10.4)$$

$$\text{Meta regioisomer} = (s^-_1 - s^+_{2'})^2 + (s^-_4 - s^+_{1'})^2 \quad (10.5)$$

where s^- and s^+ are the local softness values for nucleophilic and electrophilic reactivity, as appropriate for the reaction of a nucleophilic diene with an electrophilic dienophile.

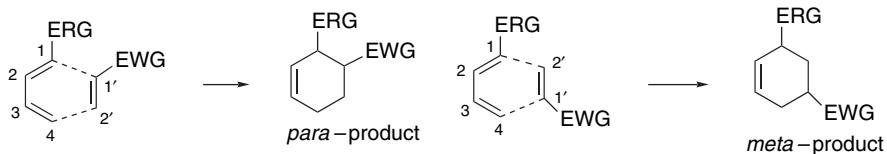


Table 10.11 gives the value of the local softness for some representative diene and dienophiles.

Qualitatively comparing these numbers to the traditional polar and resonance substituent effects, we see that for a donor substituent $s^-_4 > s^-_1$. EWG substituents make $s^+_{2'} > s^+_{1'}$. However, the trend that dominates the sum of the differences in

Table 10.11. Local Softness Parameters for Dienes and Dienophiles^a

Dienes		$s^+_{1'}$	$s^-_{1'}$	$s^+_{4'}$	$s^-_{4'}$
1-Substituent					
CH ₃		0.266	0.277	0.309	0.282
CH ₃ O		0.363	0.193	0.293	0.201
C ₂ H ₅ O		0.369	0.177	0.294	0.198
(CH ₃) ₂ N		0.413	-0.137	0.321	0.193
(C ₂ H ₅) ₂ N		0.396	-0.298	0.281	0.103
CO ₂ H		0.271	0.118	0.224	0.131
CN		0.416	0.354	0.264	0.319
Dienophiles					
1-Substituent		$s^+_{1'}$	$s^-_{1'}$	$s^+_{2'}$	$s^-_{2'}$
CO ₂ H		0.167	0.073	0.306	0.150
CO ₂ CH ₃		0.166	0.077	0.300	0.139
CH=O		0.030	0.024	0.309	0.276
CH ₃ CO		0.038	0.101	0.327	0.188
CN		0.296	-0.014	0.278	0.140
NO ₂		-0.53	-0.073	0.291	0.258

a. From J. Damoun, G. Van de Woude, F. Mendez, and P. Geerlings, *J. Phys. Chem. A*, **101**, 886 (1997).

³⁴³ J. L. Gazquez and F. Mendez, *J. Phys. Chem.*, **98**, 4591 (1994).

³⁴⁴ J. Damoun, G. Van de Woude, F. Mendez, and P. Geerlings, *J. Phys. Chem. A*, **101**, 886 (1997).

Equations (10.4) and (10.5) is the fact that the more remote positions (4 and 2') *change less than the substituted positions*. Local softness parameters have also been calculated by a bond electronegativity equalization approach.³⁴⁵ All the computations reported to date refer to diene (HOMO)-dienophile (LUMO) combination pairs, so it is not possible to see if this approach successfully predicts the case in which both the diene and the dienophile carry EWG substituents.

By comparing the FMO and DFT analyses, we see that most combinations of diene and dienophiles lead to the same prediction. The underlying physical basis of the predictions is also quite similar. In FMO theory it is the closeness in energy of the FMOs that is considered to be the origin of relative reactivity. Regioselectivity is attributed to maximum orbital overlap, as judged by the FMO coefficients. In the DFT approach, the extent of charge transfer (as measured by the global electrophilicity and nucleophilicity parameters) is considered to be the indicator of reactivity and local softness is considered to govern regioselectivity. The physical picture of the D-A reaction that emerges is one of *complementary electronic interactions* between the diene and dienophile that reduce the electron-electron repulsions that are otherwise dominant in the early stages of the reaction. Although both approaches can provide predictive relationships for a range of diene-dienophile combinations, neither has yet developed quantitative predictions of relative rates over a wide range of reactant combinations. This, of course, would be inherently difficult for combinations in which steric effects are significant, since neither FMO coefficients nor the DFT parameters take account of steric effects directly. It would be interesting to know, however, perhaps with cyanoethenes and cyanoethynes, if some combination of the local electrophilicity and softness parameters could account for relative reactivity.

Domingo and co-workers applied the DFT concepts of electrophilicity and softness in a study of all the possible cyanoethenes in reaction with cyclopentadiene, calculating the TS geometries, energies, and charge transfer at the B3LYP/6-31G* level.³⁴⁶ Both gas phase and benzene solution E_a values were calculated. The geometries indicated that the TS is slightly earlier in benzene. For symmetrically substituted ethenes, the reactions are nearly synchronous, whereas for unsymmetrical dienophiles they are asynchronous. The global and local ω parameters were determined and the local electrophilicity parameter ω_2 was found to correlate with the number of cyano substituents, as would be expected.

Substitution	ω	ω_1	f^+_1	ω_2	f^+_2
1-CN	1.74	0.46	0.266	0.82	0.469
1,1-diCN	2.82	0.59	0.209	1.41	0.499
E-1,2-diCN	3.08	0.92	0.300	0.92	0.300
Z-1,2-diCN	3.01	0.92	0.306	0.92	0.306
1,1,2-triCN	4.38	1.03	0.236	1.46	0.333
1,1,2,2-tetraCN	5.96	1.53	0.257	1.53	0.257

The calculated E_a decreased with the value of ω , whereas the extent of charge transfer at the TS increased.

³⁴⁵ Y. Cong, Z. Z. Yang, C. S. Wang, X. C. Liu, and Y. H. Bao, *Chem. Phys. Lett.*, **357**, 59 (2002).

³⁴⁶ L. R. Domingo, M. J. Aurell, P. Perez, and R. Contreras, *J. Org. Chem.*, **68**, 3884 (2003).

	Substitution	E_a (gas)	E_a (benzene)	Charge transfer
1-CN		17.5	16.7	0.15
1,1-diCN		10.5	8.7	0.28
<i>E</i> -1,2-dicN		15.2	14.3	0.25
Z-1,2-dicN		16.3	14.5	0.24
1,1,2-triCN		11.3	9.0	0.36
1,1,2,2-tetraCN		11.5	8.7	0.43

The extent of charge transfer is more closely related to the total number of CN substituents rather than their position, i.e., 1,1- \sim *E*-1,2- \sim Z-1,2, but CN < diCN < triCN < tetraCN. On the other hand, the E_a is more sensitive to the placement of the substituents with those reactants with 1,1-diCN substitution having E_a near 9 kcal/mol, whereas those with 1-CN substitution are near 15 kcal/mol. Note that the decrease of E_a is also somewhat greater in benzene for the 1,1-diCN cases. These trends suggest that ability to accept negative charge at a 1,1-disubstituted carbon facilitates the reaction. It is also worth noting that according to these calculations, tetracyanoethene *does not* have an asynchronous TS, in contrast to several other very electrophilic dienophiles such as dimethyl acetylene dicarboxylate and maleic acid (see p. 855)

The application of DFT concepts to interpretation of relative reactivity and regioslectivity of 1,3-DPCA is being explored.³⁴⁷ DFT recognizes both charge transfer interactions between the reactants and electron redistribution in the TS as key parts of the reaction process.³⁴⁸ As discussed earlier for D-A reactions, DFT theory can also be

Table 10.12. Global Electrophilicity and ΔN_{\max} Parameters for 1,3-Dipoles^a

Strongly Electrophilic			Moderately Electrophilic			Marginally Electrophilic		
$O=O-O$	ω 6.10	ΔN_{\max} 1.73	$H_2C=N=N$	ω 1.40	ΔN_{\max} 0.77	$HC\equiv N-O$	ω 0.73	ΔN_{\max} 0.43
$HN=O-O$	4.18	1.39	$N\equiv N-O$	1.37	0.56	$H_2C=N-NH$	0.72	0.54
$HN=O$	2.88	1.17	$HN=N-NH$	1.22	0.66	$HN=N=N$	0.66	0.40
$H_2C=O-O$	2.43	1.08	$HN=N-NH$	1.22	0.66	$HC\equiv N-CH_2$	0.65	0.55
$O=N-O$	2.38	0.86	$H_2C=N-O$	1.06	0.62	$HC\equiv N-CH_2$	0.37	0.41
$HN=N-O$	1.70	0.74	$CH_2=O-CH_2$	0.93	0.70	$H_2C=N-CH_2$	0.28	0.28
$H_2C=O-NH$	1.65	0.91						

a. From P. Perez, L. R. Domingo, M. J. Aurell, and R. Contreras, *Tetrahedron*, **59**, 3117 (2003).

³⁴⁷ P. Geerlings and F. De Proft, *Int. J. Quantum Chem.*, **80**, 227 (2000).

³⁴⁸ F. Mendez, J. Tamariz, and P. Geerlings, *J. Phys. Chem. A*, **102**, 6292 (1998).

applied to interpretation of the regiochemistry of 1,3-dipolar cycloaddition reactions.³⁴⁹ The DFT concept of local softness (see Topic 1.5) has been applied to regioselectivity. Chandra and co-workers have emphasized in particular that softness matching may be a determining factor in regiochemistry.³⁵⁰ As discussed in connection with the D-A reaction, the global electrophilicity parameter ω , as defined in DFT,³⁴¹ can provide some insight into relative reactivity of 1,3-dipoles. Domingo and co-workers have calculated ω and ΔN_{\max} for representative 1,3-dipoles are given in Table 10.12.

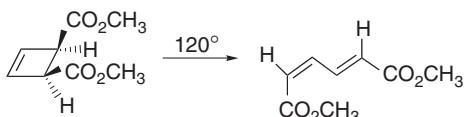
There are some anomalies in Table 10.12; for example, the nitro group is listed as strongly electrophilic, but in fact is not reactive at all in normal 1,3-dipolar cycloadditions. The ω scale is also applicable only to the reactions in which the dipolarophile is acting as the electrophilic component; that is, in FMO terminology, the $LUMO_{\text{dipole}} - HOMO_{\text{dipolarophile}}$ interaction is dominant.

Problems

(References for these problems will be found on page 1165.)

- 10.1. Show, by construction of both a TS orbital array and an orbital symmetry correlation diagram, which of the following electrocyclicizations are allowed.
- disrotatory cyclization of the pentadienyl cation to the cyclopent-2-enyl cation.
 - disrotatory cyclization of the pentadienyl anion to the 3-cyclopentenyl anion.
 - disrotatory cyclization of the heptatrienyl anion to the cyclohepta-3,5-dienyl anion.
- 10.2. Which of the following reactions are allowed according to orbital symmetry conservation rules? Explain. Discuss any special structural features that might influence the facility of the reaction.

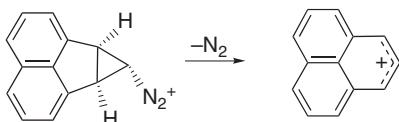
a.



b.

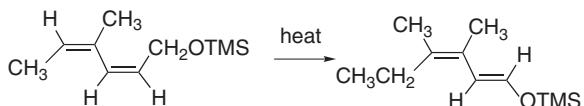
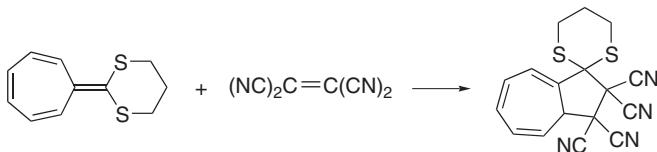


c.



³⁴⁹ F. Mendez, J. Tamariz, and P. Geerlings, *J. Phys. Chem. A*, **102**, 6292 (1998); A. K. Chandra and M. T. Nguyen, *J. Comput. Chem.*, **19**, 195 (1998).

³⁵⁰ J. Korchowiec, A. K. Chandra, and T. Uchimaru, *Theochem.*, **572**, 193 (2001).



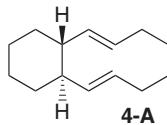
- 10.3. *Z,Z,Z,Z*-1,3,5,7-cyclononatetraene undergoes a spontaneous electrocyclic ring closure at 25°C. Predict the most likely structure for this cyclization product. Describe an alternative, symmetry-allowed electrocyclic reaction that would lead to an isomeric product. Explain why this alternate reaction pathway is not followed.

- 10.4. Offer a mechanistic explanation for each of the following reactions:

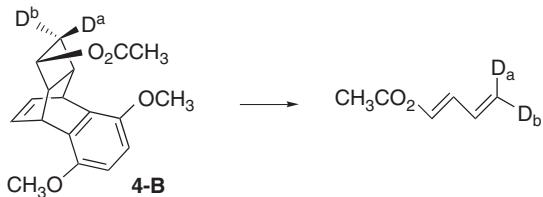
- a. The 3,5-dinitrobenzoate esters of the stereoisomeric bicyclo[2.1.0]pentan-2-ols shown below both yield cyclopent-3-enol on hydrolysis in dioxane-water. The relative rates, however, differ by a factor of 10 million! Which is more reactive and why?



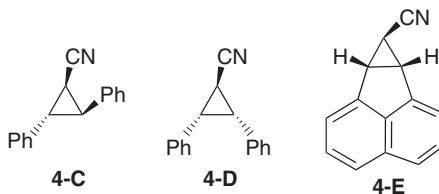
- b. Optically active **4-A** racemizes on heating at 50°C with a half-life of 24 h.



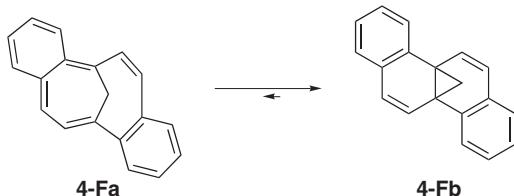
- c. On being heated to 320°–340°C, compound **4-B** produces 1,4-dimethoxynaphthalene and 1-acetoxybutadiene. Furthermore, deuterium labeling has shown that the reaction is stereospecific as indicated.



- d. It has been found that compounds **4-C** and **4-D** are opened at -25°C to allylic anions in the presence of strong bases such as lithium *t*-butylamide. In contrast, **4-E**, opens only slowly at 25°C .

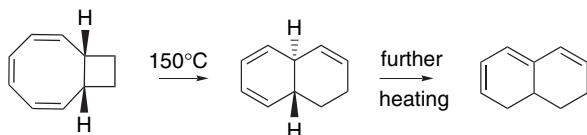


- e. When the 1,6-methano-1,3,5,7,9-pentaene structure is modified by fusion of two benzene rings as shown in **4-Fa**, a valence isomer **4-Fb** is the dominant structure.

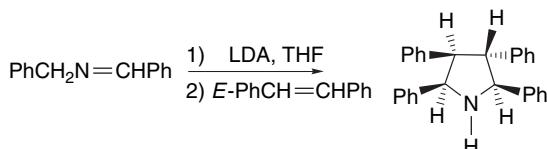


- 10.5. Suggest a mechanism by which each transformation could occur. More than one step may be involved.

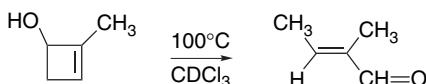
a.



b.



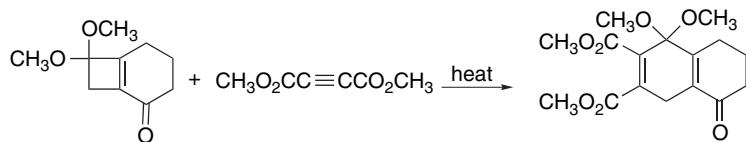
c.



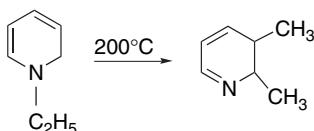
d.



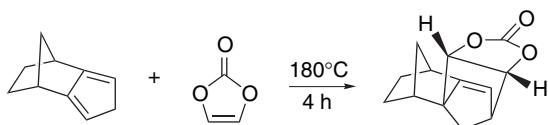
e.



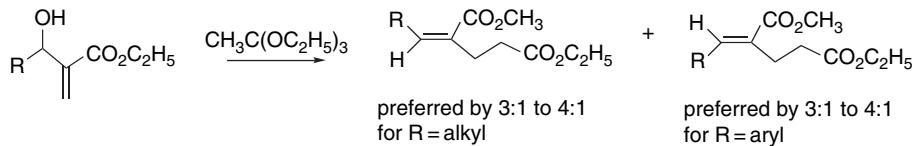
f.



g.



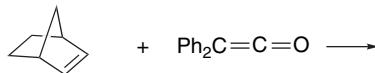
- 10.6. It has been found that 3-substituted methyl 3-hydroxy-2-methylene alkanoates give rise to a preference for the *Z*-isomer if R is alkyl, but for the *E*-isomer if R is aryl under the conditions of the thermal orthoester Claisen rearrangement.



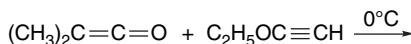
Analyze the transition structure for the reaction in terms of steric interactions and suggest a reason for the difference in stereoselectivity.

- 10.7. Give the structure, including stereochemistry, of the product expected for the following reactions:

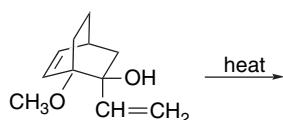
a.

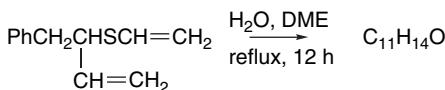


b.

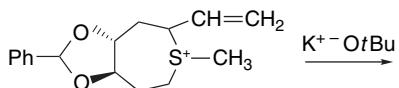


c.

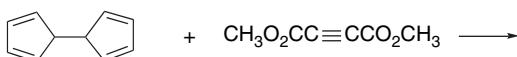




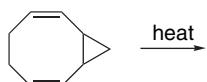
e.



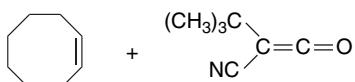
f.



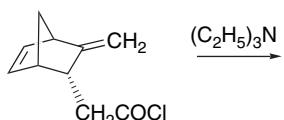
g.



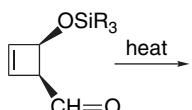
h.



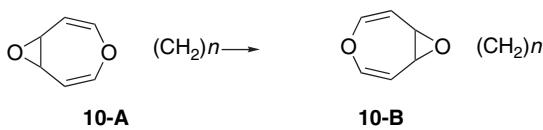
i.



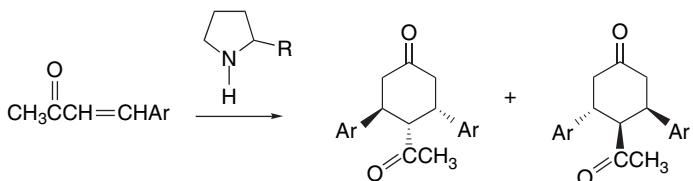
j.



- 10.8. In the series of bicyclic oxepins **10-A** ($n = 3, 4, 5$), only the compound with $n = 5$ undergoes rearrangement (at 60°C) to the isomeric oxepin **10-B**. The other two compounds ($n = 3$ or 4) are stable, even at much higher temperature. When **10-B** ($n = 3$) was synthesized by another route, it showed no tendency to revert to **10-A** ($n = 3$). Offer an explanation for these observations.

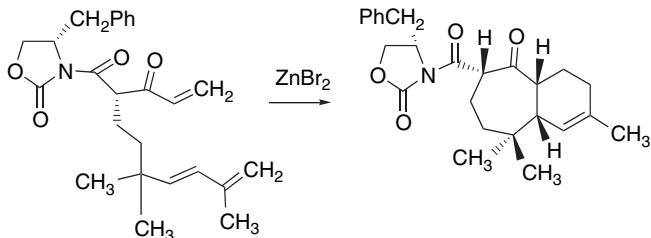


- 10.9. Bromocyclooctatetraene rearranges to *E*- β -bromostyrene. The rate of the rearrangement is solvent dependent, with the first-order rate constant increasing from about 10^{-7} s $^{-1}$ in cyclohexane to about 10^{-3} s $^{-1}$ in acetonitrile at 80°C. In the presence of lithium iodide, the product is *E*- β -iodostyrene, although *E*- β -bromostyrene is unaffected by lithium iodide under the reaction conditions. Suggest a mechanism for the rearrangement.
- 10.10. Pyrrolidine derivatives catalyze the formation of 3,5-diaryl-4-acetylcylohexanones from 4-arylbut-3-en-2-ones. A Diels-Alder reaction is believed to be involved. Suggest a mechanism.

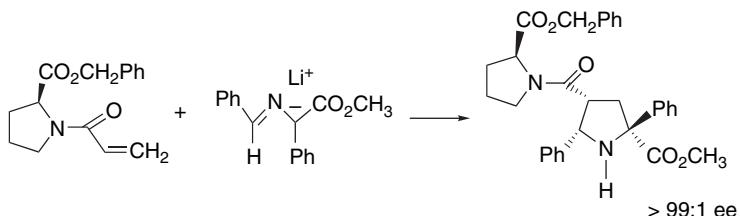


- 10.11. Propose a transition structure that would account for the stereochemistry observed in each of the following reactions:

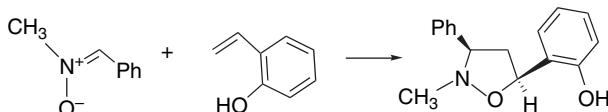
a.



b.

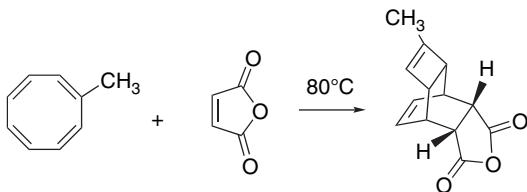


c.

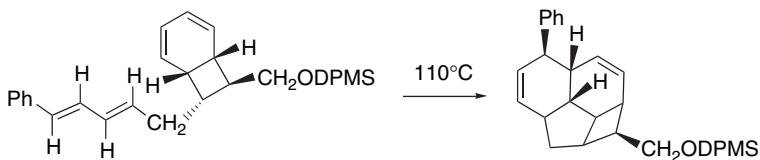


the *cis* selectivity is
100%. In the absence of the
o-hydroxy, *cis* selectivity is 2:1.

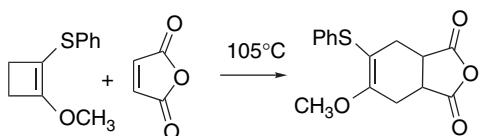
- 10.12. Classify the following reactions as electrocyclicizations, sigmatropic rearrangement, cycloaddition, etc., and give the correct symbolism for the electrons involved in each process. Some of the reactions proceed in two steps.



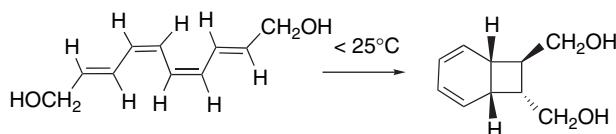
b.



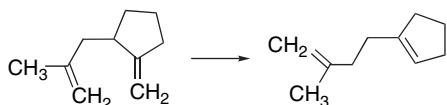
c.



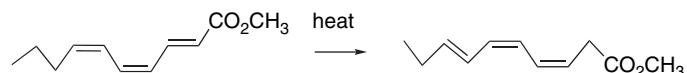
d.



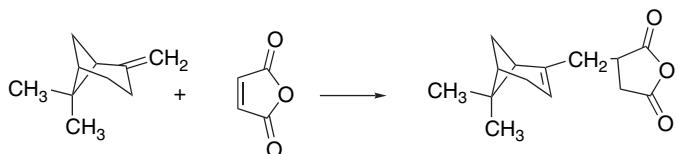
e.



f.



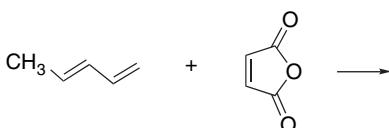
- 10.13. The “ene” reaction is a concerted reaction in which addition of an alkene and an electrophilic olefin occurs with transfer of a hydrogen to the electrophile and with a double-bond shift. For example:



Depict the orbital array through which this reaction can occur as a concerted process.

10.14. Predict the regiochemistry and stereochemistry of the following cycloaddition reactions and indicate the basis for your prediction.

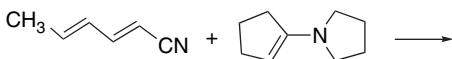
a.



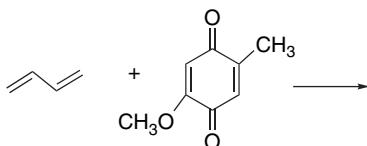
b



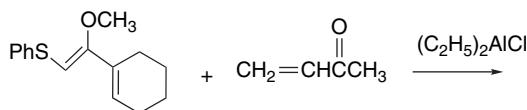
c.



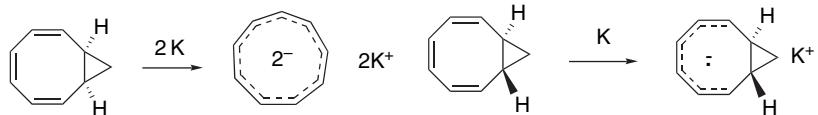
d.



e.

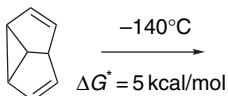


10.15. On treatment with potassium metal, *cis*-bicyclo[6.1.0]nona-2,4,6-triene gives a monocyclic aromatic dianion. The *trans* isomer under similar conditions give a bicyclic radical anion that does not undergo further reduction. Explain how the stereochemistry of the ring junction can control the course of these reductions.

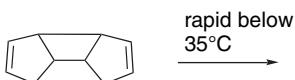


10.16. The following compounds are capable of degenerate rearrangement at the temperature given. Identify reaction processes that are consistent with the temperature and would lead to a degenerate rearrangement. Indicate by an appropriate labeling scheme the carbons and hydrogens that become equivalent as a result of the rearrangement process you have suggested.

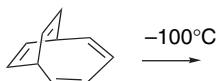
a.



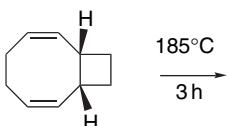
b.



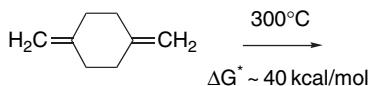
c.



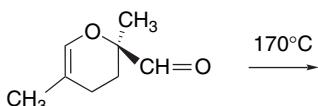
d.



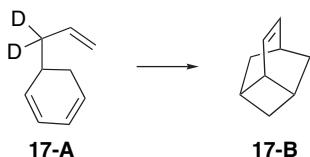
e.



f.



- 10.17. On heating at 225°C, 5-allylcyclohexa-1,3-diene, **17-A**, undergoes intramolecular cycloaddition to give the tricyclononene **17-B**. The same product is predicted for both [2 + 2] and [2 + 4] cycloaddition. The mechanism of the reaction has been probed by using the deuterium-labeled derivative, as shown. Indicate the position of the deuterium labeling in the product if the reaction proceeds by (a) a [2 + 2] cycloaddition or (b) a [2 + 4] cycloaddition.



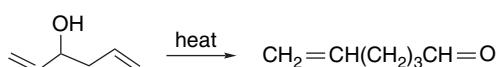
- 10.18. Computations on the cyclization of pentadienyl cations to cyclopentenyl cations has indicated increasing reactivity in the order $X = \text{NH}_2 < \text{OH} < \text{H} < \text{O}^+\text{H}_2$.



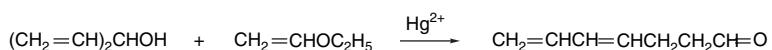
Based on these results, indicate which of the following types of groups would be favorable relative to the unsubstituted system: (a) alkyl; (b) π -conjugated EWGs, e.g., CN, CH=O; (c) σ -EWGs, e.g., CF₃, CF₃SO₂.

10.19. Suggest mechanisms for the following reactions. Classify the orbital symmetry character of the process as completely as you can.

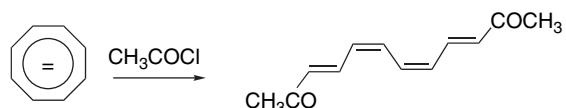
a.



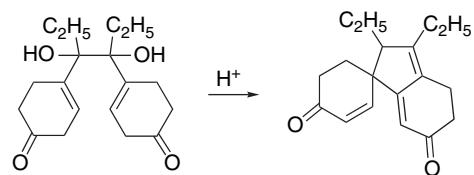
b.



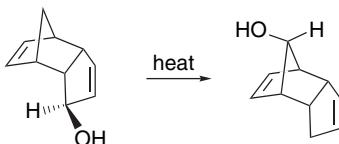
c.



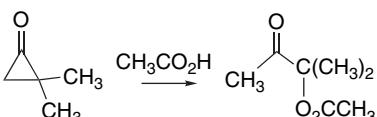
d.



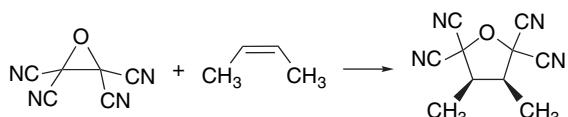
e.



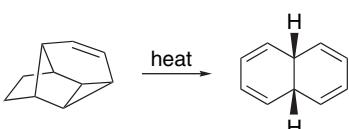
f.



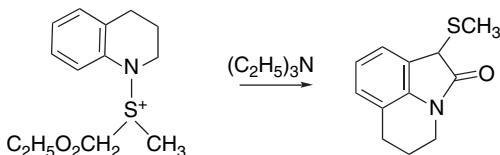
g.



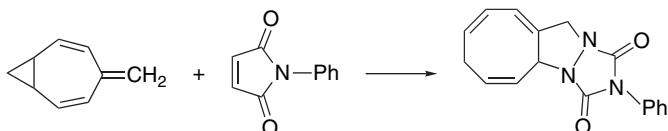
h.



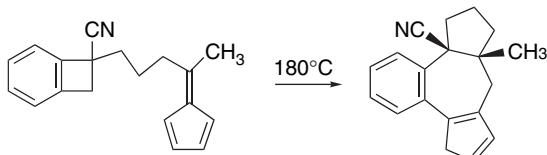
i.



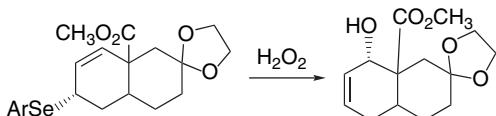
j.



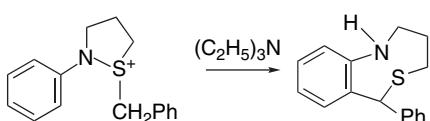
k.



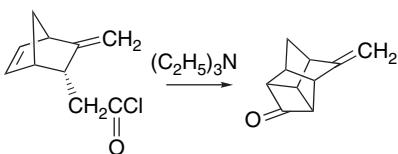
l.



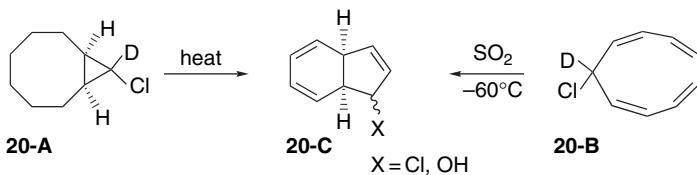
m.



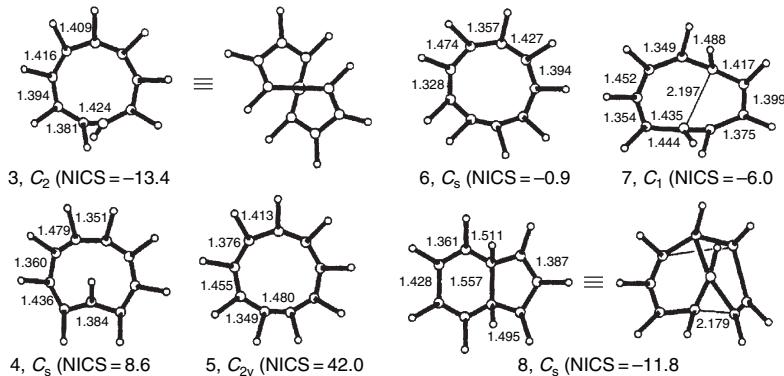
n.



- 10.20. Both compounds **20-A** and **20-B** undergo solvolysis in polar solvents at low temperature. The isolated product is **20-C**. When **20-B** is labeled with deuterium it is found that there is complete scrambling of label *equally among all positions* in the product.



It has been suggested that the cyclononatetraenyl cation might be an intermediate, and several $[C_9H_9]^+$ structures have been compared computationally to determine their relative energy. Structure **3** has the lowest energy among the monocations. It has an *E*-configuration at one double bond. Structure **4** is also an energy minimum, but it is 21.6 kcal/mol higher in energy than **3**. The calculated relative energy and nucleus independent chemical shift (NICS) values are given for several structures, including structure **6**, which gives rise to the observed product. Formulate a mechanism that is in accord with the experimental observation of label scrambling. Discuss the role of structure **3** in the mechanism.



- 10.21. Reaction of ketene with cyclopentadiene proceeds in a $[2+2]$ rather than a $[2+4]$ manner. A number of potential TSs have been characterized computationally. The diagrams below show product and TS energy, TS bond orders, and TS NPA

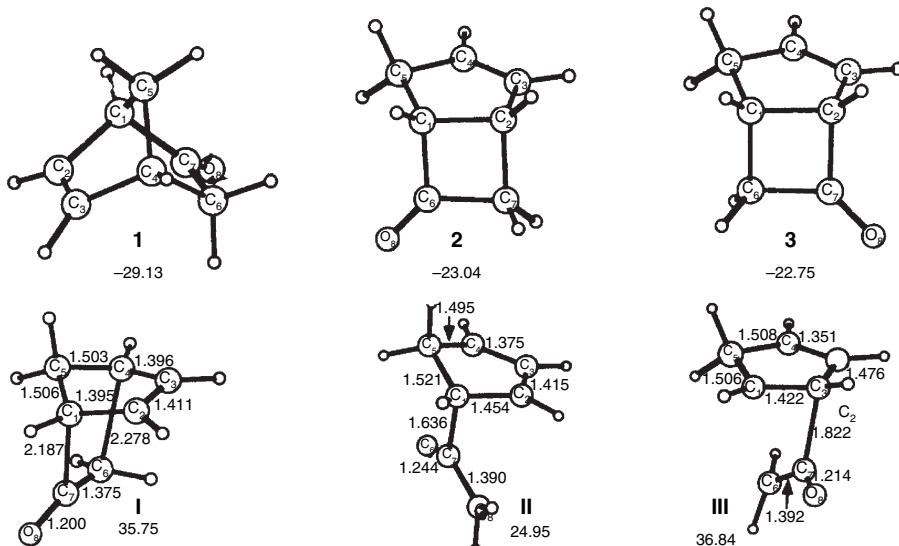


Fig. 10.P21a. ΔE and E_a (MP4SDQ/6-31G*+ ZPE) for products **1** to **3** and the corresponding lowest-energy transition structures **I**, **II**, and **III**. Reproduced by Permission of the American Chemical Society.

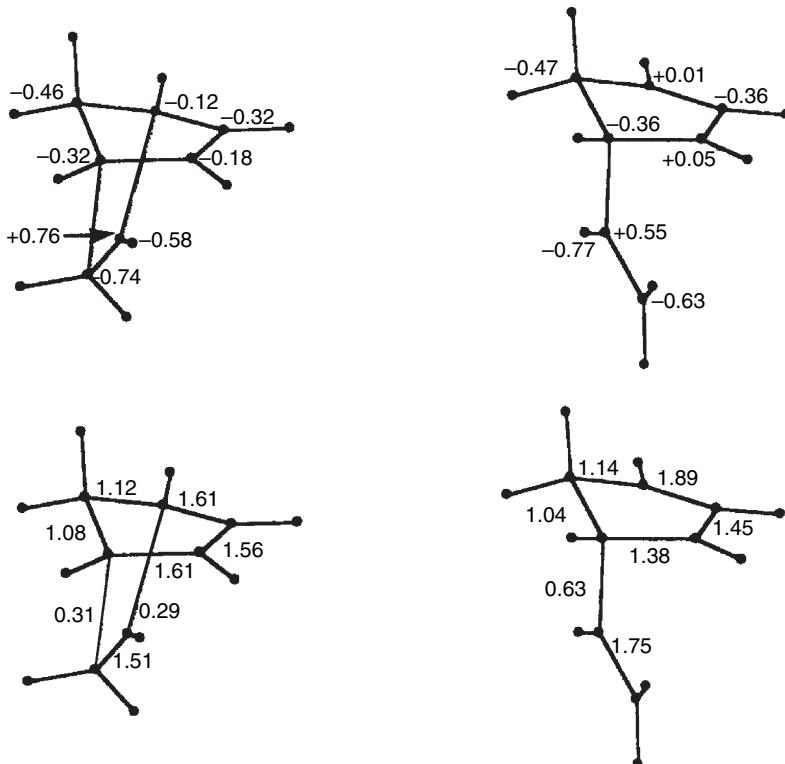


Fig. 10.P21b. NPA charges and bond orders for TS **I** and **II**. Reproduced by Permission of the American Chemical Society.

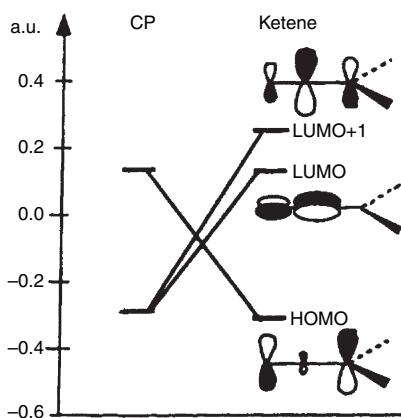
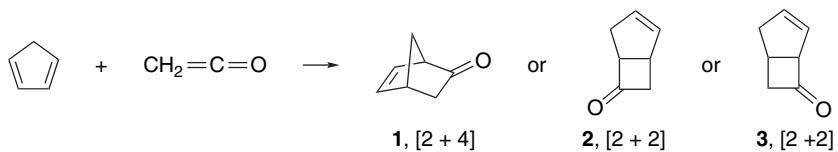


Fig. 21Pc. Relative energy (in au) of cyclopentadiene HOMO and LUMO and ketene π , $\pi^*_{C=O}$, and π^* orbitals. Reproduced by permission of the American Chemical Society.

charges from MP4SDQ/6-31G*+ ZPE computations. Analyze the computational output in order to answer the following questions:

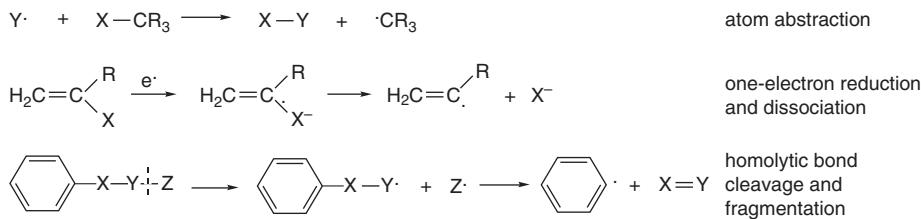


- In very broad terms, why is the [2 + 2] product **2** favored over the other possible products? Draw a reaction potential energy diagram to illustrate your conclusion.
- More specifically, why is product **2** preferred to product **3**? What structural features account for this preference?
- What structural features of TS **1** make it less favorable than TS **2**?

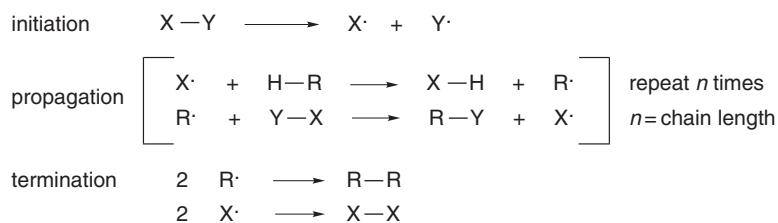
Free Radical Reactions

Introduction

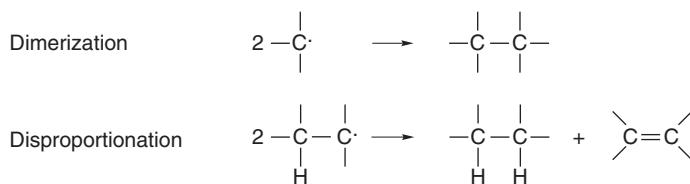
A free radical reaction involves molecules having unpaired electrons. The radical can be a starting compound or a product, but radicals are usually intermediates in reactions. Most of the reactions discussed to this point have been *heterolytic processes* involving polar intermediates and/or transition structures *in which all electrons remained paired throughout the course of the reaction*. In radical reactions, *homolytic bond cleavages* occur, with each fragment retaining one of the bonding electrons. The generalized reactions below illustrate the formation of alkyl, vinyl, and aryl free radicals by homolytic processes.



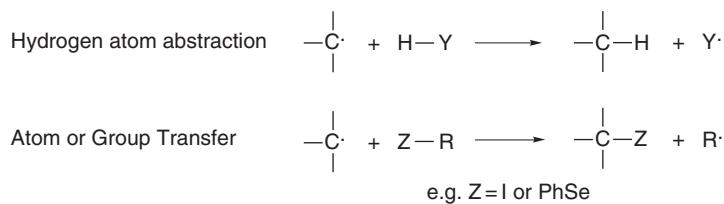
Free radicals are often involved in *chain reactions*. The overall mechanism consists of a series of reactions that regenerates a radical that can begin a new cycle of reactions. This sequence of reactions is called the *propagation phase*. Free radicals are usually highly reactive and the individual steps in a chain reaction typically have high absolute rate constants. However, the concentrations of the intermediates are low. The overall rates of reaction depend on the balance between the *initiation* and *termination* phases of the reaction, which start and end the chain sequence. The *chain length* is an important characteristic of free radical reactions. It specifies the average number of propagation sequences that occur per initiation step.



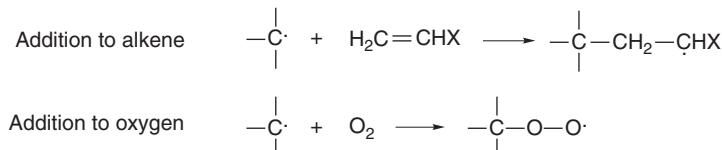
The effect of substituents on radical stability was introduced in Section 3.4.3. Most organic free radicals have very short lifetimes and dimerize or disproportionate at a diffusion-controlled rate. The usual disproportionation process for alkyl radicals involves transfer of a hydrogen from the β -carbon to the radical site, leading to formation of an alkane and an alkene. Disproportionation is facilitated by the weak β -C–H bond (see p. 311)



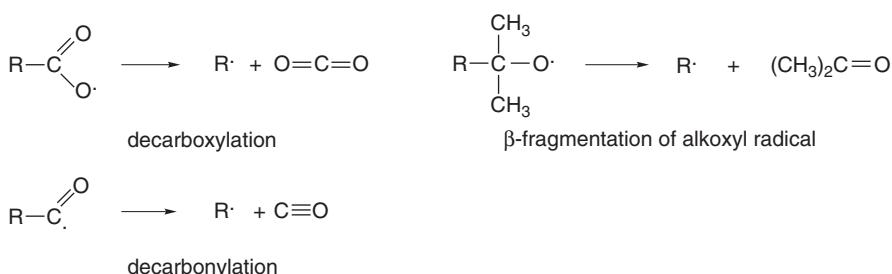
There are several fundamental types of radical reactions. Radicals can abstract hydrogen or other atoms from many types of solvents and reagents. This is a particularly important example of an *atom or group transfer reaction*.



Radicals are also capable of addition reactions. For synthetic purposes, additions to alkenes are particularly important. Most radicals are highly reactive toward O_2 .



Radicals also undergo fragmentation reactions. Most of these are β -scission reactions, such as illustrated by decarboxylation and fragmentation of alkoxy radicals, but decarbonylation, an α -cleavage, is also facile.

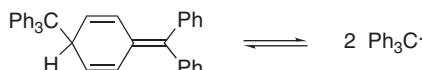


As we discuss specific reaction mechanisms, we will see that they are combinations of a relatively small number of reaction types that are applicable to a number of different reactants and reaction sequences.

11.1. Generation and Characterization of Free Radicals

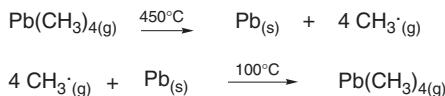
11.1.1. Background

Two early studies have special historical significance in the development of the concept of free radical reactions. The work of Gomberg around 1900 provided evidence that when triphenylmethyl chloride was treated with silver metal, the resulting solution contained $\text{Ph}_3\text{C}\cdot$ in equilibrium with a less reactive molecule. Eventually it was shown that the dimeric product is a cyclohexadiene derivative.¹



The dissociation constant is small, only about $2 \times 10^{-4} M$ at room temperature. The presence of the small amount of the radical at equilibrium was deduced from observation of reactions that could not reasonably be attributed to a normal hydrocarbon.

The second set of experiments was carried out in 1929 by Paneth. The decomposition of tetramethyllead was accomplished in such a way that the products were carried by an inert gas over a film of lead metal. The lead was observed to disappear with re-formation of tetramethyllead. The conclusion reached was that methyl radicals must exist long enough in the gas phase to be transported from the point of decomposition to the lead film, where they are reconverted to tetramethyllead.



Since these early experiments, a great deal of additional information about the structure and properties of free radical intermediates has been developed. In this chapter, we discuss the structure of free radicals and some of the special features associated with free radical reactions. We also consider some of the key chemical reactions that involve free radical intermediates.

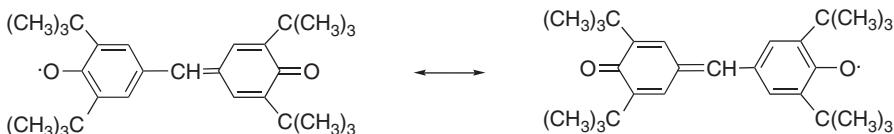
¹. H. Lankamp, W. Th. Nauta, and C. MacLean, *Tetrahedron Lett.*, 249 (1968); J. M. McBride, *Tetrahedron*, **30**, 2009 (1974); K. J. Skinner, H. S. Hochster, and J. M. McBride, *J. Am. Chem. Soc.*, **96**, 4301 (1974).

11.1.2. Long-Lived Free Radicals

Radicals that have long lifetimes and are resistant to dimerization, disproportionation, and other routes to self-annihilation are called *persistent free radicals*. Scheme 11.1 gives some examples of long-lived free radicals. A few free radicals are indefinitely stable, such as Entries 1, 3, and 6, and are just as stable to ordinary conditions of temperature and atmosphere as typical closed-shell molecules. Entry 2 is somewhat less stable to oxygen, although it can exist indefinitely in the absence of oxygen. The structures shown in Entries 1, 2, and 3 all permit extensive delocalization of the unpaired electron into aromatic rings. These highly delocalized radicals show little tendency toward dimerization or disproportionation. The radical shown in Entry 3 is unreactive under ordinary conditions and is thermally stable even at 300°C.²

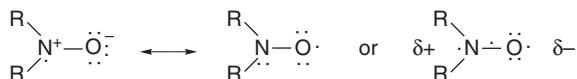
The *bis-(t-butyl)methyl* radical shown in Entry 4 has only alkyl substituents and yet has a significant lifetime in the absence of oxygen. The *tris-(t-butyl)methyl* radical has an even longer lifetime with a half-life of about 20 min at 25°C.³ The steric hindrance provided by the *t*-butyl substituents greatly retards the rates of dimerization of these radicals. Moreover, they lack β -hydrogens, precluding the normal disproportionation reaction. They remain highly reactive toward oxygen, however. The extended lifetimes have more to do with kinetic factors than with inherent stability.⁴ Entry 5 is a sterically hindered perfluorinated radical that is even more long-lived than similar alkyl radicals.

Certain radicals are stabilized by synergistic conjugation involving two or more functional groups. Entries 6 and 7 are examples. Galvinoxyl, the compound shown in Entry 6 benefits not only from delocalization over the two aromatic rings, but also from the equivalence of the two oxygens, which is illustrated by the resonance structures. The hindered nature of the oxygens also contributes to persistence.



Entry 7 also benefits from interaction between the ester and amino groups, as is discussed in Section 11.1.6.

There are only a few functional groups that contain an unpaired electron and yet are stable in a wide range of structural environments. The best example is the nitroxide group illustrated in Entry 8. There are numerous specific nitroxide radicals that have been prepared and characterized. The unpaired electron is delocalized between nitrogen and oxygen in a structure with a N–O bond order of 1.5.



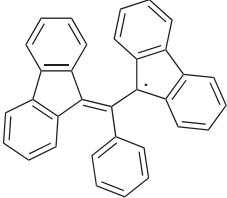
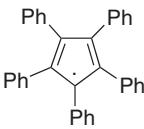
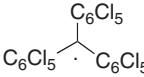
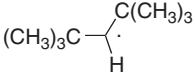
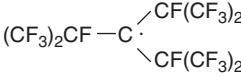
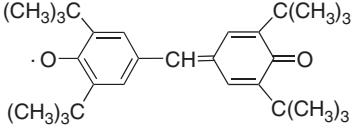
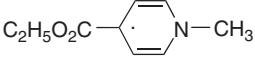
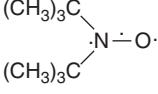
Many nitroxides are stable under normal conditions, and heterolytic reactions can be carried out on other functional groups in the molecule without affecting the nitroxide

². M. Ballester, *Acc. Chem. Res.*, **18**, 380 (1985).

³. G. D. Mendenhall, D. Griller, D. Lindsay, T. T. Tidwell, and K. U. Ingold, *J. Am. Chem. Soc.*, **96**, 2441 (1974).

⁴. For a review of various types of persistent radicals, see D. Griller and K. U. Ingold, *Acc. Chem. Res.*, **9**, 13 (1976).

Scheme 11.1. Properties of Some Long-Lived Free Radicals

Structure	Stability	SECTION 11.1
	Indefinitely stable as a solid, even in the presence of air	<i>Generation and Characterization of Free Radicals</i>
	Crystalline substance is not rapidly attacked by oxygen, although solutions are air-sensitive. The compound is stable to high temperature in the absence of air.	
	Stable in solution for days, even in the presence of air. Indefinitely stable in the solid state. Thermally stable up to 300°C.	
	Persistent in dilute solution ($<10^{-5} M$) below -30°C in the absence of oxygen; $t_{1/2}$ of 50 s at 25°C .	
	Thermally stable to 70°C ; stable to O_2 .	
	Stable to oxygen; stable to extended storage as a solid. Slowly decomposes in solution.	
	Stable distillable liquid that is only moderately sensitive to O_2 .	
	Stable to oxygen, even above 100°C	

a. C. F. Koelsch, *J. Am. Chem. Soc.*, **79**, 4439 (1957).b. K. Ziegler and B. Schnell, *Liebigs Ann. Chem.*, **445**, 266 (1925).c. M. Ballester, J. Riera, J. Castaner, C. Badia, and J. M. Monso, *J. Am. Chem. Soc.*, **93**, 2215 (1971).d. G. D. Mendenhall, D. Griller, D. Lindsay, T. T. Tidwell, and K. U. Ingold, *J. Am. Chem. Soc.*, **96**, 2441 (1974).e. K. V. Scherer, Jr., T. Ono, K. Yamanouchi, R. Fernandez, and P. Henderson, *J. Am. Chem. Soc.*, **107**, 718 (1985).f. G. M. Coppinger *J. Am. Chem. Soc.*, **79**, 501 (1957); P. D. Bartlett and T. Funahashi, *J. Am. Chem. Soc.*, **84**, 2596 (1962).g. J. Hermolin, M. Levin, and E. M. Kosower, *J. Am. Chem. Soc.*, **103**, 4808 (1981).h. A. K. Hoffmann and A. T. Henderson, *J. Am. Chem. Soc.*, **83**, 4671 (1961).

group.⁵ Nitroxides are very useful in biochemical studies by being easily detected paramagnetic probes.⁶

Although the existence of stable and persistent free radicals is of significance in establishing that free radicals can have extended lifetimes, most free radical reactions involve highly reactive intermediates that have fleeting lifetimes and are present at very low concentrations. The techniques for the study of radicals under these conditions are the subject of the next section.

11.1.3. Direct Detection of Radical Intermediates

The distinguishing characteristic of free radicals is the presence of an unpaired electron. Species with an unpaired electron are *paramagnetic*, that is, they have a nonzero electronic spin. The most useful method for detecting and characterizing unstable radical intermediates is *electron spin resonance* (ESR) spectroscopy,⁷ also known as *electron paramagnetic resonance* (EPR) spectroscopy. ESR spectroscopy detects the transition of an electron between the energy levels associated with the two possible orientations of electron spin in a magnetic field. An ESR spectrometer records the absorption of energy when an electron is excited from the lower to the higher state. The energy separation is very small on an absolute scale and corresponds to the energy of microwaves. ESR spectroscopy is a highly specific tool for detecting radical species because only molecules with unpaired electrons give rise to ESR spectra. As with other spectroscopic methods, detailed analysis of the absorption spectrum can provide structural information. One feature that is determined is the *g* value, which specifies the separation of the two spin states as a function of the magnetic field strength of the spectrometer:

$$h\nu = E = g\mu_B H \quad (11.1)$$

where μ_B is the Bohr magneton (a constant equal to 9.273 ergs/gauss) and H is the magnetic field in gauss. The measured value of *g* is a characteristic of the particular type of radical, just as the line position in NMR spectra is characteristic of the absorbing nucleus.

More detailed structural information can be deduced from the *hyperfine splitting* in ESR spectra. The origin of this splitting is closely related to the factors that cause spin-spin splitting in ¹H-NMR spectra. Certain nuclei have a magnetic moment, and among those of greatest interest in organic chemistry are ¹H, ¹³C, ¹⁴N, ¹⁹F, and ³¹P. Interaction of the electron with one or more of these nuclei splits the signal arising from the unpaired electron. The number of lines is given by the equation

$$\text{Number of lines} = 2nI + 1 \quad (11.2)$$

where *I* is the nuclear spin quantum number and *n* is the number of equivalent interacting nuclei. For ¹H, ¹³C, ¹⁹F, and ³¹P, *I* = 1/2, so a single hydrogen splits a

- ⁵. For reviews of the preparation, reactions and uses of nitroxide radicals, see J. F. W. Keana, *Chem. Rev.*, **78**, 37 (1978); L. J. Berliner, ed., *Spin-Labeling*, Vol. 2, Academic Press, New York, 1979; S. Banerjee and G. K. Trivedi, *J. Sci. Ind. Res.*, **54**, 623 (1995); L. B. Volodarsky, V. A. Reznikov, and V. I. Ovcharenko, *Synthetic Chemistry of Stable Nitroxides*, CRC Press, Boca Raton, FL, 1994.
- ⁶. G. L. Millhauser, W. R. Fiori, and S. M. Miick, *Methods Enzymol.*, **246**, 589 (1995).
- ⁷. B. Mile, *Current Org. Chem.*, **4**, 55 (2000); F. Gerson and W. Huber, *Electron Spin Resonance of Organic Radicals*, Wiley-VCH, Weinheim, 2003.

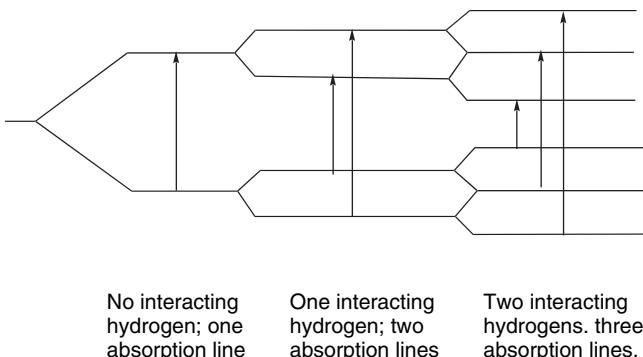


Fig. 11.1. Hyperfine splitting in ESR spectra.

signal into a doublet. Interaction with three equivalent hydrogens, as in a methyl group, gives splitting into four lines. This splitting is illustrated in Figure 11.1. Nitrogen (^{14}N) with $I = 1$ splits each energy level into three lines. Neither ^{12}C nor ^{16}O has a nuclear magnetic moment, and just as they cause no signal splitting in NMR spectra, they have no effect on the multiplicity in ESR spectra.

A great deal of structural information can be obtained by analysis of the hyperfine splitting pattern of a free radical. If we limit our discussion for the moment to radicals without heteroatoms, the number of lines indicates the number of interacting hydrogens, and the magnitude of the splitting, given by the hyperfine splitting constant a , is a measure of the unpaired electron density in the hydrogen 1s orbital. For planar conjugated systems in which the unpaired electron resides in a π -orbital system, the relationship between electron spin density and the splitting constant is given by the McConnell equation⁸:

$$a = \rho Q \quad (11.3)$$

where a is the hyperfine coupling constant for a proton, Q is a proportionality constant (about 23 G), and ρ is the spin density on the carbon to which the hydrogen is attached. For example, taking $Q = 23.0$ G, the hyperfine splitting in the benzene radical anion can be readily calculated by taking $\rho = 1/6$, because the one unpaired electron must be distributed equally among the six carbon atoms. The calculated value of $a = 3.83$ is in good agreement with the observed value. The spectrum (Figure 11.2a) consists of seven lines separated by a coupling constant of 3.75 G.⁹ Note that EPR spectra, unlike NMR and IR spectra, are displayed as the derivative of absorption rather than as absorption.

The ESR spectrum of the ethyl radical shown in Figure 11.2b is readily interpreted, and the results are of interest with respect to the distribution of unpaired electron density in the molecule.¹⁰ The 12-line spectrum is a triplet of quartets resulting from unequal coupling of the electron spin to the α - and β -hydrogens. The two coupling constants, $a_{\alpha} = 22.4$ G and $a_{\beta} = 26.9$ G, imply extensive delocalization of spin density through the σ bonds.

⁸. H. M. McConnell, *J. Chem. Phys.*, **24**, 764 (1956).

⁹. J. R. Bolton, *Mol. Phys.*, **6**, 219 (1963).

¹⁰. R. W. Fessenden and R. M. Shuler, *J. Chem. Phys.*, **33**, 935 (1960); *J. Phys. Chem.*, **39**, 2147 (1963).

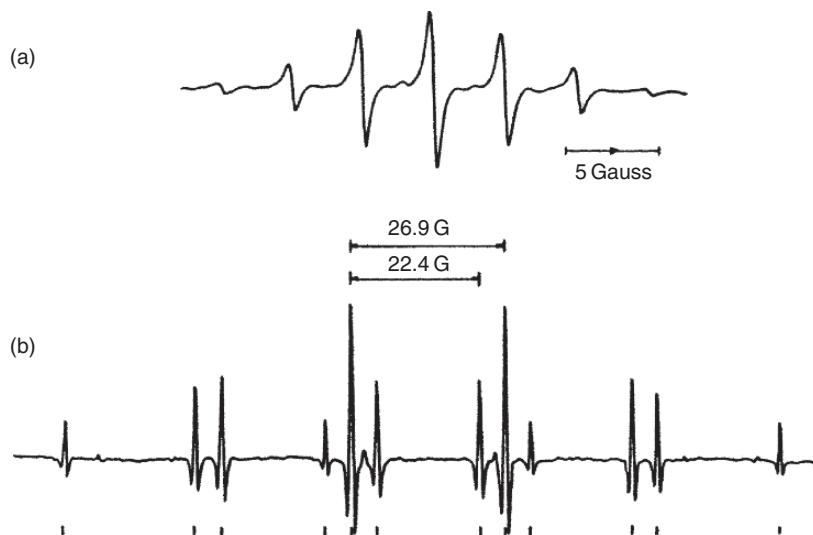
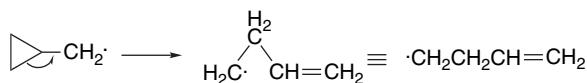
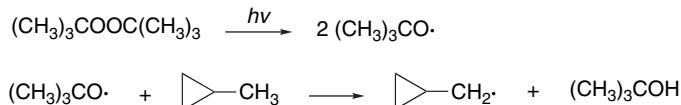


Fig. 11.2. Some EPR spectra of small radicals: (a) Spectrum of the benzene radical anion. From *Mol. Phys.*, **6**, 219 (1963); (b) Spectrum of the ethyl radical. From *J. Chem. Phys.*, **33**, 935 (1960); *J. Phys. Chem.* **67**, 2147 (1963). Reproduced by permission of Taylor and Francis, Ltd, and the American Institute of Physics, respectively.

ESR spectra have been widely used in the study of reactions to detect free radical intermediates. An important example involves the cyclopropylmethyl radical. Much chemical experience has indicated that this radical is unstable, rapidly giving rise to the 3-but enyl radical after being generated.

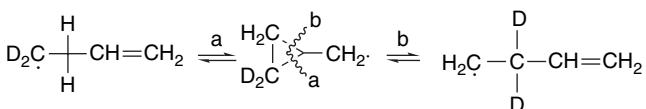


The radical was generated by photolytic decomposition of di-*t*-butyl peroxide in methylcyclopropane, a process that leads to selective abstraction of a methyl hydrogen.



Below -140°C , the ESR spectrum observed was that of the cyclopropylmethyl radical. If the photolysis was done above -140°C , however, the spectrum of a second species was seen, and above -100°C , this was the only spectrum observed. This second spectrum was shown to be that of the 3-but enyl radical.¹¹ This study also established that the 3-but enyl radical does not revert to the cyclopropylmethyl radical on being cooled back to -140°C . The conclusion is that the ring opening of the cyclopropyl radical is a very facile process and its lifetime above -100°C is very short. Even

¹¹ J. K. Kochi, P. J. Krusic, and D. R. Eaton, *J. Am. Chem. Soc.*, **91**, 1877 (1969).

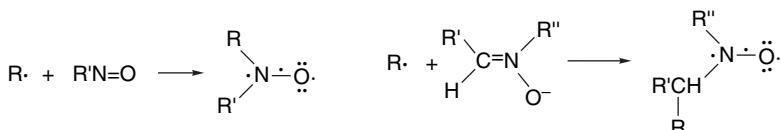


The rate of both the ring opening ($k = 1 \times 10^8 \text{ s}^{-1}$ at 25°C) and the ring closure ($k = 3 \times 10^3 \text{ s}^{-1}$) have been measured and confirm that only a very small amount of the cyclopropylmethyl radical is present at equilibrium, in agreement with the ESR results.¹²

Several MO and DFT computations on the energetics of the ring opening of the cyclopropylmethyl radical have been carried out. The computed energy profile shown in Figure 11.3 is derived from CCSD(T)/cc-pvTZ-level calculations.¹³ A barrier of 8.5 kcal/mol is calculated for the ring opening, along with smaller barriers associated with rotations in the reactant and product. A value of 7.2 kcal/mol has been obtained from CBS-RAD calculations.¹⁴ The experimental barrier is about 7.5 kcal/mol. It is worth noting that the rotational process is analogous to the interconversion of the perpendicular and bisected conformations of the cyclopropylmethyl cation. The radical rotamers differ by less than 3 kcal/mol, whereas the difference is nearly 30 kcal/mol in the cation (see Section 4.4.1).

It is important to emphasize that direct studies such as those carried out on the cyclopropylmethyl radical can be done with *low steady state concentrations of the radical*. In the case of the study of the cyclopropylmethyl radical, removal of the source of irradiation leads to rapid disappearance of the ESR spectrum because the radicals react rapidly and are not replaced by continuing radical formation. Under many conditions, the steady state concentration of a radical intermediate may be too low to permit direct detection. Therefore, failure to observe an ESR signal cannot be taken as conclusive evidence against a radical intermediate.

A technique called *spin trapping* can also be used to study radicals. A diamagnetic molecule that reacts rapidly with radicals to give a stable paramagnetic species is introduced into the reaction system being studied. As radical intermediates are generated, they are trapped by the reactive molecule to give more stable radicals that are detectable. The most useful spin traps are nitrones and nitroso compounds, which react rapidly with radicals to give stable nitroxides.¹⁵ Analysis of the ESR spectrum of the nitroxide can provide information about the structure of the original radical.



- ^{12.} A. Effio, D. Griller, K. U. Ingold, A. L. J. Beckwith, and A. K. Serelis, *J. Am. Chem. Soc.*, **102**, 1734 (1980); L. Mathew and J. Warkentin, *J. Am. Chem. Soc.*, **108**, 7981 (1986); M. Newcomb and A. G. Glenn, *J. Am. Chem. Soc.*, **111**, 275 (1989); A. L. J. Beckwith and V. W. Bowry, *J. Org. Chem.*, **54**, 2681 (1989); D. C. Nonhebel, *Chem. Soc. Rev.*, **22**, 347 (1993).
- ^{13.} A. L. Cooksy, H. F. King, and W. H. Richardson, *J. Org. Chem.*, **68**, 9441 (2003).
- ^{14.} D. M. Smith, A. Nicolaides, B. T. Golding, and L. Radom, *J. Am. Chem. Soc.*, **120**, 10223 (1998).
- ^{15.} E. G. Janzen, *Acc. Chem. Res.*, **4**, 31 (1971); E. G. Janzen, in *Free Radicals in Biology*, Vol. 4, W. A. Pryor, ed., Academic Press, New York, 1980, pp. 115–154.

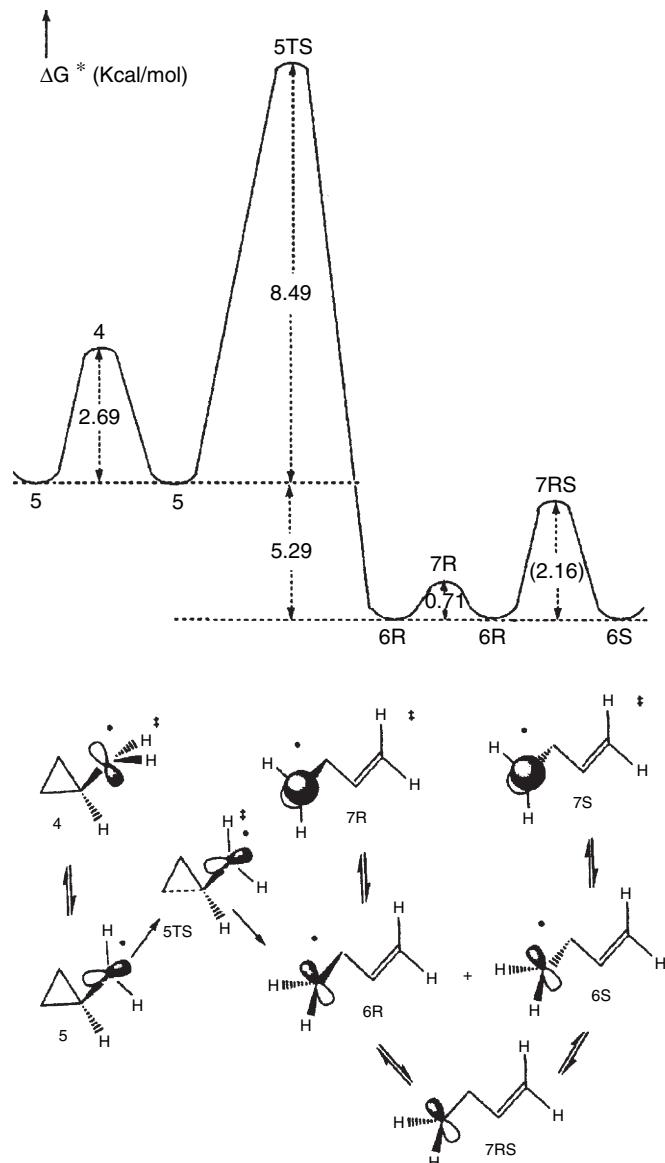


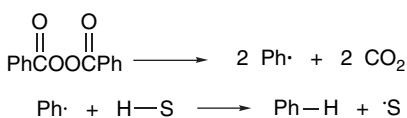
Fig. 11.3. Energy profile for rotation and ring opening of the cyclopropyl methyl radical derived from CCSD(T)/cc-pvTZ computations. Reproduced from *J. Org. Chem.*, **68**, 9441 (2003), by permission of the American Chemical Society.

Another technique that is specific for radical processes is known as CIDNP, an abbreviation for *chemically induced dynamic nuclear polarization*.¹⁶ The instrumentation required for such studies is an NMR spectrometer. CIDNP is observed as a strong perturbation of the intensity of NMR signals in products formed in certain types of free radical reactions. The variation in intensity results when the normal population of

¹⁶ H. R. Ward, *Acc. Chem. Res.*, **5**, 18 (1972); R. G. Lawler, *Acc. Chem. Res.*, **5**, 25 (1972).

nuclear spin states dictated by the Boltzmann distribution is disturbed by the presence of an unpaired electron. The magnetic moment associated with an electron causes a redistribution of the nuclear spin states. Molecules can become overpopulated in either the lower or upper spin state. If the lower state is overpopulated an enhanced absorption signal is observed. If the upper state is overpopulated, an emission signal is observed. The CIDNP method is not as general as EPR spectroscopy because not all free radical reactions can be expected to exhibit the phenomenon.¹⁷

Figure 11.4 shows the observation of CIDNP during the decomposition of benzoyl peroxide in cyclohexanone.



The emission signal corresponding to benzene confirms that it is formed by a free radical process. As in steady state ESR experiments, the enhanced emission and absorption are observed only as long as the reaction is proceeding. When the reaction is complete or is stopped in some way, the signals return to their normal intensity because equilibrium population of the two spin states is rapidly reached.

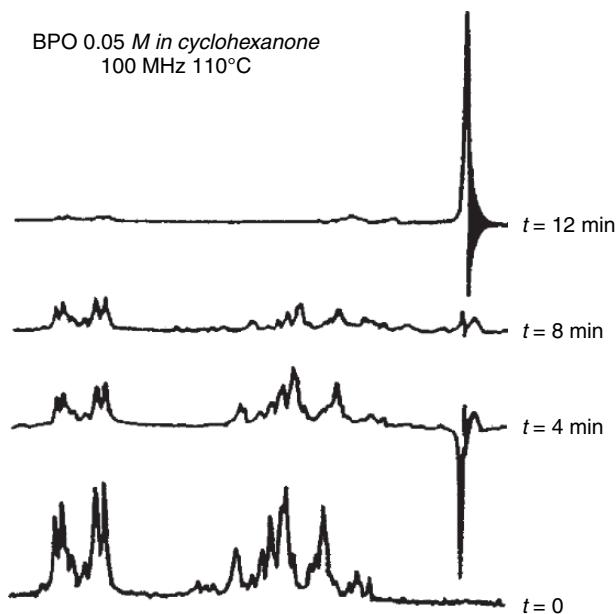
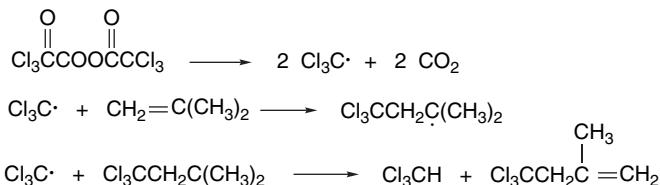


Fig. 11.4. NMR spectra recorded during decomposition of dibenzoyl peroxide. The upfield signal is due to benzene; the other signals are due to dibenzoyl peroxide. Reproduced from *Acc. Chem. Res.*, **2**, 110 (1969), by permission of the American Chemical Society.

¹⁷. For a discussion of the theory of CIDNP and the conditions under which spin polarization occurs, see G. L. Closs, *Adv. Mag. Res.*, **7**, 157 (1974); R. Kaptein, *Adv. Free Radical Chem.*, **5**, 318 (1975); G. L. Closs, R. J. Miller, and O. D. Redwine, *Acc. Chem. Res.*, **18**, 196 (1985).

One aspect of both EPR and CIDNP studies that should be kept in mind is that either is capable of detecting very small amounts of radical intermediates. Although this sensitivity makes both techniques very useful, it can also present a pitfall. The most prominent features of either ESR or CIDNP spectra may actually be due to radicals that account for only minor amounts of the total reaction process. An example of this was found in a study of the decomposition of trichloroacetyl peroxide in alkenes.

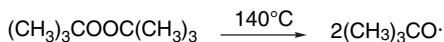


In addition to the emission signals of CHCl_3 and $\text{Cl}_3\text{CCH}_2\overset{\cdot}{\underset{\text{CH}_3}{\text{C}}}(\text{CH}_3)=\text{CH}_2$, which are the major products, a strong emission signal for $\text{Cl}_3\text{CCHCl}_2$ was identified. However, this compound is a very minor product of the reaction and when the signals have returned to their normal intensity, $\text{Cl}_3\text{CCHCl}_2$ is present in such a small amount that it cannot be detected.¹⁸

11.1.4. Generation of Free Radicals

There are several reactions that are used frequently to generate free radicals, both to study radical structure and reactivity and in synthetic processes. Some of the most general methods are outlined here. These methods will be encountered again when we discuss specific examples of free radical reactions. For the most part, we defer discussion of the reactions of the radicals until that point.

Peroxides are a common source of radical intermediates. Commonly used initiators include benzoyl peroxide, *t*-butyl peroxybenzoate, di-*t*-butyl peroxide, and *t*-butyl hydroperoxide. Reaction generally occurs at relatively low temperature ($80^\circ - 100^\circ\text{C}$). The oxygen-oxygen bond in peroxides is weak ($\sim 30\text{ kcal/mol}$) and activation energies for radical formation are low. Dialkyl peroxides decompose thermally to give two alkoxy radicals.¹⁹



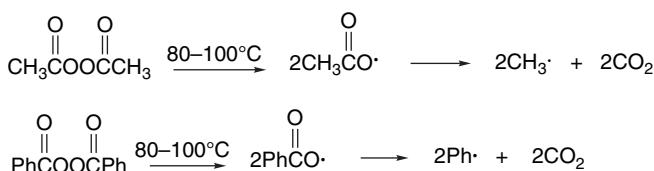
Diacyl peroxides are sources of alkyl radicals because the carboxyl radicals that are initially formed lose CO_2 very rapidly.²⁰ In the case of aryl peroxides, products can be derived from either the carboxyl radical or the radical formed by decarboxylation.²¹ The decomposition of peroxides can also be accomplished by photochemical excitation.

¹⁸. H. Y. Loken, R. G. Lawler, and H. R. Ward, *J. Org. Chem.*, **38**, 106 (1973).

¹⁹. W. A. Pryor, D. M. Huston, T. R. Fiske, T. L. Pickering, and E. Ciuffarin, *J. Am. Chem. Soc.*, **86**, 4237 (1964).

²⁰. J. C. Martin, J. W. Taylor, and E. H. Drew, *J. Am. Chem. Soc.*, **89**, 129 (1967); F. D. Greene, H. P. Stein, C.-C. Chu, and F. M. Vane, *J. Am. Chem. Soc.*, **86**, 2080 (1964).

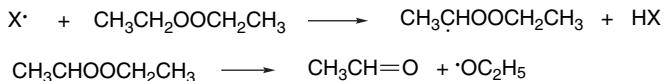
²¹. D. F. DeTar, R. A. J. Long, J. Rendleman, J. Bradley, and P. Duncan, *J. Am. Chem. Soc.*, **89**, 4051 (1967).



Peroxyesters are also sources of radicals. The acyloxy portion normally loses carbon dioxide, so peroxyesters yield an alkyl (or aryl) and alkoxy radical.²²



The thermal decompositions described above are unimolecular reactions that should exhibit first-order kinetics. Peroxides often decompose at rates faster than expected for unimolecular thermal decomposition and with more complicated kinetics. This behavior is known as *induced decomposition* and occurs when part of the peroxide decomposition is the result of bimolecular reactions with radicals present in solution, as illustrated specifically for diethyl peroxide.



The amount of induced decomposition that occurs depends on the concentration and reactivity of the radical intermediates and the susceptibility of the reactant to radical attack. The radical X· may be formed from the peroxide, but it can also be derived from subsequent reactions with the solvent. For this reason, both the structure of the peroxide and the nature of the reaction medium are important in determining the extent of induced decomposition relative to unimolecular homolysis. All of the peroxides are used in relatively dilute solution. Many peroxides are explosive, and due precautions must be taken.

Alkyl hydroperoxides give alkoxy radicals and the hydroxyl radical. *t*-Butyl hydroperoxide is often used as a radical source. Detailed studies on the mechanism of the decomposition indicate that it is a more complicated process than simple unimolecular decomposition.²³ The alkyl hydroperoxides are sometimes used in conjunction with a transition metal salt. Under these conditions, an alkoxy radical is produced, but the hydroxyl portion appears as hydroxide ion as the result of one-electron reduction by the metal ion.²⁴



A technique that provides a convenient source of radicals for study by ESR involves photolysis of a mixture of di-*t*-butyl peroxide, triethylsilane, and the alkyl bromide corresponding to the radical to be studied.²⁵ Photolysis of the peroxide gives

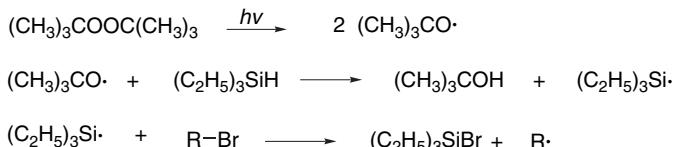
²². P. D. Bartlett and R. R. Hiatt, *J. Am. Chem. Soc.*, **80**, 1398 (1958).

²³. R. Hiatt, T. Mill, and F. R. Mayo, *J. Org. Chem.*, **33**, 1416 (1968), and accompanying papers.

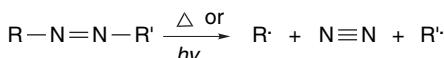
²⁴. W. H. Richardson, *J. Am. Chem. Soc.*, **87**, 247 (1965).

²⁵. A. Hudson and R. A. Jackson, *Chem. Commun.*, 1323 (1969); D. J. Edge and J. K. Kochi, *J. Am. Chem. Soc.*, **94**, 7695 (1972).

t-butoxy radicals, which selectively abstract hydrogen from the silane. This reactive silicon radical in turn abstracts bromine, generating the alkyl radical at a steady state concentration suitable for ESR study.



Another quite general source of free radicals is the decomposition of azo compounds. The products are molecular nitrogen and the radicals are derived from the substituent groups.



Both symmetrical and unsymmetrical azo compounds can be made, so a single radical or two different ones can be generated. The energy for the decomposition can be either thermal or photochemical.²⁶ The temperature at which decomposition occurs depends on the nature of the substituent groups. Azomethane does not decompose to methyl radicals and nitrogen until temperatures above 400°C are reached. Azo compounds that generate relatively stable radicals decompose at much lower temperatures. Azo compounds derived from allyl groups decompose somewhat above 100°C.



Ref. 27

Unsymmetrical azo compounds must be used to generate phenyl radicals because azobenzene is very stable thermally. Phenylazotriphenylmethane decomposes readily because of the stability of the triphenylmethyl radical.



Ref. 28

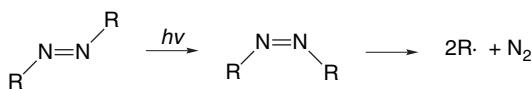
Azo compounds with functional groups that stabilize the radical are especially reactive. The stabilizing effect of the cyano substituent is responsible for the easy decomposition of azoisobutyronitrile (AIBN), which is frequently used as an initiator in radical reactions.



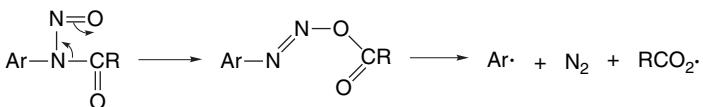
²⁶ P. S. Engel, *Chem. Rev.*, **80**, 99 (1980).

²⁷ K. Takagi and R. J. Crawford, *J. Am. Chem. Soc.*, **93**, 5910 (1971).

²⁸ R. F. Bridger and G. A. Russell, *J. Am. Chem. Soc.*, **85**, 3754 (1963).



N-Nitrosoanilides are a convenient source of aryl radicals. There is a close mechanistic relationship to the decomposition of azo compounds. The *N*-nitrosoanilides rearrange to intermediates having a nitrogen-nitrogen double bond. The intermediate then decomposes to generate aryl and acyloxy radicals.³⁰

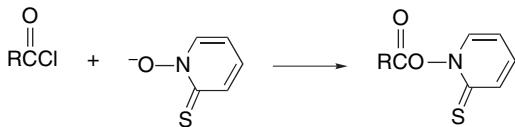


Triethylboron³¹ and 9-borabicyclo[3.3.1]nonane³² (9-BBN) are good radical sources for certain synthetic procedures. The reactions involve oxidation of the borane.



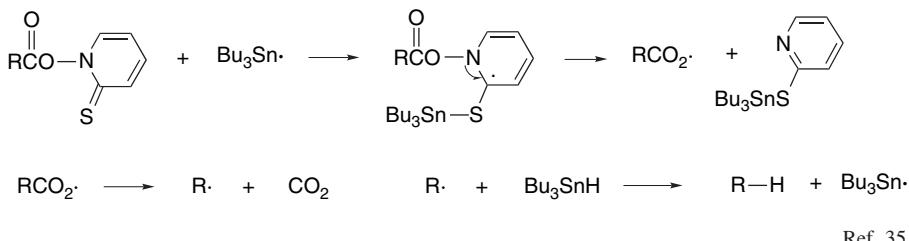
These initiators can be used in conjunction with stannanes and halides, as well as other reagents that undergo facile chain reactions. The reaction can be initiated at temperatures as low as -78°C .³³

The acyl derivatives of *N*-hydroxypyridine-2-thione are a versatile source of free radicals.³⁴ These compounds are readily prepared from reactive acylating agents, such as acyl chlorides, and a salt of the *N*-hydroxypyridine-2-thione.

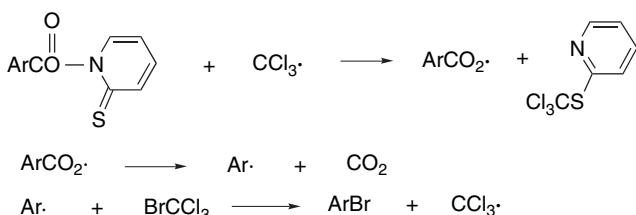


Radicals react at the sulfur and decomposition ensues, generating an acyloxy radical. The acyloxy radical undergoes decarboxylation. Usually the radical then gives product and another radical that can continue a chain reaction. The process can be illustrated by the reactions with tri-*n*-butylstannane and bromoform.

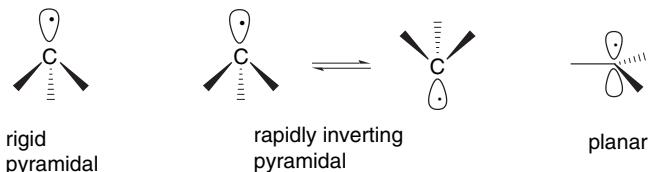
29. M. Schmittel and C. Rüchardt, *J. Am. Chem. Soc.*, **109**, 2750 (1987).
30. C. Rüchardt and B. Freudenberg, *Tetrahedron Lett.*, 3623 (1964); J. I. G. Cadogan, *Acc. Chem. Res.*, **4**, 186 (1971).
31. K. Nozaki, K. Oshima, and K. Utimoto, *J. Am. Chem. Soc.*, **109**, 2547 (1987).
32. V. T. Perchyonok and C. H. Schiesser, *Tetrahedron Lett.*, **39**, 5437 (1998).
33. K. Miura, Y. Ichinose, K. Nozaki, K. Fugami, K. Oshima, and K. Utimoto, *Bull. Chem. Soc. Jpn.*, **62**, 143 (1989).
34. D. H. R. Barton, D. Crich, and W. B. Motherwell, *Tetrahedron*, **41**, 3901 (1985).

a. Reductive decarboxylation by reaction with tri-*n*-butylstannane.

b. Conversion of arencarboxylic acid to aryl bromide by reaction with bromotrichloromethane.

**11.1.5. Structural and Stereochemical Properties of Free Radicals**

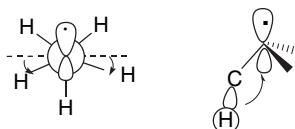
ESR studies and other physical methods have provided insight into the geometry of free radicals.³⁷ Deductions about structure can also be drawn from the study of the stereochemistry of reactions involving radical intermediates. Several structural possibilities can be considered. If discussion is limited to alkyl radicals, the possibilities include a rigid pyramidal structure, rapidly inverting pyramidal structures, or a planar structure.



Precise description of the pyramidal structures also requires that the bond angles be specified. The ESR spectrum of the methyl radical leads to the conclusion that its structure could be either planar or a shallow pyramid with a very low barrier to inversion.³⁸ The IR spectrum of methyl radical at very low temperature in frozen argon puts a maximum of about 5° on the deviation from planarity.³⁹ A microwave study has also indicated the methyl radical is planar.⁴⁰ Various MO calculations indicate a planar structure.⁴¹

- ^{35.} D. H. R. Barton, D. Crich, and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 939 (1983).
- ^{36.} D. H. R. Barton, B. Lacher, and S. Z. Zard, *Tetrahedron Lett.*, **26**, 5939 (1985).
- ^{37.} For a review, see J. K. Kochi, *Adv. Free Radicals*, **5**, 189 (1975).
- ^{38.} M. Karplus and G. K. Fraenkel, *J. Chem. Phys.*, **35**, 1312 (1961).
- ^{39.} L. Andrews and G. C. Pimentel, *J. Chem. Phys.*, **47**, 3637 (1967).
- ^{40.} E. Hirota, *J. Phys. Chem.*, **87**, 3375 (1983).
- ^{41.} F. M. Bickelhaupt, T. Ziegler, and P. v. R. Schleyer, *Organometallics*, **15**, 1477 (1996).

Simple alkyl radicals are generally pyramidal, although the barrier to inversion is very small. According to MP2/6-311G** and MM computations, substituted alkyl radicals become successively more pyramidal in the order ethyl < *i*-propyl < *t*-butyl.⁴² The *t*-butyl radical has been studied extensively, and both experimental and theoretical calculations indicate a pyramidal structure.⁴³ The pyramidal geometry results from interaction of the SOMO and alkyl group hydrogens. There is a hyperconjugative interaction between the half-filled orbital and the hydrogen that is aligned with it. The pyramidalization also leads to a staggered conformation. The hyperconjugation is stronger in the conformation in which the pyramidalization is in the same direction as to minimize eclipsing.^{42a,44} The C–H bonds *anti* to the unpaired electron are longer than those that are *gauche*. The *anti* hydrogens have maximum hyperconjugation with the orbital containing the unpaired electron and make a higher contribution to the SOMO orbital. There is also a shortening of the C–C bond, which is consistent with hyperconjugation.⁴⁵ Note that this hyperconjugative interaction accounts for the substantial hyperfine coupling with the β -H that was discussed in Section 11.1.3. The β -C–H bond is also greatly weakened by the hyperconjugation. MP4/6-311G(*d,p*) calculations assign a bond energy of only about 36 kcal/mol.⁴⁶

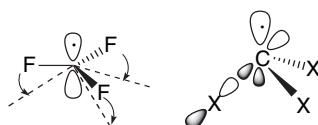


hyperconjugation in pyramidal radicals

Radical geometry is also significantly affected by substituent groups that can act as π donors. Addition of a fluorine or oxygen substituent favors a pyramidal structure. Analysis of the ESR spectra of the mono-, di-, and trifluoromethyl radicals indicate a progressive distortion from planarity.^{43d,47} Both ESR and IR studies of the trifluoromethyl radical show it to be pyramidal.⁴⁸ The basis of this structural effect has been probed by MO calculations and is considered to result from interactions of both the σ and π type. There is a repulsive interaction between the singly occupied *p* orbital and the filled orbitals occupied by unshared electrons on the fluorine or oxygen substituents. This repulsive interaction is reduced by adoption of a pyramidal geometry.

- ⁴² (a) J. Pacansky, W. Koch, and M. D. Miller, *J. Am. Chem. Soc.*, **113**, 317 (1991); (b) R. Liu and N. L. Allinger, *J. Comput. Chem.*, **15**, 283 (1994).
- ⁴³ (a) D. E. Wood, C. F. Williams, R. F. Sprecher, and W. A. Lathan, *J. Am. Chem. Soc.*, **94**, 6241 (1972); (b) T. Koenig, T. Balle, and W. Snell, *J. Am. Chem. Soc.*, **97**, 662 (1975); (c) P. J. Krusic and P. Meakin, *J. Am. Chem. Soc.*, **98**, 228 (1976); (d) P. J. Krusic and R. C. Bingham, *J. Am. Chem. Soc.*, **98**, 230 (1976); (e) L. Bonazzola, N. Leray, and J. Roncin, *J. Am. Chem. Soc.*, **99**, 8348 (1977); (f) D. Griller, K. U. Ingold, P. J. Krusic, and H. Fischer, *J. Am. Chem. Soc.*, **100**, 6750 (1978); (g) J. Pacansky and J. S. Chang, *J. Phys. Chem.*, **74**, 5539 (1978); (g) B. Schrader, J. Pacansky, and U. Pfeiffer, *J. Phys. Chem.*, **88**, 4069 (1984).
- ⁴⁴ M. N. Paddon-Row and K. N. Houk, *J. Am. Chem. Soc.*, **103**, 5046 (1981).
- ⁴⁵ M. N. Paddon-Row and K. N. Houk, *J. Phys. Chem.*, **89**, 3771 (1985).
- ⁴⁶ J. A. Seetula, *J. Chem. Soc., Faraday Trans.*, **94**, 1933 (1998).
- ⁴⁷ F. Bernardi, W. Cherry, S. Shaik, and N. D. Epotis, *J. Am. Chem. Soc.*, **100**, 1352 (1978).
- ⁴⁸ R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **43**, 2704 (1965); G. A. Carlson and G. C. Pimentel, *J. Chem. Phys.*, **44**, 4053 (1966).

The tendency for pyramidal geometry is reinforced by an interaction between the p orbital on carbon and the σ^* antibonding orbitals associated with the C–F or C–O bonds. The interaction increases electron density on the more electronegative fluorine or oxygen atom. This stabilizing p – σ^* interaction is increased by pyramidal geometry.



pyramidalization reduces electron-electron repulsion and enhances p – σ^* interaction

Computations on the FCH_2 , $\text{F}_2\text{CH}^\cdot$, and F_3C^\cdot radicals indicate successively greater pyramidalization.⁴⁹ Chlorinated methyl radicals and mixed chlorofluoro radicals show the same trend toward increasing pyramidalization,⁵⁰ as illustrated in Figure 11.5.

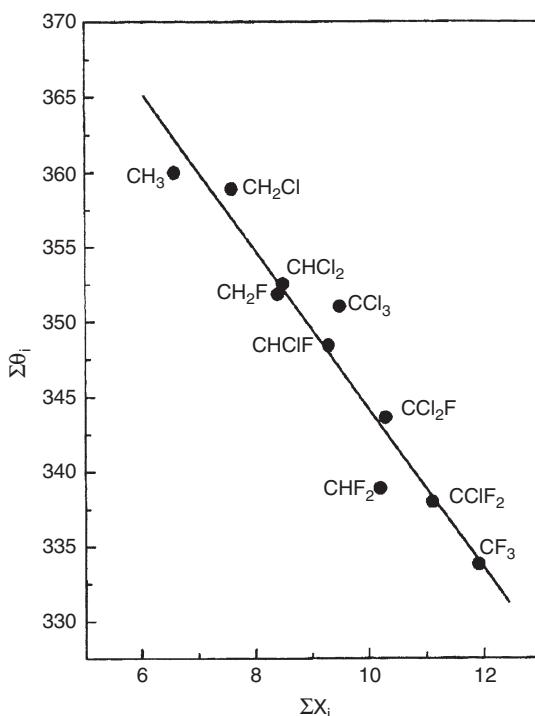


Fig. 11.5. Degree of pyramidalization of halogenated methyl radicals. The sum of the bond angles $\Sigma \theta$ is plotted against the sum of the electronegativity ($\Sigma \chi_i$) of the substituents. $\Sigma \theta = 360^\circ$ for planar and 323.7° for tetrahedral geometry. Reproduced from *J. Chem. Phys.*, **118**, 557 (2003), by permission of the American Institute of Physics.

⁴⁹ Q.-S. Li, J.-F. Zhao, Y. Xie, and H. F. Schaefer, III, *Mol. Phys.*, **100**, 3615 (2002).

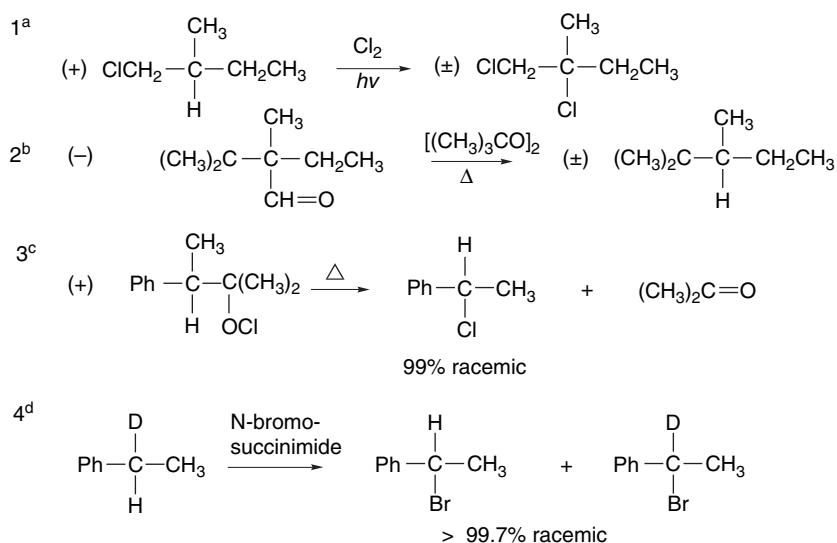
⁵⁰ M. Schwartz, L. R. Peebles, R. J. Berry, and P. Marshall, *J. Chem. Phys.*, **118**, 557 (2003).

There have been many studies aimed at deducing the geometry of radical sites by examining the stereochemistry of radical reactions. The most direct kind of study involves the generation of a radical at a carbon that is a stereogenic center. A planar or rapidly inverting radical leads to racemization, whereas a rigid pyramidal structure would lead to product of retained configuration. Some examples of reactions that have been subjected to this kind of study are shown in Scheme 11.2. In each case racemic product is formed, indicating that alkyl radicals do not retain the tetrahedral geometry of their precursors.

Entry 1 is a chlorination at a stereogenic tertiary center and proceeds with complete racemization. In Entry 2, a tertiary radical is generated by loss of C≡O, again with complete racemization. In Entry 3, an α -methylbenzyl radical is generated by a fragmentation and the product is again racemic. Entry 4 involves a benzylic bromination by NBS. The chirality of the reactant results from enantiospecific isotopic labeling of ethylbenzene. The product, which is formed via an α -methylbenzyl radical intermediate, is racemic.

Cyclic molecules permit deductions about stereochemistry without the necessity of using resolved chiral compounds. The stereochemistry of a number of reactions of 4-substituted cyclohexyl radicals has been investigated.⁵¹ In general, reactions starting from pure *cis* or *trans* stereoisomers give mixtures of *cis* and *trans* products. This result indicates that the radical intermediates do not retain the stereochemistry of the precursor. Radical reactions involving *t*-butylcyclohexyl radicals are usually not very stereoselective, but some show a preference for formation of the *cis* product. This has been explained in terms of a torsional effect. The pyramidalization of the radical is

Scheme 11.2. Stereochemistry of Radical Reactions at Stereogenic Carbon Centers



a. H. C. Brown, M. S. Kharasch, and T. H. Chao, *J. Am. Chem. Soc.*, **62**, 3435 (1940).

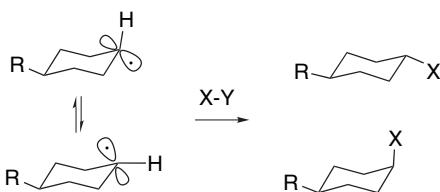
b. W. v. E. Doering, M. Farber, M. Sprecher, and K. B. Wiberg, *J. Am. Chem. Soc.*, **74**, 3000 (1952).

c. F. D. Greene, *J. Am. Chem. Soc.*, **81**, 2688 (1959); D. B. Denney and W. F. Beach, *J. Org. Chem.*, **24**, 108 (1959).

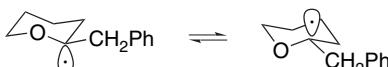
d. H. J. Dauben, Jr., and L. L. McCoy, *J. Am. Chem. Soc.*, **81**, 5404 (1959).

⁵¹. F. R. Jensen, L. H. Gale, and J. E. Rodgers, *J. Am. Chem. Soc.*, **90**, 5793 (1968).

expected to be in the direction favoring axial attack.⁵² Structural evidence suggests that the cyclohexyl radical is somewhat pyramidal with an equatorial hydrogen.⁵³ Equatorial attack leading to *trans* product causes the hydrogen at the radical site to become eclipsed with the two neighboring equatorial hydrogens. Axial attack does not suffer from this strain, since the hydrogen at the radical site moves away from the equatorial hydrogens toward the staggered conformation that is present in the chair conformation of the ring.

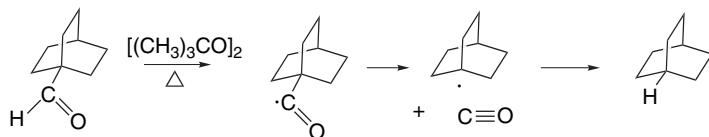


The inversion of the cyclohexyl radical can occur by a conformational process. This is expected to have a higher barrier than the radical inversion, since it involves bond rotations very similar to the ring inversion in cyclohexane. An E_a of 5.6 kcal/mol has been measured for the cyclohexyl radical.⁵⁴ A measurement of the rate of inversion of a tetrahydropyryanyl radical ($k = 5.7 \times 10^8 \text{ s}^{-1}$ at 22°C) has been reported.⁵⁵



It can be concluded from these data that radical inversion is also fast in cyclic systems.

Another approach to obtaining information about the geometric requirements of free radicals has been to examine bridgehead systems. Recall that small bicyclic rings strongly resist formation of carbocations at bridgehead centers because the skeletal rigidity prevents attainment of the preferred planar geometry. There is significant rate retardation for reactions in which the norbornyl radical is generated in a rate-determining step.⁵⁶ Typically, such reactions proceed 500 to 1000 times slower than the corresponding reaction generating the *t*-butyl radical. This is a much smaller rate retardation than the 10^{-14} found in S_N1 solvolysis (see p. 435). Rate retardation is still smaller for less strained bicyclic systems. The decarbonylation of less strained bridgehead aldehydes was found to proceed without special difficulty.⁵⁷



⁵² W. Damm, B. Giese, J. Hartung, T. Hasskerl, K. N. Houk, O. Huter, and H. Zipse, *J. Am. Chem. Soc.*, **114**, 4067 (1992).

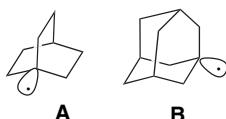
⁵³ J. E. Freitas, H. J. Wang, A. B. Ticknor, and M. A. El-Sayed, *Chem. Phys. Lett.*, **183**, 165 (1991); A. Hudson, H. A. Hussain, and J. N. Murrell, *J. Chem. Soc., A*, 2336 (1968).

⁵⁴ B. P. Roberts and A. J. Steel, *J. Chem. Soc., Perkin Trans. 2*, 2025 (1992).

⁵⁵ A. J. Buckmelter, A. I. Kim, and S. D. Rychnovsky, *J. Am. Chem. Soc.*, **122**, 9386 (2000).

⁵⁶ A. Oberlinner and C. Rüchardt, *Tetrahedron Lett.*, 4685 (1969); L. B. Humphrey, B. Hodgson, and R. E. Pincock, *Can. J. Chem.*, **46**, 3099 (1968); D. E. Applequist and L. Kaplan, *J. Am. Chem. Soc.*, **87**, 2194 (1965).

⁵⁷ W. v. E. Doering, M. Farber, M. Sprecher, and K. B. Wiberg, *J. Am. Chem. Soc.*, **74**, 3000 (1952).



Conclusions about radical structure can also be drawn from analysis of ESR spectra. The ESR spectra of the bridgehead radicals **A** and **B** are consistent with pyramidal geometry at the bridgehead carbon atoms.⁵⁸

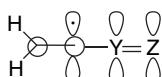
Radical	H_{α}	$^{13}\text{C}_{\beta}$	Φ^{a}
Adamantyl	6.58	132	113.6
Bicyclo[2.2.2]octyl	6.64	143	113.2
Bicyclo[2.2.1]heptyl	2.35	151	112.9
Bicyclo[2.1.1]hexyl	0	174	111.9
Bicyclo[1.1.1]pentyl	-1.2	223	110.3

a. Φ = the C–C–C bond angle at the bridgedhead radical.

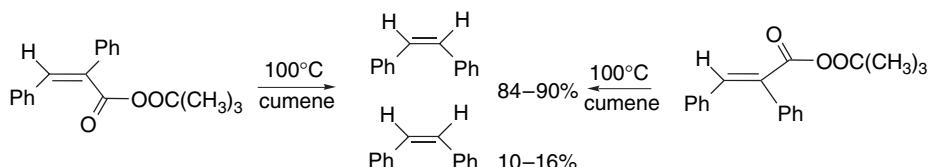
The broad conclusion of all these studies is that alkyl radicals except methyl are pyramidal, but the barrier to inversion is low. Radicals also are able to tolerate some geometric distortion associated with strained ring systems.

The allyl radical would be expected to be planar in order to maximize π delocalization. Structure parameters have been obtained from ESR, IR, and electron diffraction measurements and confirm that the radical is planar.⁶¹ The vinyl radical, $\text{CH}_2 = \text{CH}\cdot$, is found by both experiment and theory to be bent with a C–C–H bond angle of about 137°.⁶² Substituents affect the preferred geometry of vinyl radicals. Conjugation with π -acceptor substituents favors a linear geometry, whereas σ -donor substituents favor a bent geometry.⁶³ For σ -donors the barriers for isomerization are in the order $\text{CH}_3(3.1) < \text{OH}(13.3) < \text{F}(19.5)$ kcal/mol, according to BLYP/6-311G(2d,2p) calculations. Although these barriers have not been measured experimentally, reaction stereoselectivity is in agreement with the results. For the π -acceptor substituents, the preferred geometry is one in which the substituent is aligned with the singly occupied p orbital, not the π bond.

- ⁵⁸. P. J. Krusic, T. A. Rettig, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **94**, 995 (1972).
- ⁵⁹. C. J. Rhodes, J. C. Walton, and E. W. Della, *J. Chem. Soc., Perkin Trans. 2*, 2125 (1993); G. T. Binmore, J. C. Walton, W. Adcock, C. I. Clark, and A. R. Krstic, *Mag. Resonance Chem.*, **33**, Supplement S53 (1995).
- ⁶⁰. F. Recupero, A. Bravo, H. R. Bjorsvik, F. Fontana, F. Minisci, and M. Piredda, *J. Chem. Soc., Perkin Trans. 2*, 2399 (1997); K. P. Dockery and W. G. Bentruide, *J. Am. Chem. Soc.*, **119**, 1388 (1997).
- ⁶¹. R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963); A. K. Maltsev, V. A. Korolev, and O. M. Nefedov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 555 (1984); E. Vajda, J. Tremmel, B. Rozandai, I. Hargittai, A. K. Maltsev, N. D. Kagranov, and O. M. Nefedov, *J. Am. Chem. Soc.*, **108**, 4352 (1986).
- ⁶². J. H. Wang, H.-C. Chang, and Y.-T. Chen, *Chem. Phys.*, **206**, 43 (1996).
- ⁶³. C. Galli, A. Guarneri, H. Koch, P. Mencarelli, and Z. Rappoport, *J. Org. Chem.*, **62**, 4072 (1997).

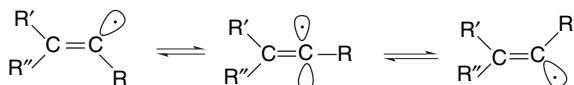


The stereochemistry of reactions involving substituted alkenyl free radicals indicates that radicals formed at trigonal centers rapidly undergo interconversion with the geometric isomer.⁶⁴ Reactions proceeding through alkenyl radical intermediates usually give rise to the same mixture from both the *E*- and *Z*-precursor. In the example given below, more *cis*- than *trans*-stilbene is formed, which is attributed to the steric effects of the β -phenyl group causing the H-abstraction to occur *anti* to the substituent.



Ref. 65

In this particular case, there is evidence from EPR spectra that the radical is not linear in its ground state, but is an easily inverted bent species.⁶⁶ The barrier to inversion is very low (0~2 kcal), so that the lifetime of the individual isomers is very short ($\sim 10^{-9}$ s). The TS for inversion approximates *sp* hybridization.⁶⁷



11.1.6. Substituent Effects on Radical Stability

The basic concepts of radical substituent effects were introduced in Section 3.4.1, where we noted that both donor and acceptor substituents can stabilize radicals. The extent of stabilization can be expressed in terms of the radical stabilization energy (RSE). The stabilization resulting from conjugation with unsaturated groups, such as in allyl and benzyl radicals, was also discussed. These substituent effects can sometimes cause synergistic stabilization. Allylic and benzylic radicals are also stabilized by both acceptor and donor substituents. Calculations at the AUMP2/6-31G* level indicate that substituents at the 2-position are only slightly less effective than 1-substituents in the stabilization of allylic radicals (Table 11.1). This is somewhat surprising in that the SOMO has a node at the 2-position. However, ψ_1 is also stabilized by interaction with the 2-substituent. Calculations have also been done on the stabilizing effect of *p*

⁶⁴. For reviews of the structure and reactivity of vinyl radicals, see W. G. Bentrude, *Annu. Rev. Phys. Chem.*, **18**, 283 (1967); L. A. Singer, in *Selective Organic Transformations*, Vol. II, B. S. Thyagarajan, ed., John Wiley, New York, 1972, p. 239; O. Simamura, *Top. Stereochem.*, **4**, 1 (1969).

⁶⁵. L. A. Singer and N. P. Kong, *J. Am. Chem. Soc.*, **88**, 5213 (1966); J. A. Kampmeier and R. M. Fantazier, *J. Am. Chem. Soc.*, **88**, 1959 (1966).

⁶⁶. R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).

⁶⁷. P. R. Jenkins, M. C. R. Symons, S. E. Booth, and C. J. Swain, *Tetrahedron Lett.*, **33**, 3543 (1992).

Table 11.1. Substituent Effects on the Stability of Allylic and Benzylic Radical from Calculation of Radical Stabilization Energy

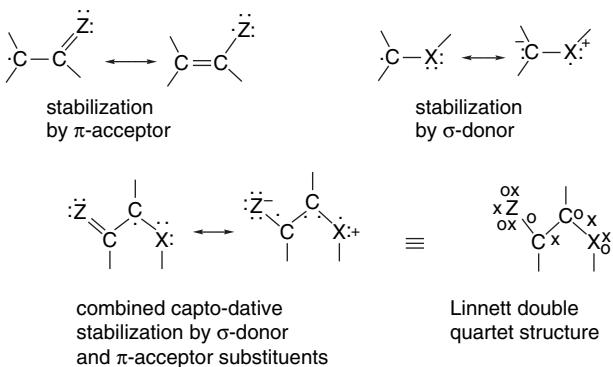
Substituent	Relative Stabilization in kcal/mol		
	Allylic ^a	Benzyllic ^b	
	1-position	2-position	<i>p</i> -position
H	0	0	0
CH ₃	5.6	4.3	0.3
CN	9.9	3.0	1.4
CH=O	11.7	11.6	
F	8.3	11.0	-0.1
HO	12.8	12.6	
CH ₃ O			0.7
H ₂ N	13.7	9.4	
(CH ₃) ₂ N			1.8

a. AUMP2/6-31G* calculation from M. Lehd and F. Jensen, *J. Org. Chem.*, **56**, 884 (1991).

b. BLYP/6-31G* calculations from Y.-D. Wu, C.-L. Wong, K. W. K. Chan, G.-Z. Ji, and X.-K. Jang, *J. Org. Chem.*, **61**, 746 (1996).

substituents on benzylic radicals, and the results indicate that both donor and acceptor substituents are stabilizing. The effects are greatly attenuated in the case of the benzyl substituents, owing to the leveling effect of the delocalization in the ring.

Radicals are particularly strongly stabilized when both an electron-attracting and an electron-donating substituent are present at the radical site. This has been called “*mero-stabilization*”⁶⁸ or “*capto-dative stabilization*,”⁶⁹ and results from mutual reinforcement of the two substituent effects.⁷⁰ The bonding in capto-dative radicals can be represented by resonance or Linnett-type structures (see p. 8).

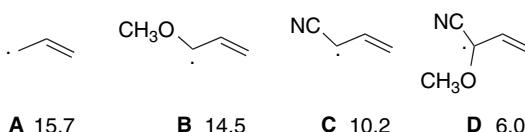


A comparison of the rotational barriers in allylic radicals **A** to **D** provides evidence for the stabilizing effect of the capto-dative combination.

⁶⁸. R. W. Baldock, P. Hudson, A. R. Katritzky, and F. Soti, *J. Chem. Soc., Perkin Trans. 1*, 1422 (1974).

⁶⁹. H. G. Viehe, R. Merenyi, L. Stella, and Z. Janousek, *Angew. Chem. Int. Ed. Engl.*, **18**, 917 (1979).

⁷⁰. R. Sustmann and H.-G. Korth, *Adv. Phys. Org. Chem.*, **26**, 131 (1990).



The decreasing barrier at the formal single bond along the series **A** to **D** implies decreasing π -allyl character in this bond. The decrease in the importance of the π bonding in turn reflects a diminished degree of interaction of the radical center with the adjacent double bond. The fact that the decrease from **C** \rightarrow **D** is greater than for **A** \rightarrow **B** indicates a synergistic effect, as implied by the capto-dative formulation. The methoxy group is more stabilizing when it can interact with the cyano group than as an isolated substituent.⁷¹

The capto-dative effect has also been demonstrated by studying the bond dissociation process in a series of 1,5-dienes substituted at C(3) and C(4).

	2			
<hr/>				
X	Y	X'	Y'	ΔH
CO_2R	CO_2R	CO_2R	CO_2R	38.1
CO_2R	CO_2R	CO_2R	OR'	28.2
CN	OR'	CN	OR'	24.5
CN	NR_2	CN	NR_2	8.1

When the combinations X,Y and X',Y' are of the capto-dative type, as is the case for an alkoxy and ester group, the enthalpy of bond dissociation is 10–15 kcal lower than when all four groups are electron attracting. When the capto-dative combination CN/NR₂ occupies both X,Y and X',Y' positions, the enthalpy for dissociation of the C(3)–C(4) bond is less than 10 kcal/mol.⁷² Scheme 11.3 gives some information on the stability of other examples of this type of radical.

11.1.7. Charged Radicals

Unpaired electrons can be present in ions as well as in the neutral systems that have been considered up to this point. There are many such *radical cations* and *radical anions*, and we consider some representative examples in this section. Various aromatic and conjugated polyunsaturated hydrocarbons undergo one-electron reduction by alkali metals.⁷³ Benzene and naphthalene are examples. The ESR spectrum of the benzene radical anion was shown earlier in Figure 11.2a. These reductions must be carried out in aprotic solvents, and ethers are usually used for that purpose. The ease of formation of the radical anion increases as the number of fused rings increases. The electrochemical reduction potentials of some representative compounds are given in

⁷¹. H.-G. Korth, P. Lommes, and R. Sustmann, *J. Am. Chem. Soc.*, **106**, 663 (1984).

⁷². M. Van Hoecke, A. Borghese, J. Penelle, R. Merenyi, and H. G. Viehe, *Tetrahedron Lett.*, **27**, 4569 (1986).

⁷³. D. E. Paul, D. Lipkin, and S. I. Weissman, *J. Am. Chem. Soc.*, **78**, 116 (1956); T. R. Tuttle, Jr., and S. I. Weissman, *J. Am. Chem. Soc.*, **80**, 5342 (1958).

Scheme 11.3. Radicals with Capto-Dative Stabilization

SECTION 11.1

Generation and Characterization of Free Radicals

^{1^a}		Wurster's salts. Generated by one-electron oxidation of the corresponding diamine. Indefinitely stable to normal conditions.
^{2^b}		Generated by one-electron reduction of the corresponding pyridinium salt. Thermally stable to distillation and only moderately reactive toward oxygen.
^{3^c}		Stable to distillation. A small amount of the dimer is present in equilibrium with the radical.
^{4^d}		In equilibrium with the dimer Sensitive to oxygen.
^{5^e}		Generated by spontaneous dissociation of the dimer. Stable for several days at room temperature, but sensitive to oxygen.
^{6^f}		Generated spontaneously from dimethylamino-malonitrile at room temperature. Observed to be persistent over many hours by ESR.
^{7^g}		Radical stabilization energy of 19.6 kcal/mol implies about 10 kcal/mol of excess stabilization relative to the combined substituents. The CH-N(CH ₃) ₂ rotational barrier is >17 kcal/mol, indicating a strong resonance interaction.
^{8^h}		Synergistic stabilization of about 6.3 kcal/mol, based on thermodynamics of dimerization.

- a. A. R. Forrester, J. M. Hay, and R. H. Thompson, *Organic Chemistry of Stable Free Radicals*, Academic Press, New York, 1968, pp. 254–261.
 b. J. Hermolin, M. Levin, and E. M. Kosower, *J. Am. Chem. Soc.*, **103**, 4808 (1981).
 c. J. Hermolin, M. Levin, Y. Ikegami, M. Sawayangai, and E. M. Kosower, *J. Am. Chem. Soc.*, **103**, 4795 (1981).
 d. T. H. Koch, J. A. Oleson, and J. DeNiro, *J. Am. Chem. Soc.*, **97**, 7285 (1975).
 e. J. M. Burns, D. L. Wharry, and T. H. Koch, *J. Am. Chem. Soc.*, **103**, 849 (1981).
 f. L. de Vries, *J. Am. Chem. Soc.*, **100**, 926 (1978).
 g. F. M. Welle, H.-D. Beckhaus, and C. Rüchardt, *J. Org. Chem.*, **62**, 552 (1997).
 h. F. M. Welle, S. P. Verevkin, H.-D. Beckhaus and C. Rüchardt, *Liebigs Ann. Chem.*, 115 (1997).

Table 11.2. The potentials correlate with the energy of the LUMO as calculated by simple Hückel MO theory.⁷⁴ Note that polycyclic aromatics are easier both to reduce and to oxidize than benzene. This is because the HOMO-LUMO gap decreases with

⁷⁴. E. S. Pysh and N. C. Yang, *J. Am. Chem. Soc.*, **85**, 2124 (1963); D. Bauer and J. P. Beck, *Bull. Soc. Chim. Fr.*, 1252 (1973); C. Madec and J. Courtot-Coupez, *J. Electroanal. Chem. Interfacial Electrochem.*, **84**, 177 (1977).

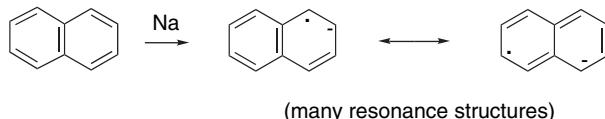
Table 11.2. Oxidation and Reduction Potentials for Some Aromatic Hydrocarbons^a

Hydrocarbon	$\text{Ar}-\text{H} \rightarrow [\text{Ar}-\text{H}]^-$	$\text{Ar}-\text{H} \rightarrow [\text{Ar}-\text{H}]^+$
Benzene	-3.42 ^b	+2.06
Naphthalene	-2.95	+1.33
Phenanthrene	-2.87	+1.34
Anthracene	-2.36	+0.89
Tetracene	-1.92	+0.57

a. Except where noted otherwise, the data are from C. Madec and J. Courtot-Coupez, *J. Electroanal. Chem., Interfacial Electrochem.*, **84**, 177 (1977).

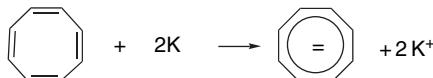
b. J. Mortensen and J. Heinze, *Angew. Chem. Int. Ed. Engl.* **13**, 84 (1984).

the size of the molecule, with the HOMO being higher in energy and the LUMO lower than in benzene. A correlation that includes a more extensive series of compounds can be observed using somewhat more sophisticated MO methods.⁷⁵



In the presence of a proton source, the radical anion is protonated and further reduction occurs (Birch reduction; Part B, Section 5.6.2). In general, when no proton source is present, it is relatively difficult to add a second electron. Solutions of the radical anions of aromatic hydrocarbons can be maintained for relatively long periods in the absence of oxygen or protons.

Cyclooctatetraene provides a significant contrast to the preference of aromatic hydrocarbons for one-electron reduction. It is converted to a diamagnetic dianion by addition of two electrons.⁷⁶ It is easy to understand the ease with which the cyclooctatetraene radical accepts a second electron because of the aromaticity of the ten π -electron aromatic system that results (see Section 8.3).



Radical cations can be derived from aromatic hydrocarbons or alkenes by one-electron oxidation. Antimony trichloride and pentachloride are among the chemical oxidants that have been used.⁷⁷ Photodissociation or γ -radiation can generate radical cations from aromatic hydrocarbons.⁷⁸ Most radical cations derived from hydrocarbons

⁷⁵. C. F. Wilcox, Jr., K. A. Weber, H. D. Abruna, and C. R. Cabrera, *J. Electroanal. Chem. Interfacial Electrochem.*, **198**, 99 (1986).

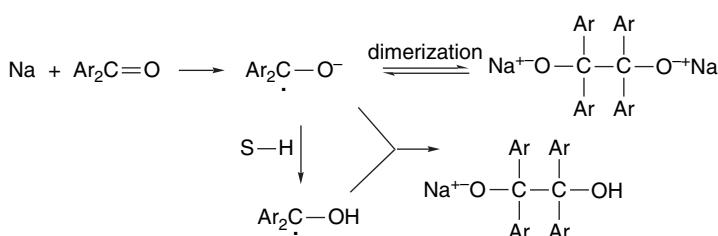
⁷⁶. T. J. Katz, *J. Am. Chem. Soc.*, **82**, 3784 (1960).

⁷⁷. I. C. Lewis and L. S. Singer, *J. Chem. Phys.*, **43**, 2712 (1965); R. M. Dessau, *J. Am. Chem. Soc.*, **92**, 6356 (1970).

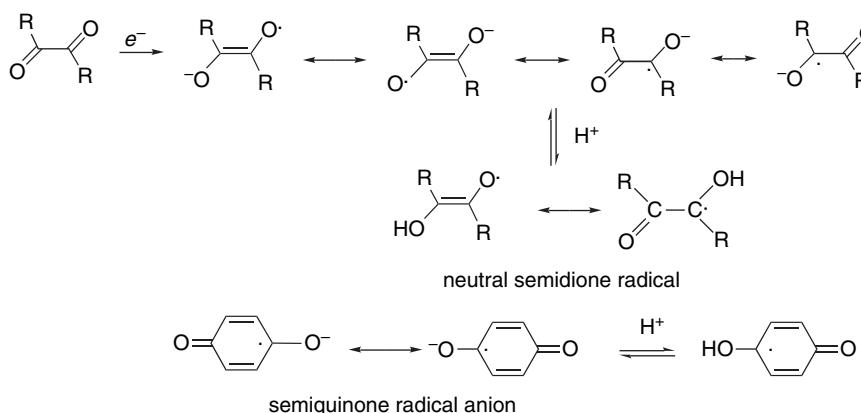
⁷⁸. R. Gschwind and E. Haselbach, *Helv. Chim. Acta*, **62**, 941 (1979); T. Shida, E. Haselbach, and T. Bally, *Acc. Chem. Res.*, **17**, 180 (1984); M. C. R. Symons, *Chem. Soc. Rev.*, **13**, 393 (1984).

have limited stability, but ESR spectral parameters have permitted structural characterization.⁷⁹ The radical cations can be generated electrochemically and the oxidation potentials are included in Table 11.2. The potentials correlate with the HOMO levels of the hydrocarbons. The higher the HOMO, the more easily the hydrocarbon is oxidized.

Two classes of charged radicals derived from ketones have been well studied. *Ketyl*s are radical anions formed by one-electron reduction of carbonyl compounds. The formation of the benzophenone radical anion by reduction with sodium metal is an example. This radical anion is deep blue in color and is very reactive toward both oxygen and protons. There have been many detailed studies on the structure and spectral properties of this and related radical anions.⁸⁰ A common chemical reaction of the ketyl radicals is coupling to form a diamagnetic dianion, which occurs reversibly for simple aromatic ketyl s. The dimerization is promoted by protonation of one or both of the ketyl s because the electrostatic repulsion is then removed. The coupling process leads to reductive dimerization of carbonyl compounds, a reaction that is discussed in detail in Section 5.6.3 of Part B.



One-electron reduction of α -dicarbonyl compounds gives radical anions known as *semidiones*.⁸¹ Closely related are the one-electron reduction products of aromatic quinones, the *semiquinones*. Both the semidiones and semiquinones can be protonated to give neutral radicals that are relatively stable. The semidiones and semiquinones belong to the *capto-dative* class of radicals, having both donor and acceptor substituents.

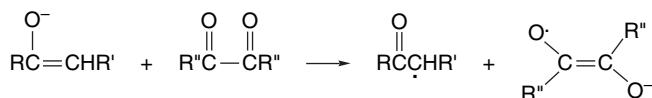


⁷⁹ J. L. Courneidge and A. G. Davies, *Acc. Chem. Res.*, **20**, 90 (1987).

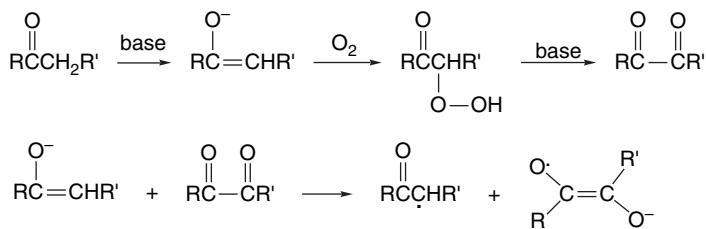
⁸⁰ For a summary, see N. Hirota, in *Radical Ions*, E. T. Kaiser and L. Kevan, eds., Interscience, New York, 1968, pp. 35–85.

⁸¹ G. A. Russell, in *Radical Ions*, E. T. Kaiser and L. Kevan, eds., Interscience, New York, 1968, pp. 87–150.

Reductants such as zinc or sodium dithionite generate the semidiones from diketones. Electrolytic reduction can also be used. Enolates can reduce diones to semidiones by electron transfer.



The radicals that are formed from the enolate are rapidly destroyed so only the stable semidione radical remains detectable for ESR study. Semidiones can also be generated oxidatively from ketones by reaction with oxygen in the presence of base.⁸²



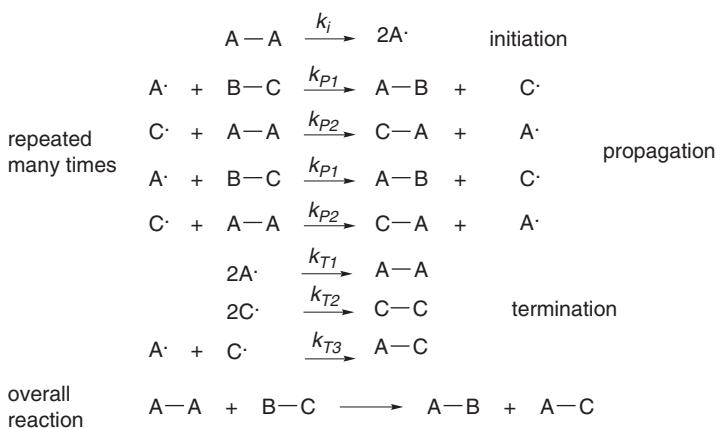
The diketone is presumably generated oxidatively and then reduced to the semidione via reduction by the enolate derived from the original ketone. The ESR spectra of semidione radical anions can provide information on the spin density at the individual atoms. The semidione derived from butane-2,3-dione, for example, has a spin density of 0.22 at each oxygen and 0.23 at each carbonyl carbon. The small amount of remaining spin density is associated with the methyl groups. This extensive delocalization is consistent with the resonance picture of the semidione radical anion.

11.2. Characteristics of Reactions Involving Radical Intermediates

11.2.1. Kinetic Characteristics of Chain Reactions

Certain kinetic aspects of free radical reactions are unique in comparison with other reaction types that have been considered to this point. The underlying difference is that many free radical reactions are chain reactions. The reaction mechanism consists of a cycle of repetitive steps that form many product molecules for each initiation event. The hypothetical mechanism below illustrates a chain reaction.

⁸². G. A. Russell and E. T. Strom, *J. Am. Chem. Soc.*, **86**, 744 (1964).



The step in which the radical intermediate, in this case $\text{A}\cdot$, is generated is called the *initiation step*. In the next four equations of the example, a sequence of two reactions is repeated; this is the *propagation phase*. Chain reactions are characterized by a *chain length*, which is the number of propagation steps that take place per initiation step. Finally, there are *termination steps*, which include all reactions that destroy one of the reactive intermediates necessary for the propagation of the chain. Clearly, the greater the frequency of termination steps, the smaller the chain length will be. The stoichiometry of a free radical chain reaction is independent of the initiating and termination steps because the reactants are consumed and products are formed almost entirely in the propagation steps.



The rate of a chain process is determined by the rates of initiation, propagation, and termination reactions. Analysis of the kinetics of chain reactions normally depends on application of the steady state approximation (see Section 3.2.3) to the radical intermediates. Such intermediates are highly reactive, and their concentrations are low and nearly constant through the course of the reaction. A result of the steady state condition is that the overall rate of initiation must equal the total rate of termination. The application of the steady state approximation and the resulting equality of the initiation and termination rates permits formulation of a rate law for the reaction mechanism above.

The overall reaction rate is given by

$$\text{Rate} = \frac{d[\text{A—B}]}{dt} = \frac{d[\text{A—C}]}{dt} = \frac{-d[\text{A}_2]}{dt} = \frac{-d[\text{B—C}]}{dt}$$

Setting the rate of initiation equal to the rate of termination and assuming that k_{t2} is the dominant termination process gives

$$\begin{aligned}
 k_i[\text{A}_2] &= 2k_{t2}[\text{C}\cdot]^2 \\
 [\text{C}\cdot] &= \left(\frac{k_i}{2k_{t2}}\right)^{1/2} [\text{A}_2]
 \end{aligned}$$

Termination reactions involving coupling or disproportionation of two radicals ordinarily occurs at diffusion-controlled rates. Since the concentration of the reactive

intermediates is very low and these steps involve the reactants, which are present at much higher concentrations, the overall rate of termination is low enough that the propagation steps can compete. The rate of the overall reaction is that of either propagation step:

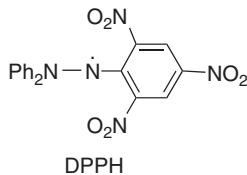
$$\text{Rate} = k_{p2}[\text{C}\cdot][\text{A}_2] = k_{p1}[\text{A}\cdot][\text{B} - \text{C}]$$

After the steady state approximation, both propagation steps must proceed at the same rate or the concentration of $\text{A}\cdot$ or $\text{C}\cdot$ would build up. By substituting for the concentration of the intermediate $\text{C}\cdot$, we obtain

$$\text{Rate} = k_{p2} \left(\frac{k_i}{2k_{t2}} \right)^{1/2} [\text{A}_2]^{3/2} = k_{\text{obs}}[\text{A}_2]^{3/2}$$

The observed rate law is then three-halves order in the reagent A_2 . In most real systems, the situation is somewhat more complicated because more than one termination reaction makes a contribution to the total termination rate. A more complete discussion of the effect of termination steps on the form of the rate law is given by Huyser.⁸³

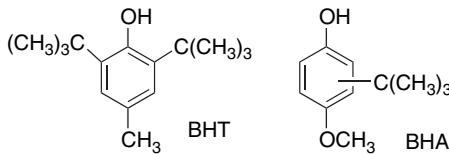
The overall rates of chain reactions can be greatly modified by changing the rate at which initiation or termination steps occur. The idea of initiation was touched on in Section 11.1.4, where sources of free radicals were discussed. Many radical reactions of interest in organic chemistry depend on the presence of an *initiator*, which serves as a source of free radicals to start chain sequences. Peroxides are frequently used as initiators, since they give radicals by thermal decomposition at relatively low temperatures. Azo compounds are another very useful class of initiators, with azoisobutyronitrile, AIBN, being the most commonly used compound. Initiation by irradiation of a photosensitive compound that generates radical products is also a common procedure. Conversely, chain reactions can be retarded by *inhibitors*. A compound can act as an inhibitor if it is sufficiently reactive toward a radical involved in the chain process that it effectively traps the radical, thus terminating the chain. Certain stable free radicals, for example, galvinoxyl (Scheme 11.1, Entry 6) and the hydrazinyl radical diphenylipicrylhydrazyl (DPPH) are used in this way. As they contain an unpaired electron, they are usually very reactive toward radical intermediates. The sensitivity of the rates of free radical chain reactions to both initiators and inhibitors can be used in mechanistic studies to distinguish radical chain reactions from polar or concerted processes.



Free radical chain inhibitors are of considerable economic importance. The term *antioxidant* is commonly applied to inhibitors that retard the free radical chain oxidations that can cause deterioration of many commercial materials derived from organic molecules, including foodstuffs, petroleum products, and plastics. The substituted

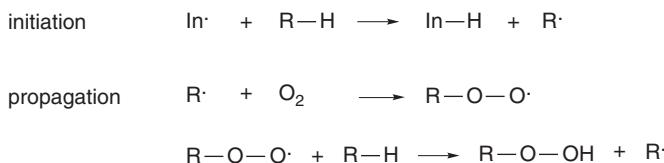
⁸³ E. S. Huyser, *Free Radical Chain Reactions*, Wiley-Interscience, New York, 1970, pp. 39–54.

phenols BHT, “butylated hydroxytoluene,” and BHA, “butylated hydroxyanisole,” are used in many commercial foodstuffs.



mixture of 2-
and 3-isomers

The chain mechanism for autoxidation of hydrocarbons is:



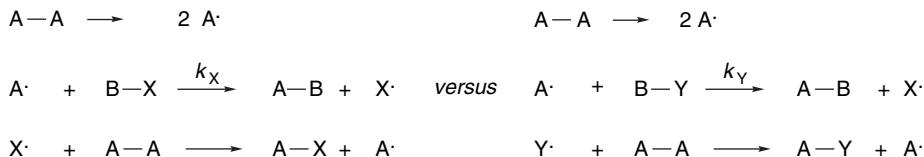
The function of an antioxidant is to divert the peroxy radicals and thus prevent a chain process. The hydroperoxides generated by autoxidation are themselves potential chain initiators, so autoxidations have the potential of being autocatalytic. Some antioxidants function by reducing hydroperoxides and thereby preventing their accumulation. Other antioxidants function by reacting with potential initiators, and retard oxidative degradation by preventing the initiation of autoxidation chains.

The presence of oxygen can modify the course of a free radical chain reaction if a radical intermediate is diverted by reaction with molecular oxygen. The oxygen molecule, with its two unpaired electrons, is extremely reactive to most free radical intermediates. The product that is formed is a reactive peroxy radical that can propagate a chain reaction leading to oxygen-containing products:



11.2.2. Determination of Reaction Rates

Structure-reactivity relationships can be probed by measurements of rates and equilibria, as was discussed in Chapter 3. Direct comparison of reaction rates is used relatively less often in the study of radical reactions than for heterolytic reactions. Instead, *competition methods* have frequently been used. The basis of a competition method lies in the rate expression for a reaction, and the results can be just as valid a comparison of relative reactivity as directly measured rates, *provided the two competing processes are of the same kinetic order*. Suppose we want to compare the reactivity of two related compounds, B–X and B–Y, in a hypothetical sequence:



The data required are the relative magnitudes of k_X and k_Y . When both B–X and B–Y are present in the reaction system, they will be consumed at rates that are a function of their reactivity and concentration.

$$\frac{-d[B-X]}{dt} = k_x[A\cdot][B-X]$$

$$\frac{-d[B-Y]}{dt} = k_y[A\cdot][B-Y]$$

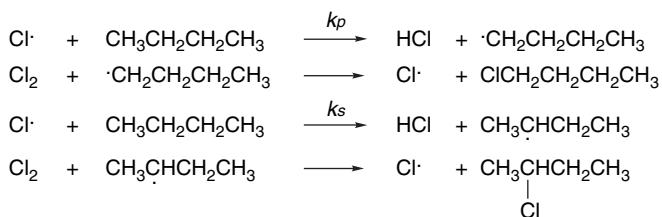
$$\frac{k_x}{k_y} = \frac{d[B-X]/[B-X]}{d[B-Y]/[B-Y]}$$

Integration of this expression with the limits $[B-X]=[B-X]_{in}$ to $[B-X]_t$, where t is a point in time during the course of the reaction gives

$$\frac{k_x}{k_y} = \frac{\ln([B-X]_{in}/[B-X]_t)}{\ln([B-Y]_{in}/[B-Y]_t)}$$

This relationship permits the measurement of the ratio k_X/k_Y . The initial concentrations $[B-X]_{in}$ and $[B-Y]_{in}$ are known from the conditions of the experiment. The reaction can be stopped at some point when some of both B–X and B–Y remain unreacted, or an excess of B–X and B–Y can be used so that neither is completely consumed when A–A has reacted completely. Determination of $[B-X]_t$ and $[B-Y]_t$ then provides the information needed to calculate k_X/k_Y . It is clear that the reactions being compared must be of the same kinetic order. If they are not, division of the two rate expressions would leave uncanceled concentration terms.

Another experiment of the competition type involves the comparison of the reactivity of different atoms in the same molecule. For example, gas phase chlorination of butane can lead to 1- or 2-chlorobutane. The relative reactivity (k_p/k_s) of the primary and secondary hydrogens is the sort of information that helps to characterize the details of the reaction process.



The value of k_p/k_s can be determined by measuring the ratio of the products 1-chlorobutane:2-chlorobutane during the course of the reaction. A statistical correction must be made to take account of the fact that the primary hydrogens outnumber the secondary ones by 3:2. This calculation provides the relative reactivity of chlorine atoms toward the primary and secondary hydrogens in butane:

$$\frac{k_p}{k_s} = \frac{2[1\text{-chlorobutane}]}{3[2\text{-chlorobutane}]}$$

Techniques for measuring the rates of very fast reactions have permitted absolute rates to be measured for fundamental types of free radical reactions.⁸⁴ Some examples

⁸⁴ M. Newcomb, *Tetrahedron*, **49**, 1151 (1993).

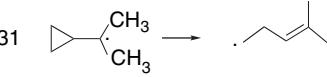
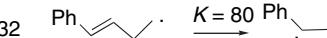
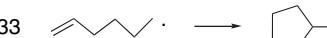
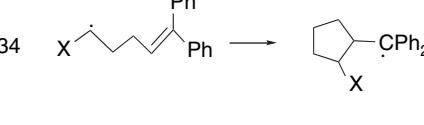
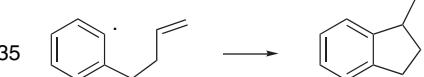
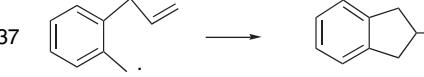
of absolute rates and E_a are given in Table 11.3. The examples include hydrogen abstraction (Section A), addition (Section B), ring closure and opening (Section C), and other types of reactions such as fragmentation and halogen atom abstraction (Section D). In the sections that follow, we discuss some of the reactivity relationships revealed by these data.

Table 11.3. Absolute Rates for Some Free Radical Reactions^a

	Reaction	Rate/ E_a	Reference
A. Hydrogen abstraction reactions			
1	$\text{Ph}\cdot + \text{C}_4\text{H}_7\text{O} \longrightarrow \text{Ph}-\text{H} + \cdot\text{C}_4\text{H}_7\text{O}$	$4.8 \times 10^6 M^{-1}\text{s}^{-1}$	b
2	$(\text{CH}_3)_3\text{CO}\cdot + (\text{CH}_3)_2\overset{\underset{\text{H}}{ }}{\text{CPh}} \longrightarrow (\text{CH}_3)_3\text{COH} + (\text{CH}_3)_2\overset{\cdot}{\text{CPh}}$	$8.7 \times 10^5 M^{-1}\text{s}^{-1}$	c
3	$(\text{CH}_3)_3\text{CO}\cdot + \text{C}_4\text{H}_7\text{O} \longrightarrow (\text{CH}_3)_3\text{COH} + \cdot\text{C}_4\text{H}_7\text{O}$	$8.3 \times 10^6 M^{-1}\text{s}^{-1}$	c
4	$\text{Cl}\cdot + (\text{free}) \text{C}_5\text{H}_10 \longrightarrow \text{H-Cl} + \cdot\text{C}_5\text{H}_10$	$4.7 \times 10^9 M^{-1}\text{s}^{-1}$	d
5	$\text{Cl}\cdot + (\text{benzene complex}) \text{C}_5\text{H}_10 \longrightarrow \text{H-Cl} + \cdot\text{C}_5\text{H}_10$	$4.3 \times 10^7 M^{-1}\text{s}^{-1}$	d
6	$\text{CH}_3\cdot + \text{Bu}_3\text{SnH} \longrightarrow \text{CH}_4 + \text{Bu}_3\text{Sn}\cdot$	$1.0 \times 10^7 M^{-1}\text{s}^{-1}$ $E_a = 3.2 \text{ kcal/mol}$	e
7	$(\text{CH}_3)_3\text{C}\cdot + \text{Bu}_3\text{SnH} \longrightarrow (\text{CH}_3)_3\text{CH} + \text{Bu}_3\text{Sn}\cdot$	$1.8 \times 10^7 M^{-1}\text{s}^{-1}$ $E_a = 2.95 \text{ kcal/mol}$	e
8	$\text{Ph}\cdot + \text{Bu}_3\text{SnH} \longrightarrow \text{C}_6\text{H}_6 + \text{Bu}_3\text{Sn}\cdot$	$7.8 \times 10^8 M^{-1}\text{s}^{-1}$	f
9	$\text{CF}_3\text{CF}_2\text{CF}_2\cdot + \text{Bu}_3\text{SnH} \longrightarrow \text{CF}_3\text{CF}_2\text{CF}_2\text{H} + \text{Bu}_3\text{Sn}\cdot$	$2.0 \times 10^9 M^{-1}\text{s}^{-1}$	g
10	$\text{PhCH}_2\cdot + \text{PhSH} \longrightarrow \text{PhCH}_3 + \text{PhS}\cdot$	$3.1 \times 10^5 M^{-1}\text{s}^{-1}$	h
11	$\text{RCH}_2\cdot + (\text{CH}_3)_3\text{CSH} \longrightarrow \text{RCH}_3 + (\text{CH}_3)_3\text{CS}\cdot$	$8 \times 10^6 M^{-1}\text{s}^{-1}$	i
12	$\text{C}_5\text{H}_10\cdot + \text{PhSeH} \longrightarrow \text{C}_5\text{H}_10 + \text{PhSe}\cdot$	$2.1 \times 10^9 M^{-1}\text{s}^{-1}$	j
13	$(\text{CH}_3)_3\text{CC=O} + \text{Bu}_3\text{SnH} \longrightarrow (\text{CH}_3)_3\text{CCH=O} + \text{Bu}_3\text{Sn}\cdot$	$3.0 \times 10^5 M^{-1}\text{s}^{-1}$	k
14	$\text{RC=O} + \text{Bu}_3\text{SnH} \longrightarrow \text{RCH=O} + \text{Bu}_3\text{Sn}\cdot$	$1.3 \times 10^6 M^{-1}\text{s}^{-1}$	l
15	$\text{Ph}_2\text{C=CPh} + \text{Bu}_3\text{SnH} \longrightarrow \text{Ph}_2\text{C=CHPh} + \text{Bu}_3\text{Sn}\cdot$	$7.5 \times 10^8 M^{-1}\text{s}^{-1}$	m
16	$\text{RCH}_2\cdot + [(\text{CH}_3)_3\text{Si}]_3\text{SiH} \longrightarrow \text{RCH}_3 + [(\text{CH}_3)_3\text{Si}]_3\text{Si}\cdot$	$1.0 \times 10^5 M^{-1}\text{s}^{-1}$	n
17	$\text{Ph}_2\text{C=CPh} + [(\text{CH}_3)_3\text{Si}]_3\text{SiH} \longrightarrow \text{Ph}_2\text{C=CHPh} + [(\text{CH}_3)_3\text{Si}]_3\text{Si}\cdot$	$1.6 \times 10^9 M^{-1}\text{s}^{-1}$	m
18	$\text{RC=O} + [(\text{CH}_3)_3\text{Si}]_3\text{SiH} \longrightarrow \text{RCH=O} + [(\text{CH}_3)_3\text{Si}]_3\text{Si}\cdot$	$1.0 \times 10^5 M^{-1}\text{s}^{-1}$	l

(Continued)

Table 11.3. (Continued)

B. Additions to Alkenes and Aromatic Rings					
19	$\text{CH}_3\cdot + \text{H}_2\text{C}=\text{CHPh} \longrightarrow \text{CH}_3\text{CH}_2\text{CHPh}$		$2.6 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ $E_a = 4.9 \text{ kcal/mol}$		o
20	$\text{CH}_3\cdot + \text{H}_2\text{C}=\text{CHCN} \longrightarrow \text{CH}_3\text{CH}_2\text{CHCN}$		$6.1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$		o
21	$\text{CF}_3\cdot + \text{H}_2\text{C}=\text{CHPh} \longrightarrow \text{CF}_3\text{CH}_2\text{CHPh}$		$5.3 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$		p
22	$\text{Ph}\cdot + \text{CH}_2=\text{CHPh} \longrightarrow \text{PhCH}_2\text{CHPh}$		$1.1 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$		b
23	$\text{Ph}\cdot + \text{C}_6\text{H}_6 \longrightarrow \text{Ph}-\text{C}_6\text{H}_4\cdot$		$2.1 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$		q
24	$\text{PhCH}_2\cdot + \text{H}_2\text{C}=\text{C}(\text{CH}_3)_2 \longrightarrow \text{PhCH}_2\text{CH}_2\text{C}(\text{CH}_3)_2$		$18 \text{ M}^{-1}\text{s}^{-1}$		r
25	$(\text{CH}_3)_2\text{CCN} + \text{CH}_2=\text{CHPh} \longrightarrow (\text{CH}_3)_2\text{CCH}_2\text{CHPh}$ CN		$7.0 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$ $E_a = 6.4 \text{ kcal/mol}$		s
26	$\text{CH}_3\cdot + \text{C}_6\text{H}_6 \longrightarrow \text{CH}_3-\text{C}_6\text{H}_4\cdot$		$46 \text{ M}^{-1}\text{s}^{-1}$ $E_a = 8.9 \text{ kcal/mol}$		t
27	$\text{Ph}\cdot + \text{C}_6\text{H}_6 \longrightarrow \text{Ph}-\text{C}_6\text{H}_4\cdot$		$4.5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$		b
28	$(\text{CH}_3)_3\text{CO}\cdot + \text{H}_2\text{C}=\text{CH}(\text{CH}_2)_5\text{CH}_3 \longrightarrow (\text{CH}_3)_3\text{COCH}_2\text{CH}(\text{CH}_2)_5\text{CH}_3$		$1.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$		c
29	$\text{PhS}\cdot + \text{CH}_2=\text{CHPh} \longrightarrow \text{PhSCH}_2\text{CHPh}$		$2.0 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$		u
C. Cyclization and Ring-Opening					
30			$9.4 \times 10^7 \text{ s}^{-1}$ $E_a = 7-7.5 \text{ kcal/mol}$		v
31			$1.8 \times 10^7 \text{ s}^{-1}$		w
32			$5.4 \times 10^6 \text{ s}^{-1}$		x
33			$2.4 \times 10^5 \text{ s}^{-1}$ $E_a = 6.2 \text{ kcal/mol}$		e, y
34		X = H X = CH3 X = OCH3 X = CO2C2H5	$4 \times 10^7 \text{ s}^{-1}(20^\circ\text{C})$ $2 \times 10^7 \text{ s}^{-1}(20^\circ\text{C})$ $4 \times 10^7 \text{ s}^{-1}(20^\circ\text{C})$ $5.4 \times 10^7 \text{ s}^{-1}(20^\circ\text{C})$		z
35			$4 \times 10^8 \text{ s}^{-1}$ $E_a = 3.6 \text{ kcal/mol}$		aa
36			$1.5 \times 10^5 \text{ s}^{-1}$ $E_a = 7.3 \text{ kcal/mol}$		bb
37			$2 \times 10^{-1} \text{ s}^{-1}$ $E_a = 16.3 \text{ kcal/mol}$		cc

(Continued)

Table 11.3. (Continued)

					SECTION 11.2 <i>Characteristics of Reactions Involving Radical Intermediates</i>
38			2.8 x 10 ⁴ s ⁻¹ $E_a = 8.3 \text{ kcal/mol}$	dd	
39			4.2 x 10 ⁸ s ⁻¹	ee	
40			1.4 x 10 ⁵ s ⁻¹ 9.1 x 10 ⁷ s ⁻¹ $E_a = 6.8 \text{ kcal/mol}$	ff	
41			2.5 x 10 ⁵ s ⁻¹ $E_a = 5.4 \text{ kcal/mol}$	gg	
D. Other Reactions					
42	(CH ₃) ₃ C· + O ₂ → (CH ₃) ₃ C—O—O·		4.9 x 10 ⁹ M ⁻¹ s ⁻¹	gg	
43	PhCH ₂ · + O ₂ → PhCH ₂ —O—O·		2.4 x 10 ⁹ M ⁻¹ s ⁻¹	k	
44			4 x 10 ⁵ s ⁻¹ 10.2 kcal/mol	hh	
45	(CH ₃) ₃ CC=O → (CH ₃) ₃ C· + C≡O		3.0 x 10 ⁵ s ⁻¹	ii	
46	PhCH ₂ C=O → PhCH ₂ · + C≡O		5.2 x 10 ⁷ s ⁻¹ $E_a = 7.2 \text{ kcal/mol}$	jj	
47			5.2 x 10 ⁵ s ⁻¹ $E_a = 10.0 \text{ kcal/mol}$	aa	
48			11 x 10 ⁷ s ⁻¹	kk	
49	PhC(CH ₃) ₂ O· → PhC(=O)CH ₃ + CH ₃ ·		7 x 10 ⁵ s ⁻¹	ll	
50	Ph· + CCl ₄ → PhCl + ·CCl ₃		2.3 x 10 ⁶ M ⁻¹ s ⁻¹	kk	
51	CH ₃ (CH ₂) ₃ · + BrCCl ₃ → CH ₃ (CH ₂) ₃ Br + ·CCl ₃	2.6 x 10 ⁸ M ⁻¹ s ⁻¹ (80°C)	mm		
52	Ph· + BrCCl ₃ → PhBr + ·CCl ₃	1.6 x 10 ⁹ M ⁻¹ s ⁻¹	nn		
53	CH ₂ =CHCH ₂ · + ClOC(CH ₃) ₃ → CH ₂ =CHCH ₂ Cl + (CH ₃) ₃ CO·	2.6 x 10 ⁹ M ⁻¹ s ⁻¹	nn		
54	C ₈ H ₁₉ · + PhSeCH ₂ CO ₂ C ₂ H ₅ → C ₈ H ₁₉ SePh + ·CH ₂ CO ₂ C ₂ H ₅	1.0 x 10 ⁵ M ⁻¹ s ⁻¹	oo		
55	C ₈ H ₁₉ · + PhSeC(CO ₂ C ₂ H ₅) ₂ → C ₈ H ₁₉ SePh + CH ₃ C(CO ₂ C ₂ H ₅) ₂	8 x 10 ⁵ M ⁻¹ s ⁻¹	oo		

a. Unless otherwise noted, the rates are for temperatures near 25°C. The reference should be consulted for precise temperature and other conditions.

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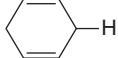
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11.2.3. Structure-Reactivity Relationships

11.2.3.1. Hydrogen Abstraction Reactions In hydrogen atom abstraction reactions, the strength of the bond to the reacting hydrogen is a major determinant of the rate at which reaction occurs. Table 11.4 gives some bond dissociation energies (BDE) that are particularly relevant to free radical reactions.

Generally, the ease of hydrogen atom abstraction parallels the BDE. Several of the trends, such as those for hydrocarbons and alkyl halides were discussed in Sections 3.1.2 and 3.4.3. The general tendency for functional groups to weaken α -CH bond is illustrated by the values for methanol, diethyl ether, acetone, and acetonitrile. The bond order relationship Si–H > Ge–H > Sn–H is particularly important in free radical chemistry. Entries 16 and 18 in Table 11.3 provide abstraction rates for silanes. The comparison between Entries 6 and 16 and 14 and 18 shows that silanes are somewhat less reactive than stannanes. Trisubstituted stannanes are among the most reactive hydrogen atom donors. As indicated by Entries 6 to 8, hydrogen abstractions from stannanes proceed with rates higher than $10^7 M^{-1}s^{-1}$ and have very low activation energies. This high reactivity correlates with the low bond strength of the Sn–H bond (78 kcal). For comparison, Entries 1 to 3 give the rates of hydrogen abstraction from two of the more reactive C–H hydrogen atom donors, tetrahydrofuran and isopropylbenzene. For the directly comparable reaction with the phenyl radical

Table 11.4. Selected Bond Dissociation Energies (kcal/mol)^a

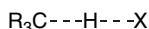
Bond	BDE	Bond	BDE	SECTION 11.2
CH ₃ -H	105.0	CH ₃ S-H	87	<i>Characteristics of Reactions Involving Radical Intermediates</i>
CH ₃ CH ₂ -H	100.5	PhS-H	83	
(CH ₃) ₂ CH-H	98.1	(CH ₃) ₃ Si-H	93	
(CH ₃) ₃ C-H	95.7	(CH ₃) ₃ Ge-H	87	
CH ₂ =CH-H	111	(C ₄ H ₉) ₃ Sn-H	78	
 -H	106			
 -H	76	[CH ₃ C(=O)O-] ₂	30	
HOCH ₂ -H	96	(CH ₃) ₃ CO-OH	44	
C ₂ H ₅ OCH(CH ₃)-H	93	CH ₃ S-SCH ₃	65	
CH ₃ C(=O)CH ₂ -H	96	C ₂ H ₅ -F	113	
N-CCH ₂ -H	96	C ₂ H ₅ -Cl	84	
F ₃ C-H	107	C ₂ H ₅ -Br	70	
Cl ₃ C-H	94	C ₂ H ₅ -I	56	
F-H	136	F-F	38	
Cl-H	102	Cl-Cl	57	
Br-H	87	Br-Br	45	
I-H	71	I-I	36	

a. From Y.-R. Luo, *Bond Dissociation Energies of Organic Compounds*, CRC Press, Boca Raton, FL, 2003.

(Entries 1 and 8), tri-*n*-butylstannane is about 100 times more reactive than tetrahydrofuran as a hydrogen atom donor. Thiols are also quite reactive as hydrogen atom donors, as indicated by Entries 10 and 11. Phenylselenol is an even more reactive hydrogen atom donor than tri-*n*-butylstannane (see Entry 12).

Entries 4 and 5 point to another important aspect of free radical reactivity. The data given indicate that the observed reactivity of the chlorine atom is strongly influenced by the presence of benzene. Evidently a complex is formed that attenuates the reactivity of the chlorine atom. Another case is chlorination in bromomethane, where the pri:sec:tert selectivity increases to 1:8.8:38.⁸⁵ This is probably a general feature of radical chemistry, but there are relatively few data available on solvent effects on either absolute or relative reactivity of radical intermediates.

The TS for hydrogen atom abstraction is pictured as having the hydrogen partially bonded to the donor carbon and the abstracting radical. Generally, theoretical models of such reactions indicate a linear alignment, although there are exceptions:



The Bell-Evans-Polanyi relationship and the Hammond postulate (see Section 3.3) provide a basic framework within which to discuss structure-reactivity relationships. The Bell-Evans-Polanyi equation implies that there will be a linear relationship between E_a and the C-H BDE.

$$E_a = \alpha \Delta H_r + E_0 \quad (11.4)$$

⁸⁵. A. Dneprovskii, D. V. Kuznetsov, E. V. Eliseenkov, B. Fletcher, and J. M. Tanko, *J. Org. Chem.*, **63**, 8860 (1998).

which can be rearranged to

$$E_a = \alpha(BDE) + \beta \quad (11.5)$$

We would therefore expect the E_a to decrease as the reacting C–H bond becomes weaker. The Hammond postulate relates position on the reaction coordinate to TS structure. Hydrogen atom abstractions with early TS will be reactant-like and those with late TS will be radical-like. We expect highly exothermic atom transfers to have early TSs and to be less sensitive to radical stability factors. Energy neutral reactions should have later TSs.

Table 11.5 summarizes some activation energies and relative reactivity data for some of the types of radicals that we are discussing, including alkyl, allyl, phenyl, benzyl, halomethyl, and hydroxyl radicals, and halogen atoms. These data provide confirmation of the widely recognized reactivity order *tert* > *sec* > *pri* for formation of alkyl radicals by hydrogen atom abstraction. They also provide some examples of the *reactivity-selectivity principle*, which is the premise that the most reactive radicals are the least selective and vice versa. The halogens are a familiar example of this idea. Chlorine atom selectivity is low, corresponding to very small E_a values and an early TS. Bromine, by contrast, has a significant E_a and is quite selective. The hydroxyl and alkoxy radicals are only modestly selective, whereas the $\text{CF}_3\cdot$ and $\text{CCl}_3\cdot$ radicals have higher E_a and greater selectivity.

Relative reactivity information such as that in Table 11.5 can be used in interpreting and controlling reactivity. For example, the high selectivity of the $\text{CBr}_3\cdot$ and $\text{CCl}_3\cdot$ is the basis for a recently developed halogenation procedure that is especially

Table 11.5. Activation Energies (kcal/mol) and Approximate Selectivity Ratios for Hydrogen Atom Abstraction Reactions

Radical	$\text{CH}_3\text{-H}$	$\text{CH}_3\text{CH}_2\text{-H}$	$(\text{CH}_3)_2\text{CH-H}$	$(\text{CH}_3)_3\text{C-H}$	$\text{PhCH}_2\text{-H}$	$\text{CH}_2=\text{CHCH}_2\text{-H}$	<i>pri:sec:tert</i>
$\text{CH}_3\text{·}^{\text{a,b,c}}$	14.0	11.6	9.6	8.1	9.5	7.7	1.0:4.8:61
$\text{C}_2\text{H}_5\text{·}^{\text{d}}$		13.3	11.4	10.0	9.3		
$(\text{CH}_3)_2\text{CH}\text{·}^{\text{d}}$				10±2			
$(\text{CH}_3)_3\text{C}\text{·}^{\text{d}}$				10.5	10.3		
$\text{Ph}\text{·}^{\text{d,e,f}}$	10.3	4.4		3.0	2.0		1:8.5:40
$\text{PhCH}_2\text{·}^{\text{d}}$					17.0		
$\text{HC}\equiv\text{C}\text{·}^{\text{g}}$	~2.5	0	0	0			
$\text{CF}_3\text{·}^{\text{a}}$	10.9	8.0	6.5	4.9	5.8		
$\text{CCl}_3\text{·}^{\text{c}}$	17.9	14.2	10.6	7.7			
$\text{F}\text{·}^{\text{c}}$	1–1.5	< 1		< 1			
$\text{Cl}\text{·}^{\text{c}}$	3.4	1.1					1:2.8:2.1
$\text{Br}\text{·}^{\text{g}}$	17.5	13.0	9.5	6.9			1:250:6300
$\text{HO}\text{·}^{\text{c}}$	3.6	1.0	0.6	0.3			
$\text{CH}_3\text{O}\text{·}^{\text{a}}$	10.1	7.1		2.4			
$(\text{CH}_3)_3\text{CO}\text{·}^{\text{c}}$					3.5 ^h		1:12:50

a. B. P. Roberts and A. J. Steel, *J. Chem. Soc., Perkin Trans. 2*, 2155 (1994).

b. N. Kobko and J. J. Dannenberg, *J. Phys. Chem. A*, **105**, 1944 (2001).

c. A. A. Fokin and P. Schreiner, *Chem. Rev.*, **102**, 1551 (2002); see also P. A. Hooshayar and H. Niki, *Int. J. Chem. Kinetics*, **27**, 1197 (1995).

d. A. A. C. Pais, L. G. Arnaut, and S. J. Formosinho, *J. Chem. Soc., Perkin Trans. 2*, 2577 (1998).

e. J. Park, D. Chakraborty, D. M. Bhusari, and M. C. Lin, *J. Phys. Chem. A*, **103**, 4002 (1999). T. Yu and M. C. Lin, *J. Phys. Chem.*, **99**, 8599 (1955).

f. B. Ceursters, H. M. T. Ngugen, J. Peeters and M. T. Nguyen, *Chem. Phys. Lett.*, **329**, 412 (2000). R. J. Hoobler, B. J. Opansky, and S. R. Leone, *J. Phys. Chem. A*, **101**, 1338 (1997). J. Parks, S. Gheysas, and M. C. Lin, *Int. J. Chem. Kinetics*, **33**, 64 (2001).

g. A. F. Trotman-Dickenson, *Adv. Free Radical Chem.*, **1**, 1 (1965).

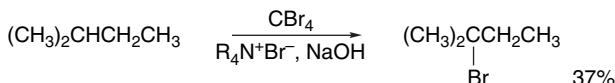
h. M. Finn, R. Friedline, N. K. Suleman, G. J. Wohl, and J. M. Tanko, *J. Am. Chem. Soc.*, **126**, 7578 (2004).

applicable to polycyclic hydrocarbons such as cubane, which do not react cleanly by direct halogenation. The reactions are carried out under phase transfer conditions using CBr_4 or CCl_4 as the halogen source and the $\text{CBr}_3\cdot$ and $\text{CCl}_3\cdot$ as the chain carriers. The reactions are initiated by electron transfer from hydroxide ion.

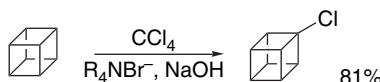
Initiation



Propagation

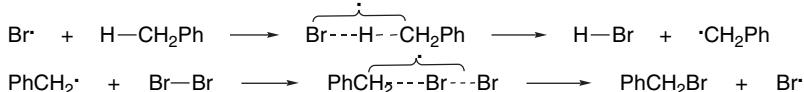


Ref. 86



Ref. 87

Many free radical reactions respond to introduction of polar substituents, just as do heterolytic processes that involve polar or ionic intermediates. The case of toluene bromination can be used to illustrate this point.



The substituent effects on toluene bromination are correlated by the Hammett equation, which gives a ρ value of -1.4 , indicating that the benzene ring acts as an electron donor in the TS.⁸⁸ Other radicals, for example, the *t*-butyl radical, show a positive ρ for hydrogen abstraction reactions involving toluene,⁸⁹ which indicates that radicals can exhibit either electrophilic or nucleophilic character. Why do free radical reactions involving neutral reactants and intermediates respond to substituent changes that modify electron distribution? One explanation is based on the idea that there is some polar character in the TS because of the electronegativity differences of the reacting atoms.⁹⁰



⁸⁶ P. R. Schreiner, O. Lauenstein, I. V. Kolomitsyn, S. Nadi, and A. A. Fokin, *Angew. Chem. Int. Ed. Engl.*, **37**, 1895 (1998).

⁸⁷ A. A. Fokin, O. Lauenstein, P. A. Gunchenko, and P. R. Schreiner, *J. Am. Chem. Soc.*, **123**, 1842 (2001).

⁸⁸ J. Hradil and V. Chvalovsky, *Collect. Czech. Chem. Commun.*, **33**, 2029 (1968); S. S. Kim, S. Y. Choi, and C. H. Kong, *J. Am. Chem. Soc.*, **107**, 4234 (1984); G. A. Russell, C. DeBoer, and K. M. Desmond, *J. Am. Chem. Soc.*, **85**, 365 (1963); C. Walling, A. L. Rieger, and D. D. Tanner, *J. Am. Chem. Soc.*, **85**, 3129 (1963).

⁸⁹ W. A. Pryor, F. Y. Tang, R. H. Tang, and D. F. Church, *J. Am. Chem. Soc.*, **104**, 2885 (1982); R. W. Henderson and R. O. Ward, Jr., *J. Am. Chem. Soc.*, **96**, 7556 (1974); W. A. Pryor, D. F. Church, F. Y. Tang, and R. H. Tang, *Frontiers of Free Radical Chemistry*, W. A. Pryor, ed., Academic Press, New York, 1980, pp. 355–380.

⁹⁰ E. S. Huyser, *Free Radical Chain Reactions*, Wiley-Interscience, New York, 1970, Chap. 4; G. A. Russell, in *Free Radicals*, Vol. 1, J. Kochi, ed., Wiley, New York, 1973, Chap. 7.

This idea receives support from the fact that the most negative ρ values are found for more electronegative radicals such as $\text{Br}\cdot$, $\text{Cl}\cdot$, and $\text{Cl}_3\text{C}\cdot$. There is, however no simple correlation with a single property and this probably reflects the fact that the *selectivity* of the radicals is also different. Furthermore, in hydrogen abstraction reactions, where many of the quantitative measurements have been done, the C–H bond dissociation energy is also subject to a substituent effect.⁹¹ Thus the extent of bond cleavage and formation at the TS may be different for various radicals. Successful interpretation of substituent effects in radical reactions therefore requires consideration of factors such as the electronegativity and polarizability of the radicals as well as the bond energy of the reacting C–H bond. The relative importance of these effects may vary from system to system. As a result, substituent effect trends in radical reactions can appear to be more complicated than those for heterolytic reactions, where substituent effects are usually dominated by the electron-releasing or electron-donating capacity of the substituent.⁹²

11.2.3.2. Addition Reactions Section B of Table 11.3 gives some rates of addition reactions involving carbon–carbon double bonds and aromatic rings. Comparison of Entries 23 and 24 shows that the phenyl radical is much more reactive toward addition to alkenes than the benzyl radical. Comparison of Entries 26 and 27 shows the same effect on additions to an aromatic ring. Delocalized benzyl and cumyl radicals have somewhat reduced reactivity.⁹³ Additions to aromatic rings are much slower than additions to alkenes (compare Entries 23 and 27). This kinetic relationship shows that it is more difficult to disrupt an aromatic ring than an alkene π bond.

Despite their overall electrical neutrality, carbon-centered radicals can show pronounced electrophilic or nucleophilic character, depending on the substituents present.⁹⁴ This electrophilic or nucleophilic character is reflected in rates of reaction with nonradical species, for example, in additions to substituted alkenes. Alkyl radicals and α -alkoxyalkyl radicals are distinctly nucleophilic in character and react most rapidly with alkenes having EWG substituents. Even methyl radicals with a single EWG, such as *t*-butoxycarbonyl or cyano are weakly nucleophilic.⁹⁵ Radicals having two EWGs, such as those derived from malonate esters, react preferentially with double bonds having ERG substituents.⁹⁶ Perfluoro radicals are electrophilic and are about 10^3 more reactive than alkyl radicals.⁹⁷

These substituent effects are consistent with an FMO interpretation with a dominant SOMO-LUMO interaction.⁹⁸ As shown in Figure 11.6, ERG substituents will raise the energy of the radical SOMO and increase the strength of interaction with the relatively low-lying LUMO of alkenes having electron-withdrawing groups. When

91. A. A. Zavitsas and J. A. Pinto, *J. Am. Chem. Soc.*, **94**, 7390 (1972); W. M. Nau, *J. Phys. Org. Chem.*, **10**, 445 (1997).
92. W. H. Davis, Jr., and W. A. Pryor, *J. Am. Chem. Soc.*, **99**, 6365 (1972); W. H. Davis, Jr., J. H. Gleason, and W. A. Pryor, *J. Org. Chem.*, **42**, 7 (1977); W. A. Pryor, G. Gojon, and D. F. Church, *J. Org. Chem.*, **43**, 793 (1978).
93. M. Walbiner, J. Q. Wu, and H. Fischer, *Helv. Chim. Acta*, **78**, 910 (1995).
94. B. Giese, *Angew. Chem. Int. Ed. Engl.*, **22**, 753 (1983); H. Fischer and L. Radom, *Angew. Chem. Int. Ed. Engl.*, **40**, 1340 (2001).
95. K. Heberger and A. Lopata, *J. Org. Chem.*, **63**, 8646 (1998).
96. B. Giese, H. Horler, and M. Leising, *Chem. Ber.*, **119**, 444 (1986).
97. D. V. Avila, K. U. Ingold, J. Lusztyk, W. R. Dolbier, and H. Q. Pan, *J. Am. Chem. Soc.*, **115**, 1577 (1993).
98. U. Berg, E. Butkus, and A. Stoncius, *J. Chem. Soc., Perkin Trans. 2*, 97 (1995); M. W. Wong, A. Pross, and L. Radom, *J. Am. Chem. Soc.*, **116**, 6284 (1994).

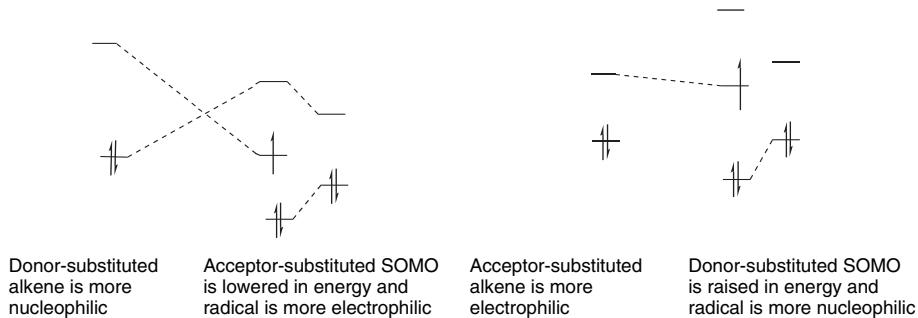


Fig. 11.6. Frontier orbital interactions between different combinations of substituted radicals and alkenes showing enhanced interaction relative to unsubstituted systems.

the radical site is substituted by an electron-attracting group, the SOMO is lower. A complementary interaction between the radical and alkene is possible.

The TS for radical additions is quite early and correlates with ground state characteristics of the reactant alkene. In particular there is a strong correlation between relative reactivity and the LUMO energy of the reactant alkene for addition reactions of the *t*-butyl radical, as shown in Figure 11.7.⁹⁹ The rate constants range over ten \ln exponents and the correlation coefficient is 0.971. π -Donor substituents

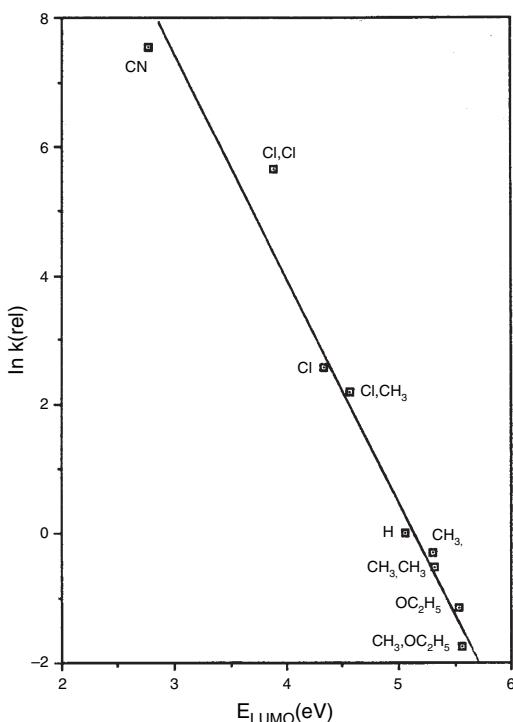


Fig. 11.7. Correlation between relative rates of addition reactions of *t*-butyl radicals and E_{LUMO} for alkenes. Reproduced from *J. Org. Chem.*, **57**, 1139 (1992), by permission of the American Chemical Society.

⁹⁹ D. J. Pasto, *J. Org. Chem.*, **57**, 1139 (1992).

(e.g., OR) retard reaction, whereas EWGs (e.g., CN) accelerate reaction, which is in agreement with the classification of alkyl radicals as nucleophilic. A relationship was also found between reactivity and the ground state stabilization of the alkene. Certain substituent combinations (e.g., CN,CN or Cl,Cl) significantly destabilize the alkene, and these compounds are highly reactive toward alkyl radicals. On the other hand, the (OC₂H₅, CH₃) combination stabilizes the alkene and such compounds are less reactive toward alkyl radicals. These results are consistent with an early TS for radical addition controlled by SOMO-LUMO interactions. The regiochemistry, which generally involves addition at the β -carbon, also correlates with the coefficient of the LUMO, as would be expected for an FMO-controlled reaction.

Some other representative rate data are given in Table 11.6. Methyl radicals are somewhat more reactive toward alkenes bearing EWG substituents than with ERG substituents. Secondary cyclohexyl radicals show a stronger trend in this direction. Some of this effect can be attributed to the stabilizing influence that these substituents have on the product radical. There is a strong correlation of reaction rate with the overall exothermicity of the reaction.¹⁰⁰

Related trends are seen in data for radicals with functional group substituents. Hydroxymethyl and 2-hydroxy-2-propyl radicals show nucleophilic character.¹⁰¹ The hydroxymethyl radical shows a slightly enhanced rate toward acrylonitrile and acrolein, but a sharply decreased rate toward ethyl vinyl ether. The more electrophilic cyanomethyl radical shows reactivity enhancement not only with radical-stabilizing EWGs, but also with ERGs. Table 11.7 gives some of the reactivity data.

α -Fluoro substituents enhance reactivity toward alkene addition. The effect of polyfluorination is more than cumulative. The rates of RCH₂[·] (1); RCHF[·] (3.5); RCF₂[·]

Table 11.6. Relative Rates of Radical Additions as a Function of Alkene Substitution^a

A. Addition to substituted ethenes, CH₂=CH-X

X	CH ₃ [·]	CH ₃ CH ₂ [·]	c-C ₆ H ₁₁ [·]
CN	2.2	5.1	24
COCH ₃	2.3		13
CO ₂ CH ₃	1.3	1.9	6.7
Ph	1.0	1.0	1.0
O ₂ CCH ₃		0.05	0.016

B. Additions to α -substituted styrenes. CH₂=CXPh

X	c-C ₆ H ₁₁ [·]	\cdot CH(CO ₂ C ₂ H ₅) ₂
CN	122	
CO ₂ C ₂ H ₅	11.7	0.28
Ph	1.0	1.0
CH ₃	0.28	1.06
CH ₃ O		0.78
(CH ₃) ₂ N		6.6

a. Data from B. Giese, H. Horler, and M. Leising, *Chem. Ber.*, **119**, 444 (1986); B. Giese, *Angew. Chem. Int. Ed. Engl.*, **22**, 753 (1983).

¹⁰⁰. M. W. Wong, A. Pross, and L. Radom, *J. Am. Chem. Soc.*, **115**, 11050 (1993); R. Arnaud, N. Bugaud, V. Vetere, and V. Barone, *J. Am. Chem. Soc.*, **120**, 5733 (1998).

¹⁰¹. J. Q. Wu and H. Fischer, *Int. J. Chem. Kinetics*, **27**, 167 (1995); S. N. Batchelor and H. Fischer, *J. Chem. Phys.*, **100**, 9794 (1996).

Table 11.7. Absolute Rates of Addition Reactions of Methyl, Cyanomethyl, and Hydroxymethyl Radicals toward Substituted Alkenes, $\text{CH}_2=\text{CHX}$

X	$\cdot\text{CH}_3^{\text{a}}$	$\cdot\text{CH}_2\text{CN}^{\text{b}}$	$\cdot\text{CH}_2\text{OH}^{\text{c}}$
H	3.5×10^3	3.3×10^3	4.1×10^2
Ph	2.6×10^5	3.8×10^3	2.3×10^4
CN	6.1×10^5	1.1×10^5	1.1×10^6
$\text{CH}=\text{O}$	7.4×10^5	2.5×10^4	2.1×10^6
CO_2CH_3	3.4×10^5	1.1×10^5	7.1×10^5
OC_2H_5	1.4×10^4	1.2×10^4	1.8×10^2
CH_3	4.3×0^3	1.2×10^4	2.7×10^2

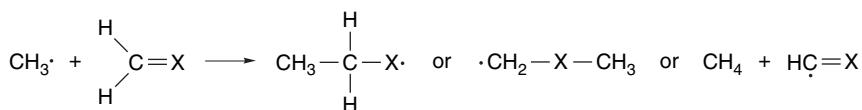
a. T. Zytowski and H. Fischer, *J. Am. Chem. Soc.*, **118**, 437 (1996); T. Zytowski and H. Fischer, *J. Am. Chem. Soc.*, **119**, 12869 (1997).

b. J. Q. Wu and H. Fischer, *Int. J. Chem. Kinet.*, **27**, 167 (1995).

c. J. Q. Wu, I. Beranek, and H. Fischer, *Helv. Chim. Acta*, **78**, 194 (1995).

(20); and $\text{CF}_3\cdot$ (300) show this trend.¹⁰² Further accumulation of fluorine enhances this effect still further and the perfluoro-*t*-butyl radical is typically eight to ten times more reactive than $\text{CF}_3\cdot$ toward alkenes.

Computational studies have also compared some of the fundamental substituent effects on addition reactions for other functional groups. The relative barriers for addition and hydrogen abstraction were compared for ethene, formaldehyde, methylene imine, and formaldehyde nitrone. The data shown below are the result of B3LYP/6-311+G(2df,p) calculations, but G2 and CBS calculations were carried out in some cases.¹⁰³



X	Addition at C		Addition at X		H Abstraction	
	ΔH	ΔH^\ddagger	ΔH	ΔH^\ddagger	ΔH	ΔH^\ddagger
=CH ₂	-20	+ 7	-20	+ 7	+ 5	+ 15
=O	-13	+4.5	-7.4	+15	-17	+ 5
=NH	-18	+6.5	-19	+9.5	-18	+4
=N ⁺ (O ⁻)H	-44	+ 1.7	+ 6.2	+ 22	-34	-1

Addition is preferred to hydrogen atom abstraction for alkenes. Addition at carbon and hydrogen abstraction are competitive for aldehydes and imines. Both addition at carbon and hydrogen abstraction reactions are very exothermic for nitrones and are calculated to have low barriers. There are two possible modes of addition for the unsymmetrical systems. For the carbonyl and nitrone groups, addition at the carbon is preferred. The same is true for imines, but the balance is much closer. The activation

¹⁰². D. V. Avila, K. U. Ingold, J. Lusztyk, W. R. Dolbier, Jr., and H.-Q. Pan, *J. Org. Chem.*, **61**, 2027 (1996); D. Avila, K. U. Ingold, J. Lusztyk, W. R. Dolbier, Jr., and H.-Q. Pan, *Tetrahedron*, **52**, 12351 (1996).

¹⁰³. S. L. Boyd and R. J. Boyd, *J. Phys. Chem. A*, **105**, 7096 (2001).

enthalpies follow the same trend. For imines, there are two potential hydrogen abstraction sites, the CH or NH. Similarly for nitrones derived from aldehydes, there are two possible sites for abstraction. In both cases, the H abstraction from N is preferred. Either of these sites can be eliminated from competition by substitution. Another study of this type included thiocarbonyl groups.¹⁰⁴ For methyl radicals, the barrier to addition at sulfur (~ 2 kcal/mol) is substantially lower than at carbon (~ 8 kcal/mol), although both are lower than for the carbonyl group. The relative reactivity of alkenes, carbonyl, thiocarbonyl, imine, and nitrone groups is relevant in intramolecular additions, which are discussed in Section 11.2.3.2.

The energetics of addition reactions of alkyl radicals with aldehyde groups have been studied as a function of radical structure.¹⁰⁵ According to G3(MP2) computations, alkyl radicals show a lower barrier to carbonyl addition as they become more substituted. As shown in Figure 11.8, these reactions interrelate acyl, alkoxyalkyl, and alkoxy radicals. For the simplest system, the addition at O is also energetically favorable, but the activation barrier is higher. Experimental studies indicate that the barrier for H abstraction from formaldehyde by primary radicals is around 7.5 kcal/mol, which is significantly lower than is calculated. Hydrogen abstraction from the α -position is calculated to have a significantly higher barrier and is not competitive.

11.2.3.3. Radical Cyclizations Section C of Table 11.3 shows some reactions involving cyclization of unsaturated radicals. This type of reaction is an important application of free radical chemistry in synthesis, and is discussed more thoroughly in Section 10.3.3 of Part B. Rates of cyclization reactions have also proven useful in mechanistic studies, where they can serve as reference points for comparison with other reaction rates.

Entry 30 is the case of ring opening of the cyclopropylmethyl radical, which was discussed on p. 973. Note that the activation energy is somewhat higher than a normal single bond rotation but less than that for cyclohexane inversion. Entry 32 shows that

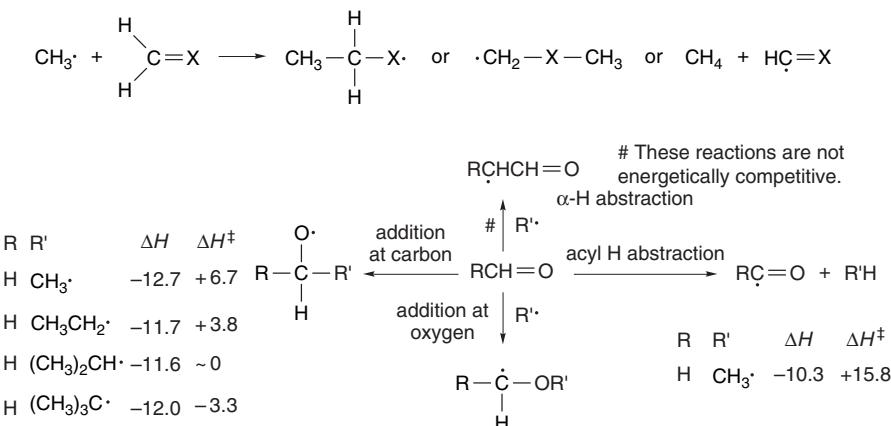


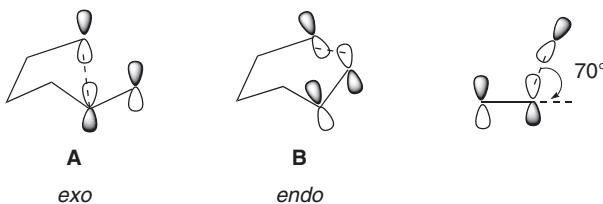
Fig. 11.8. G3(MP2) computational ΔH and ΔH^\ddagger in kcal/mol for reactions of alkyl radicals with aldehydes.

¹⁰⁴. D. J. Henry, M. L. Coote, R. Gomez-Balderas, and L. Radom, *J. Am. Chem. Soc.*, **126**, 1732 (2004).

¹⁰⁵. H. Hippler and B. Viskolcz, *Phys. Chem. Chem. Phys.*, **4**, 4663 (2002).

the stabilization by a phenyl substituent shifts the cyclopropyl \rightleftharpoons butenyl equilibrium to favor the cyclic form.

The cyclization of the 5-hexenyl radical to cyclopentylmethyl (Entry 33) is a commonly observed reaction. The E_a is 6 kcal/mol. The cyclization shows a preference for *exo* cyclization to a five-membered ring over *endo* cyclization to a six-membered ring,¹⁰⁶ even though it results in formation of a less stable primary radical. The cause for this preference has been traced to stereoelectronic effects. In order for a bonding interaction to occur, the radical center must interact with the π^* orbital of the alkene. According to MO calculations, the preferred direction of attack is from an angle of about 70° with respect to the plane of the double bond.¹⁰⁷



When this stereoelectronic requirement is included with a calculation of the steric and angle strain imposed on the TS, as determined by MM-type calculations, preferences of the *exo* versus *endo* modes of cyclization are predicted to be as summarized in Table 11.8.

The observed results agree with the calculated trend. Relative rates of cyclization are in the order 5-*exo* > 6-*endo* \sim 6-*exo* > 7-*endo*.¹⁰⁸ The relationship holds only for terminal double bonds. An additional alkyl substituent at either end of the double bond reduces the relative reactivity by a steric effect. The underlying conformational and stereoelectronic effects can be modified by both steric and electronic effects of substituents. For example, a 5-methoxycarbonyl substituent promotes the 6-*endo* mode of cyclization by an electronic effect.¹⁰⁹ The reactivity of the β -carbon is enhanced by the substituent.

Table 11.8. Regioselectivity of Radical Cyclization as a Function of Ring Size^a

Ring size	<i>exo:endo</i> Ratio	
	Calculated	Found
5:6	10:1	50:1
6:7	> 100 : 1	10:1
7:8	1:5.8	< 1 : 100

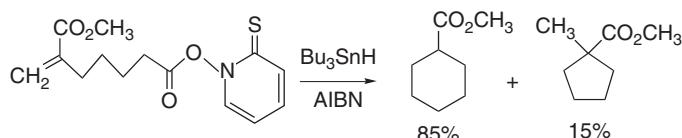
a. D. C. Spellmeyer and K. N. Houk, *J. Org. Chem.*, **52**, 959 (1987).

¹⁰⁶ A. L. J. Beckwith, C. J. Eaton, and A. K. Serelis, *J. Chem. Soc., Chem. Commun.*, 482 (1980); A. L. J. Beckwith, T. Lawrence, and A. K. Serelis, *J. Chem. Soc., Chem. Commun.*, 484 (1980); A. L. J. Beckwith, *Tetrahedron*, **37**, 3073 (1981).

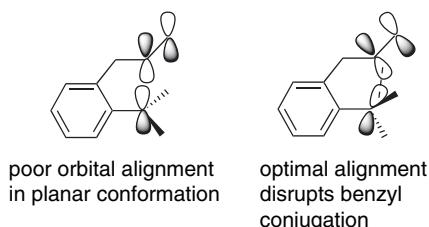
¹⁰⁷ M. J. S. Dewar and S. Olivella, *J. Am. Chem. Soc.*, **100**, 5290 (1978); D. C. Spellmeyer and K. N. Houk, *J. Org. Chem.*, **52**, 959 (1987).

¹⁰⁸ A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron*, **41**, 3925 (1985).

¹⁰⁹ E. W. Della, C. Kostakis, and P. A. Smith, *Org. Lett.*, **1**, 363 (1999).



The relatively low rate and high activation energy noted for Entry 37 of Table 11.3 also reflects a stereoelectronic effect. The preference for delocalization at the radical center requires coplanarity of the substituents at the radical site, which results in poor alignment. In view of the restrictions on the mode of approach of the radical to the double bond, significant strain develops in the TS and requires rotation of the benzylic methylene group out of its preferred coplanar alignment.¹¹⁰



Several computational studies have explored the cyclization of the 5-hexenyl radical. CBS-RAD(B3LYP) calculations provided thermochemical and kinetic parameters that are in good agreement with experiment.¹¹¹ Similar results were obtained with UB3LYP/6-31G(*d*) calculations.¹¹²

	5-exo	6- <i>endo</i>
ΔG	-13.7 kcal/mol	-16.5 kcal/mol
ΔG^\ddagger	9.3 kcal/mol	12.0 kcal/mol
E_a	6.3 kcal/mol	8.7 kcal/mol
k_{gas}	$1.2 \times 10^7 \text{ s}^{-1}$	$2.7 \times 10^5 \text{ s}^{-1}$
k_{benzene}	$8.2 \times 10^6 \text{ s}^{-1}$	$1.6 \times 10^5 \text{ s}^{-1}$

Cyclization of 5-hexenyl radicals has been compared computationally (BLYP/31+G***) with 2-oxo-5-hexenyl radicals.¹¹³ Several methyl-substituted analogs

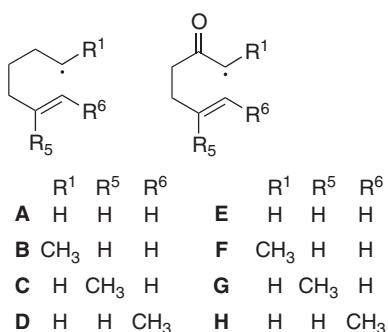
¹¹⁰. J. A. Franz, N. K. Suleman, and M. S. Alnajjar, *J. Org. Chem.*, **51**, 19 (1986).

¹¹¹. B. J. Maxwell, B. J. Smith, and J. Tsanaktsidis, *J. Chem. Soc., Perkin Trans. 2*, 425 (2000).

¹¹². B. S. Jursic, *Theochem*, **492**, 285 (1999).

¹¹³. A. G. Leach, R. Wang, G. E. Wohlhieter, S. I. Khan, M. E. Jung, and K. N. Houk, *J. Am. Chem. Soc.*, **125**, 4271 (2003).

were included in the study. There is a change to a preference from 5-*exo* to 6-*endo* with the introduction of the 2-oxo group.



Experimentally, it is found that the hexenyl radicals prefer the 5-*exo* route, whereas the α -keto radicals prefer the 6-*endo* path. This effect is mirrored in the calculations, which find the 5-*exo* route strongly favored in the 5-hexenyl system (except for the 5-methyl derivative **C**), whereas for the α -keto radicals the 6-*endo* TS is preferred, although again the steric effect of a 6-methyl group somewhat disfavors this mode. Figure 11.9 shows various TSs. The conjugation present in the α -keto radicals imparts a planarity to the radical that favors the *endo* structure.¹¹⁴

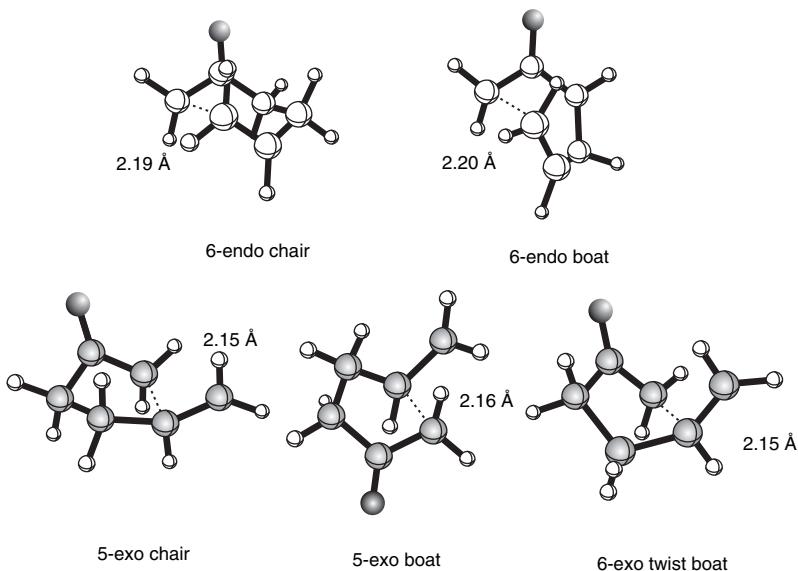
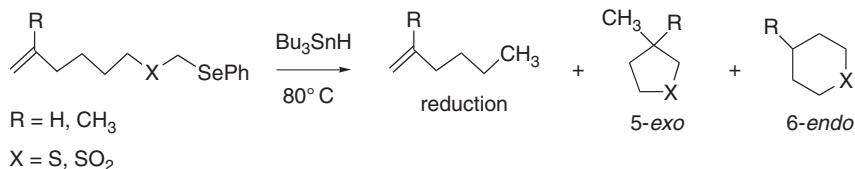


Fig. 11.9. Structures for various conformations of the radical cyclization transition structures for 2-oxo-5-hexenyl radical. Reproduced from *J. Am. Chem. Soc.*, **125**, 4271 (2003), by permission of the American Chemical Society.

¹¹⁴ J. L. Broeker and K. N. Houk, *J. Org. Chem.*, **56**, 3651 (1991).

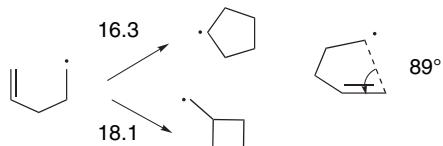
	Computed Transition Structure Energy (kcal/mol)				
	5-exo(chair)	5-exo(boat)	6-endo(chair)	6-endo(boat)	endo:exo ratio
A	6.4	8.1	9.1	11.6	1:99
B	7.0	8.7	9.6	12.2	1:99
C	9.1	10.3	8.4	10.7	75:25
D	6.5	8.1	9.8	12.5	1:99
E	13.3	12.6	10.0	16.5	98:2
F	15.9	14.4	12.6	19.1	95:5
G	15.8	14.7	8.6	15.2	> 99 : 1
H	12.7	12.1	10.9	17.2	84:16

Competition between *5-exo* and *6-endo* has also been examined for the 2-thia and 2-sulfonyl analogs of the 5-hexenyl radicals.¹¹⁵ As in the case of the parent radical, a 5-methyl substituent favors the *6-endo* mode and this is reinforced in the case of the sulfonyl substituent, where the electrophilic radical prefers the more electron-rich alkene position.



R	X	Product composition		
		Reduction	5-exo	6-endo
H	S	17.1	70.1	12.8
H	SO ₂	3.8	73.1	23.1
CH ₃	S	38.6	7.1	54.3
CH ₃	SO ₂	3.9	2.5	93.6

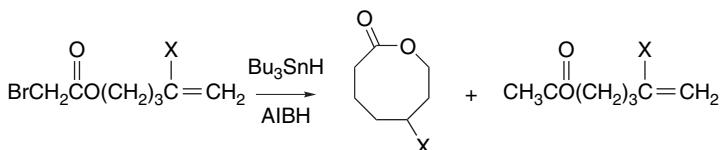
The 4-pentenyl radical can undergo *4-exo* or *5-endo* cyclization. UB3LYP/6-31G* calculations find a preference of 1.8 kcal/mol for the *5-endo* TS. The angle to approach to the double bond is found to be about 89°.¹¹⁶



¹¹⁵. E. W. Della and S. D. Graney, *Org. Lett.*, **4**, 4065 (2002); E. W. Della and S. D. Graney, *J. Org. Chem.*, **69**, 3824 (2004).

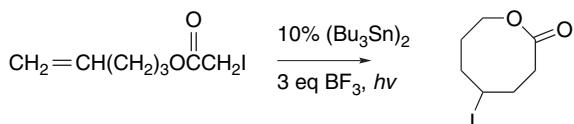
¹¹⁶. P. S. Engel, S. L. He, and W. B. Smith, *J. Am. Chem. Soc.*, **119**, 6059 (1997); C. Chatgilialoglu, C. Ferreri, M. Guerra, V. Timokhin, G. Froudakis, and T. Gimisis, *J. Am. Chem. Soc.*, **124**, 10765 (2002).

Reactions of 4-substituted 4-pentenyl bromoacetates with tri-*n*-butylstannane resulted in modest yields of eight-membered *endo*-cyclization products, along with reduction products.¹¹⁷



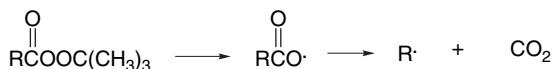
X	Product yield	
	Cyclization	Reduction
H	38%	31%
CH ₃	38%	18%
(CH ₃) ₃ Si	54%	32%

This type of cyclization can be further improved by use of a BF₃ catalyst.¹¹⁸



Systems with the potential for forming nine-, ten-, or sixteen-membered rings gave only reduction. The relatively favorable formation of eight-membered rings is attributed to the *s-trans* conformation of the ester group. The relative energies of the 8-*endo* and 7-*exo* TS were calculated for both the *s-trans* and *s-cis* conformations by ROHF/MP2/3-21G computations.¹¹⁷ The most favorable TS is the 8-*endo-cis* structure. The relative energies are shown in Figure 11.10. The general pattern that emerges from these experimental and computational results is that trajectory of approach, steric effects, and reactant conformation are the controlling factors in the ring size selectivity for radical cyclizations.

11.2.3.4. Other Radical Reactions Section D of Table 11.3 includes several examples of *radical fragmentation reactions*. Entries 44, 48, and 49 are examples of *β-scission reactions*. The facile decarboxylation of acyloxy radicals is an example.



¹¹⁷ E. Lee, C. H. Yoon, T. H. Lee, S. Y. Kim, T. J. Ha, Y. Sung, S.-H. Park, and S. Lee, *J. Am. Chem. Soc.*, **120**, 7469 (1998).

¹¹⁸ J. Wang and C. Li, *J. Org. Chem.*, **67**, 1271 (2002).

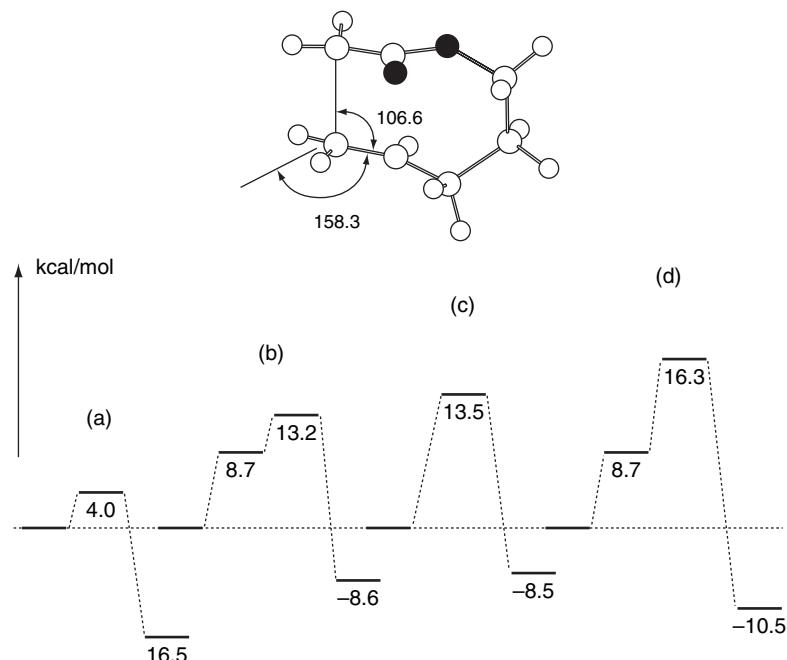
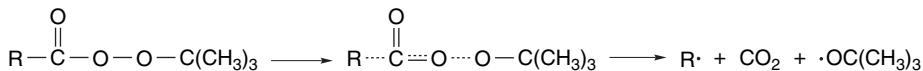


Fig. 11.10. Comparison of energies of (a) 8-*endo*-*s*-*cis*, (b) 8-*endo*-*s*-*trans*, (c) 7-*exo*-*s*-*cis*, and (d) 7-*exo*-*s*-*trans* transition structures. The *s*-*trans* conformation is 8.7 kcal/mol less stable than its *s*-*cis*. Reproduced from *J. Am. Chem. Soc.*, **120**, 7469 (1998), by permission of the American Chemical Society.

The rate of decarboxylation of aroyloxy radicals is about 10^6 s^{-1} near room temperature.¹¹⁹ Decarboxylation of alkanoyloxy radicals is even faster. Thus only very rapid reactions can compete with decarboxylation. Hydrogen abstraction from very reactive hydrogen atom donors, such as triethylsilane, can compete with decarboxylation at moderate temperatures.

These radical stability effects can be observed in the *rates of formation of radicals as well as their lifetimes*. It has already been indicated that radical structure and stability determines the temperature at which azo compounds undergo decomposition with elimination of nitrogen (see Section 11.1.4). Similar trends have been established in other radical-forming reactions. Rates of thermal decomposition of *t*-butyl peroxyesters, for example, vary over a wide range, depending on the structure of the carbonyl substituent.¹²⁰ These data clearly indicate that the bonding changes involved in the rate-determining step are not localized in the O—O bond. Radical character must also be developing at the alkyl group by partial cleavage of the alkyl-carbonyl bond.



¹¹⁹ J. Chateauneuf, J. Lusztyk, and K. U. Ingold, *J. Am. Chem. Soc.*, **110**, 2886 (1988); H. Misawa, K. Sawabe, S. Takahara, H. Sakuragi, and K. Tokumaru, *Chem. Lett.*, 357 (1988).

¹²⁰ P. D. Bartlett and R. R. Hiatt, *J. Am. Chem. Soc.*, **80**, 1398 (1958).

SECTION 11.2

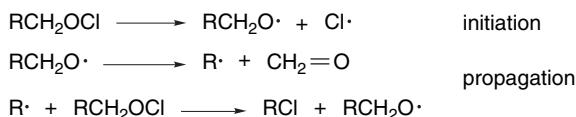
Characteristics of
Reactions Involving
Radical Intermediates

R	Relative rate at 60°C
CH ₃	1
C ₆ H ₅	17
PhCH ₂	290
(CH ₃) ₃ C	1,700
Ph ₂ CH	19,300
Ph(CH ₃) ₂ C	41,500
PhCHCH=CH ₂	125,000

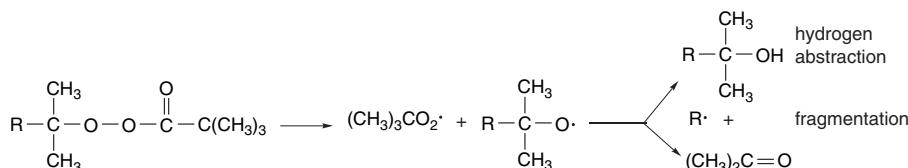
Another common fragmentation reaction is the cleavage of an alkoxy radical to an alkyl radical and a carbonyl compound.¹²¹



This type of fragmentation is involved in the chain decomposition of alkyl hypochlorites.¹²² In this reaction, too, the stability of the radical being eliminated is the major factor in determining the rate of fragmentation.



Radical trapping by a nitroxide was used to determine the ratio between β -fragmentation and hydrogen abstraction by alkoxy radicals generated by thermal decomposition of peroxy pivalate esters.¹²³ The ratio of fragmentation:hydrogen abstraction increased sharply with radical substitution and stability.



R	Fragmentation relative to CH ₃	Rate of decomposition (60°C, $\times 10^{-5} s^{-1}$)
CH ₃	1	2.95
CH ₃ CH ₂	252	3.51
CH ₃ CH ₂ CH ₂	254	3.37
(CH ₃) ₃ CCH ₂	2670	6.18
(CH ₃) ₂ CH	3300	5.14
Cyclohexyl	28000	5.72
(CH ₃) ₃ C	86400	9.10
PhCH ₂		9.91
Ph		10.32

¹²¹ P. Gray and A. Williams, *Chem. Rev.*, **59**, 239 (1959).

¹²² F. D. Greene, M. L. Savitz, F. D. Osterholtz, H. H. Lau, W. N. Smith, and P. M. Zanet, *J. Org. Chem.*, **28**, 55 (1963); C. Walling and A. Padwa, *J. Am. Chem. Soc.*, **85**, 1593, 1597 (1963).

¹²³ T. Nakamura, Y. Watanabe, S. Suyama, and H. Tezuka, *J. Chem. Soc., Perkin Trans. 2*, 1364 (2002).

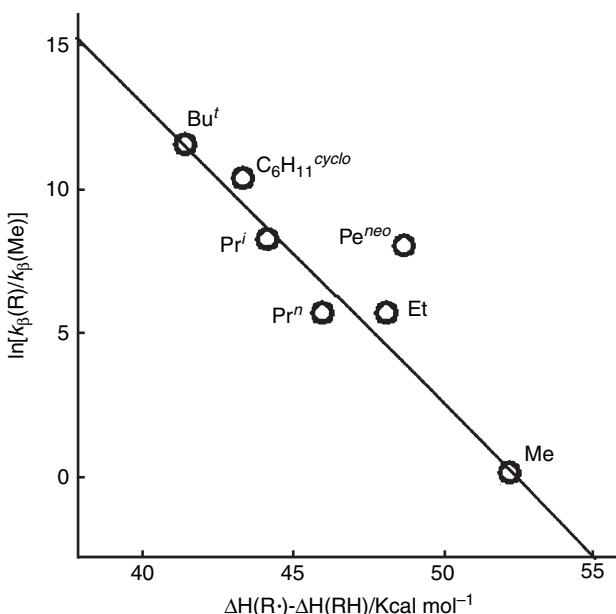
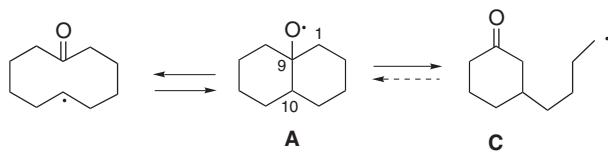


Fig. 11.11. Correlation between fragmentation of 2-alkyl-2-propoxy radicals and radical stability as measured by $\Delta H(R\cdot) - \Delta H(R-H)$. Reproduced from *J. Chem. Soc., Perkin Trans. 2*, 1364 (2002), by permission of the Royal Society of Chemistry.

As shown in Figure 11.11, there is a strong correlation between the ratio and radical stability, as measured by the difference in the enthalpy of formation. The outlying value for neopentyl can be improved by a correction for steric strain. On the other hand, the *rate of decomposition of the peroxy ester* is nearly independent of the nature of R, even for the stabilized benzyl or destabilized phenyl cases.¹²⁴ This is in marked contrast to a strong dependence on the structure of the acyl group (see above) and indicates that the fragmentation of the alkoxy radical is not concerted with the peroxy bond cleavage, but must be a separate step.

In cyclic systems the fragmentation of alkoxy radicals can be a reversible process. The 9-decalyloxy radical can undergo fragmentation of either the 1–9 or the 9–10 bond:

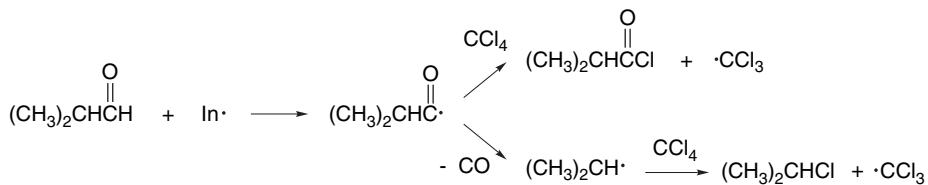


By using various trapping reagents it has been deduced that the transannular fragmentation is rapidly reversible. The cyclization of the fragmented radical C is less favorable and it is trapped at rates that exceed recyclization under most circumstances.¹²⁵

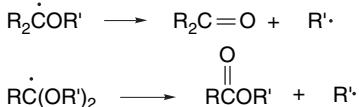
¹²⁴. T. Nakamura, W. K. Busfield, I. D. Jenkins, O. Rizzardo, S. H. Thang, and S. Suyama, *J. Org. Chem.*, **65**, 16 (2000).

¹²⁵. A. L. J. Beckwith, R. Kazlauskas, and M. R. Syner-Lyons, *J. Org. Chem.*, **48**, 4718 (1983).

Acyl radicals can fragment by loss of carbon monoxide. Decarbonylation is slower than decarboxylation, but the rate also depends on the stability of the radical that is formed.¹²⁶ For example, rates for decarbonylations giving tertiary benzylic radicals are on the order of 10^8 s^{-1} , whereas the benzoyl radical decarbonylates to phenyl radical with a rate on the order of 1 s^{-1} (see also Table 11.3, Entries 45 to 48). When reaction of isobutyraldehyde with carbon tetrachloride is initiated by *t*-butyl peroxide, both isopropyl chloride and isobutyroyl chloride are formed, indicating that decarbonylation is competitive with the chlorine atom transfer.

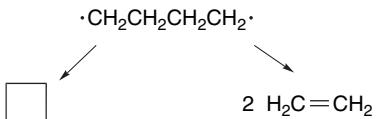


Radicals derived from ethers and acetals by hydrogen abstraction are subject to β -scission, with formation of a ketone or ester, respectively.

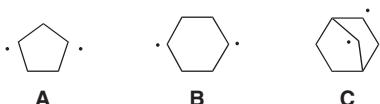


These fragmentations are sufficiently slow that the initial radicals can undergo reactions such as addition to alkenes at rates that are competitive with fragmentation.

A special case of fragmentation is that of 1,4-diradicals, where it can lead to two alkene molecules. In the case of 1,4-diradicals without functional group stabilization, reclosure to cyclobutanes is competitive with fragmentation to two molecules of alkene. The most recent of many detailed computational studies indicates that there is no barrier between the diradical and either the cyclization or fragmentation products.¹²⁷



A study of the lifetimes of the triplet biradicals **A**, **B**, and **C**, which were generated from the corresponding photoexcited azo compounds, gave the order of lifetime **A** > **B** > **C**. The lifetime of **A** is about $2.6 \times 10^{-7}\text{ s}$, which is quite long for a 1,4-diradical.¹²⁸



¹²⁶ D. E. Applequist and L. Kaplan, *J. Am. Chem. Soc.*, **87**, 2194 (1965); W. H. Urry, D. J. Trecker, and H. D. Hartzler, *J. Org. Chem.*, **29**, 1663 (1964); H. Fischer and H. Paul, *Acc. Chem. Res.*, **20**, 200 (1987).

¹²⁷ E. Ventura, M. Dallos, and H. Lischka, *J. Chem. Phys.*, **118**, 10963 (2003).

¹²⁸ W. Adam, K. Hannemann, and R. M. Wilson, *J. Am. Chem. Soc.*, **106**, 7646 (1984); W. Adam, K. Hannemann, and R. M. Wilson, *Angew. Chem. Int. Ed. Engl.*, **24**, 1071 (1985); W. Adam, H. Platsch, J. Sendelbach, and J. Wirz, *J. Org. Chem.*, **58**, 1477 (1993).

The major factor identified in controlling the lifetimes of these diradicals is the orientation of the singly occupied orbitals with respect to one another. One factor determining the lifetime is the rate of conversion (intersystem crossing) to the singlet biradical. The rate of conversion is dependent on the orientation of the orbitals having the unpaired electrons. In **A** the orbitals are essentially parallel, which is a poor orientation for intersystem crossing. Diradical **B** is more flexible and the triplet is converted more rapidly to the singlet diradical, which reacts rapidly to give the cyclization and fragmentation products.



The geometry of the bicyclic ring system in radical **C** directs the half-filled orbitals toward one another and its lifetime is less than 1×10^{-10} s.¹²⁹

11.3. Free Radical Substitution Reactions

11.3.1. Halogenation

The basic reactivity and selectivity relationships for halogenation of alkanes can be understood in terms of bond dissociation energies. Bond dissociation energies such as those in Part B of Table 3.2 can be used to estimate the energy balance in individual steps in a free radical reaction sequence. This is an important factor in assessing the feasibility of chain reaction sequences because only reactions with low activation energies are fast enough to sustain a chain process. If individual steps are identified as being endothermic by more than a few kcal, it is unlikely that a chain mechanism can operate.

Example 11.1 Calculate the enthalpy for each step in the bromination of ethane by bromine atoms from molecular bromine. Determine the overall enthalpy of the reaction.

			bond energy (kcal/mol)
initiation	$\text{Br}-\text{Br} \longrightarrow 2 \text{Br}^{\bullet}$		$\text{Br}-\text{Br} \quad +45$
propagation	$\text{Br}^{\bullet} + \text{CH}_3\text{CH}_3 \longrightarrow \text{H}-\text{Br} + \text{CH}_3\text{CH}_2^{\bullet}$		$\text{H}-\text{Br} \quad -87$
			$\text{H}-\text{C} \quad +100.5$
			<hr/> $+13.5$
	$\text{CH}_3\text{CH}_2^{\bullet} + \text{Br}-\text{Br} \longrightarrow \text{CH}_3\text{CH}_2\text{Br} + \text{Br}^{\bullet}$		$\text{Br}-\text{Br} \quad +45$
			$\text{Br}-\text{C} \quad -70$
			<hr/> -25
			$\text{total} \quad -11.5$

The enthalpy of the reaction is given by the sum of the propagation steps and is -11.5 kcal/mol. Analysis of the enthalpy of the individual steps indicates that the first step is somewhat endothermic ($+13.5$ kcal). This endothermicity is the lower limit of the E_a for the step. An E_a of 14.0 ± 0.25 kcal/mol has been reported.¹³⁰

Radical chain processes depend on a series of fast steps that maintain the reactive intermediates at low concentration. Since termination reactions are usually very fast,

¹²⁹ W. Adam, S. Grabowski, and R. M. Wilson, *Acc. Chem. Res.*, **23**, 165 (1990).

¹³⁰ K. D. King, D. M. Golden, and S. W. Benson, *Trans. Faraday Soc.*, **66**, 2794 (1970).

the presence of an endothermic step in a chain sequence means that the chains will be short. The value for ethane is borderline, which suggests that radical bromination of ethane will exhibit only short chain lengths. As the enthalpy of the corresponding steps for abstraction of secondary or tertiary hydrogen is less positive, the bromination selects for tertiary > secondary > primary in compounds with more than one type of hydrogen. Enthalpy calculations cannot give a direct evaluation of the activation energy of either exothermic or endothermic steps, since these depend on the energy of the TS. The bond dissociation energies can therefore provide only permissive, not definitive, conclusions. For single atom abstraction reactions such as these involved in hydrocarbon halogenation, the enthalpy correlates with E_a for both steps.

—	$\text{CH}_4(105.0)$	+18.0
—	$\text{C}_2\text{H}_5(100.5)$	+13.5
—	$(\text{CH}_3)_2\text{CH}_2(98.1)$	+11.1
—	$(\text{CH}_3)_3\text{CH}(95.7)$	+9.7

The thermochemistry of radical chain halogenations varies strongly with the halogens. Fluorination is strongly exothermic and difficult to control. Iodination is endothermic and cannot sustain a chain reaction. Both chlorination and bromination are moderately exothermic and chain reactions with hydrocarbons are feasible. Figure 11.12 summarizes these energies for reaction with methane, ethane, propane, and isobutane. By tracking each hydrocarbon-halogen combination, the energy profile can be obtained. From these data we can, for example, determine and compare the minimum E_a for chlorination and bromination at C(2) in propane.



The two energy profiles are significantly different in that bromination, but not chlorination, has an endothermic step.

Free radical bromination is an important method of selective functionalization of hydrocarbons.¹³¹ The reaction is often initiated by photolysis of bromine. The hydrogen atom abstraction step is rate limiting and the product composition is governed by the selectivity of the hydrogen abstraction step. Based on BDE (see Table 3.2, p. 258), the enthalpy requirements for abstraction of hydrogen from methane, ethane (primary), propane (secondary), and isobutane (tertiary) by bromine atoms are +18.0, +13.5, +11.1, and +9.7 kcal/mol, respectively (see Figure 11.12).¹³² These differences are reflected in the E_a and there is a substantial kinetic preference for hydrogen abstraction in the order tertiary > secondary > primary. Substituents that promote radical stability, such as phenyl, vinyl, or carbonyl groups, also lead to kinetic selectivity in radical brominations. Bromination at benzylic positions is a particularly efficient process.

In addition to Br_2 , *N*-bromosuccinimide is an important reagent for radical chain bromination, especially at allylic and benzylic positions. Mechanistic investigations have established that Br_2 is the active halogenating agent under the conditions used

¹³¹ W. A. Thaler, *Meth. Free Radical Chem.*, **2**, 121 (1969); A. Nechvatal, *Adv. Free Radicals*, **4**, 175 (1972).

¹³² E. S. Huyser, *Free Radical Chain Reactions*, Wiley-Interscience, New York, 1970, p. 91.

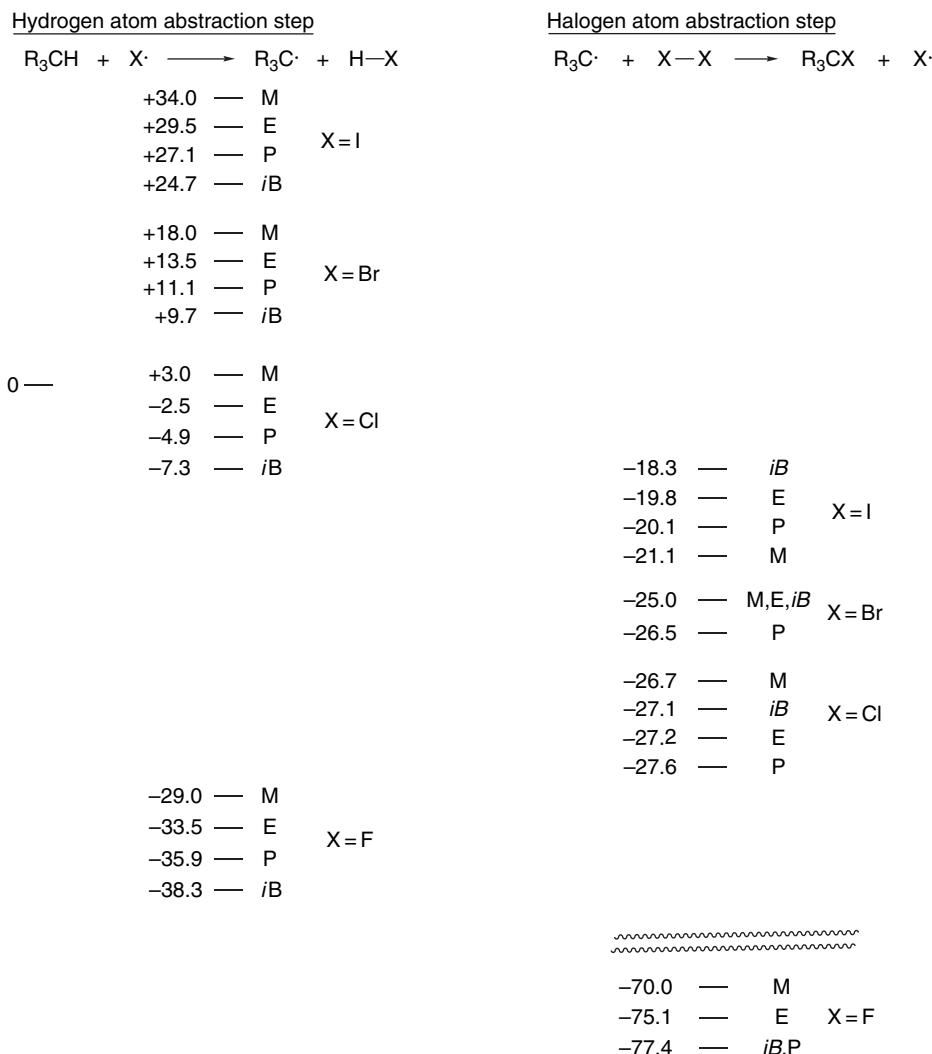
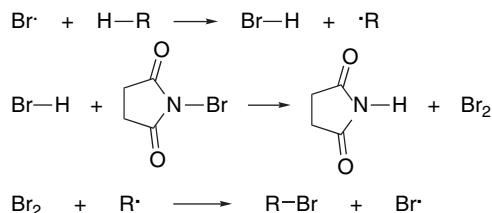


Fig. 11.12. Thermochemical relationships for steps in radical chain halogenation M = methane, E = ethane, P = propane, and iB = isobutane.

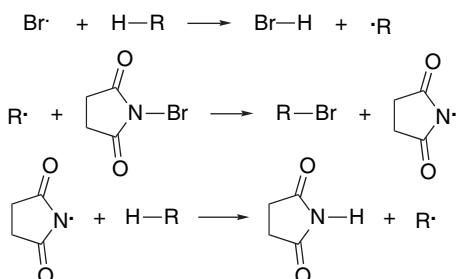
for NBS bromination.¹³³ Br₂ is maintained at a low concentration during the course of the reaction by formation from NBS and HBr.



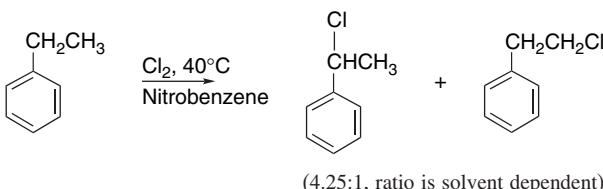
¹³³ R. E. Pearson and J. C. Martin, *J. Am. Chem. Soc.*, **85**, 354, 3142 (1963); G. A. Russell, C. DeBoer, and K. M. Desmond, *J. Am. Chem. Soc.*, **85**, 365 (1963); J. H. Incremona and J. C. Martin, *J. Am. Chem. Soc.*, **92**, 627 (1970); J. C. Day, M. J. Lindstrom, and P. S. Skell, *J. Am. Chem. Soc.*, **96**, 5616 (1974).

The fact that the Br_2 concentration remains at very low levels is important to the success of the allylic halogenation process. The allylic bromination of alkenes must compete with polar addition of bromine via a bromonium ion intermediate. The reactions differ in their dependence on bromine concentration. The allylic substitution is one-half order in bromine, whereas the addition reaction follows a first- or second-order dependence on $[\text{Br}_2]$ (see Section 5.3). Therefore a low concentration of Br_2 favors substitution over addition.¹³⁴

NBS can also be used to brominate alkanes. For example, cyclopropane, cyclopentane, and cyclohexane give the corresponding bromides when irradiated with NBS in dichloromethane.¹³⁵ Under these conditions, the succinimidyl radical appears to be involved as the hydrogen-abstrating intermediate.



Significant differences are seen with the reactions of the other halogens relative to bromination. In the case of chlorination, although the same chain mechanism is operative, there is a key difference in the *diminished selectivity of the chlorination*. For example, the *pri:tert* selectivity in 2,3-dimethylbutane for chlorination is 1:3.6 in typical solvents.¹³⁶ Owing to the greater reactivity of the chlorine atom, abstractions of primary, secondary, and tertiary hydrogens are all *exothermic* (see Figure 11.12). As a result of this exothermicity, the stability of the product radical has less influence on the E_a . In terms of the Hammond postulate (Section 3.3.2.2), the TS is expected to be more *reactant-like*. As an example of the low selectivity, ethylbenzene is chlorinated at both the methyl and the methylene positions, despite the much greater stability of the benzyl radical.¹³⁷



Isotope effect and relative rate studies also suggest an early TS for benzylic chlorination and bromination. The benzylic position is only moderately activated toward uncomplexed chlorine atoms. Relative to ethane, toluene reactivity is increased only by a factor of 3.3.¹³⁷ The kinetic isotope effect observed for bromination¹³⁸ and chlorination¹³⁹ of toluene suggest little rehybridization at the TS.

¹³⁴ C. C. Wamser and L. T. Scott, *J. Chem. Educ.*, **62**, 650 (1985); D. W. McMillen and J. B. Grutzner, *J. Org. Chem.*, **59**, 4516 (1994).

¹³⁵ J. G. Trayham and Y.-S. Lee, *J. Am. Chem. Soc.*, **96**, 3590 (1974).

¹³⁶ K. D. Raner, J. Lusztyk, and K. U. Ingold, *J. Org. Chem.*, **53**, 5220 (1988).

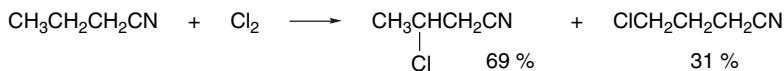
¹³⁷ G. A. Russell, A. Ito, and D. G. Hendry, *J. Am. Chem. Soc.*, **85**, 2976 (1963).

¹³⁸ R. P. Hanzlik, A. R. Schaefer, J. B. Moon, and C. M. Judson, *J. Am. Chem. Soc.*, **109**, 4926 (1987).

¹³⁹ K. B. Wiberg and L. H. Slaugh, *J. Am. Chem. Soc.*, **80**, 3033 (1958).

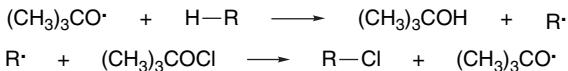
The selectivity of chlorination is influenced by solvents. For example, the chlorination of 2,3-dimethylbutane shows increased preference for the tertiary position in benzene.¹⁴⁰ The complexation with solvent attenuates the reactivity of chlorine atoms. Halogenated solvents also give evidence of complex formation. Brominated solvents lead to greater selectivity.¹⁴¹

Radical chlorination shows a substantial polar effect. Positions substituted by EWG are relatively unreactive toward chlorination, even though the substituents are capable of stabilizing the radical intermediate.¹⁴² For example, butanonitrile is chlorinated at C(3) and C(4), but not at C(2), despite the greater stability of the C(2) radical.



Similarly, carboxylic acid and ester groups tend to direct chlorination to the β - and γ -positions, because attack at the α -position is electronically disfavored. The polar effect is attributed to the fact that the chlorine atom is an electrophilic species, and the relatively electron-poor methylene group adjacent to the EWG is avoided. Because the chlorine atom is highly reactive, the reaction is expected to have a very early TS and the electrostatic effect predominates over the stabilizing effect of the substituent on the intermediate. The electrostatic effect is the dominant factor in the *kinetic selectivity* of the reaction and the relative stability of the radical intermediate has little influence.

Another reagent that effects chlorination by a radical mechanism is *t*-butyl hypochlorite. The hydrogen-abtracting species in the chain mechanism is the *t*-butoxy radical.



For this reason, selectivity and product composition is different from direct chlorination. The *t*-butoxy radical is intermediate in selectivity between chlorine and bromine atoms. The selectivity is also solvent and temperature dependent. A typical ratio in chlorobenzene as the solvent is *tert:sec:pri* = 60:10:1.¹⁴³

Radical substitution reactions by iodine are not practical because the abstraction of hydrogen from hydrocarbons by iodine is endothermic, even for stable radicals. The enthalpy of the overall reaction is also slightly endothermic (see Figure 11.12). Thus, both because of the kinetic problem precluding a chain reaction and an unfavorable equilibrium constant for substitution, iodination does not proceed by a radical chain mechanism.

Fluorination presents problems at the other extreme. Both steps in the substitution chain reaction are exothermic and the reaction is violent if not performed under

¹⁴⁰ G. A. Russell, *J. Am. Chem. Soc.*, **80**, 4987, 4997, 5002 (1958); C. Walling and M. F. Mayahi, *J. Am. Chem. Soc.*, **81**, 1485 (1959).

¹⁴¹ A. S. Dneprovskii, D. V. Kuznetsov, E. V. Eliseenkov, B. Fletcher, and J. M. Tanko, *J. Org. Chem.*, **63**, 8860 (1998).

¹⁴² A. Bruylants, M. Tits, C. Dieu, and R. Gauthier, *Bull. Soc. Chim. Belg.*, **61**, 266 (1952); A. Bruylants, M. Tits, and R. Danby, *Bull. Soc. Chim. Belg.*, **58**, 210 (1949); M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.*, **62**, 925 (1940).

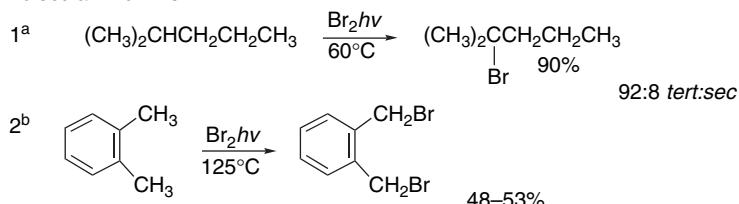
¹⁴³ C. Walling and P. J. Wagner, *J. Am. Chem. Soc.*, **86**, 3368 (1964).

carefully controlled conditions. Furthermore, fluorine atoms are capable of cleaving carbon-carbon bonds.

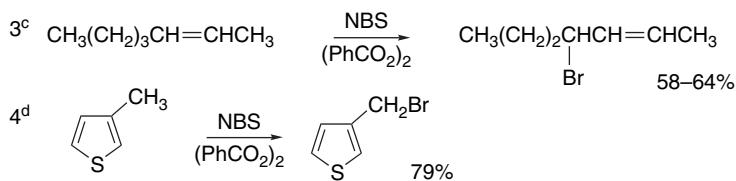
Saturated hydrocarbons such as neopentane, norbornane, and cyclooctane have been converted to the corresponding perfluoro derivatives in 10–20% yield by reaction

Scheme 11.4. Radical Chain Halogenation

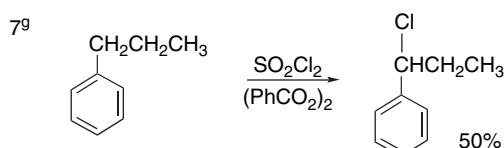
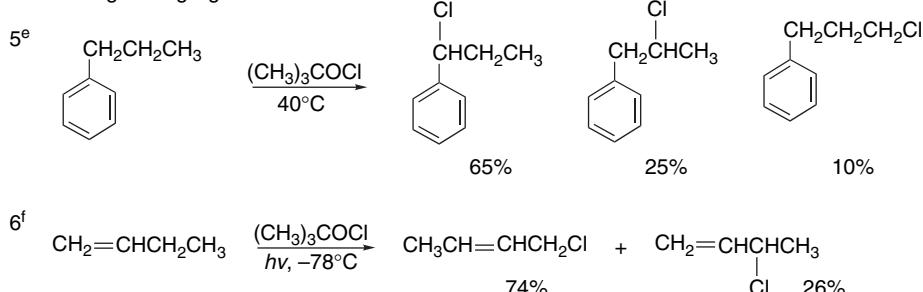
Molecular Bromine



N-Bromosuccinimide



Other Halogenating Agents



a. G. A. Russell and H. C. Brown, *J. Am. Chem. Soc.*, **77**, 4025 (1955).

b. E. F. M. Stephenson, *Org. Synth.*, **IV**, 984 (1963).

c. F. L. Greenwood, M. D. Kellert, and J. Sedlak, *Org. Synth.*, **IV**, 108 (1963).

d. E. Campagne and B. F. Tullar, *Org. Synth.*, **IV**, 921 (1963).

e. C. Walling and B. B. Jacknow, *J. Am. Chem. Soc.*, **82**, 6108 (1960).

f. C. Walling and W. Thaler, *J. Am. Chem. Soc.*, **83**, 3877 (1961).

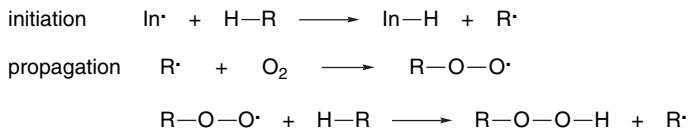
g. H. C. Brown and A. B. Ash, *J. Am. Chem. Soc.*, **77**, 4019 (1955).

with fluorine gas diluted with helium at -78°C .¹⁴⁴ Simple ethers can be completely fluorinated under similar conditions.¹⁴⁵ Crown polyethers can be fluorinated by passing a F_2/He stream over a solid mixture of sodium fluoride and the crown ether.¹⁴⁶ Liquid phase fluorination of hydrocarbons has also been observed, but the reaction is believed to be ionic, rather than radical, in character.¹⁴⁷

Scheme 11.4 illustrates some representative halogenation reactions. The reaction in Entry 1 was conducted by slow addition of bromine to excess 2-methylpentane at 60°C , with irradiation from a tungsten light bulb. The reaction in Entry 2 is a typical benzylic bromination, carried out at 125°C with irradiation from a sun lamp. Entries 3 and 4 are examples of NBS bromination using benzoyl peroxide as the initiator. Entry 3 is interesting in that none of the allylic isomer 2-bromo-3-heptene is found. Entries 5 and 6 are examples of chlorination by *t*-butyl hypochlorite in which the *t*-butoxy radical is the chain carrier. Note that in Entry 6, both the primary and secondary allylic products are formed. The reaction in Entry 7 uses sulfuryl chloride as the halogenation reagent. Note that in contrast to chlorination with Cl_2 (see p. 1021), the reaction shows selectivity for the benzylic position.

11.3.2. Oxygenation

Free radical chain oxidation of organic molecules by molecular oxygen is often referred to as *autoxidation*. The general mechanism is outlined below.



The reaction of oxygen with most radicals is very fast because of the triplet character of molecular oxygen (see Table 11.2, Entries 42 and 43). The ease of autoxidation is therefore governed by the rate of hydrogen abstraction in the second step of the propagation sequence. The alkylperoxyl radicals that act as the chain carriers are fairly selective. Positions that are relatively electron rich or provide particularly stable radicals are the most easily oxidized. Benzylic, allylic, and tertiary positions are the most susceptible to oxidation. This selectivity makes radical chain oxidation a preparatively useful reaction in some cases.

The reactivity of a series of hydrocarbons toward oxygen measured under a standard set of conditions gives some indication of the susceptibility of various structural units to autoxidation.¹⁴⁸ Table 11.9 gives the results for a series of hydrocarbons. These data indicate the activating effect of alkyl, vinyl, and phenyl substituents.

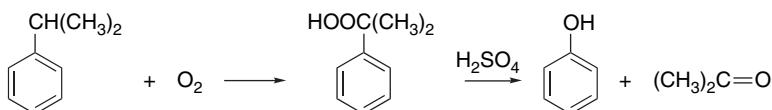
- ¹⁴⁴ N. J. Maraschin, D. B. Catsikis, L. H. Davis, G. Jarvinen, and R. J. Lagow, *J. Am. Chem. Soc.*, **97**, 513 (1975).
- ¹⁴⁵ D. F. Persico, H.-N. Huang, R. J. Lagow, Jr., and L. C. Clark, Jr., *J. Org. Chem.*, **50**, 5156 (1985).
- ¹⁴⁶ W.-H. Lin, W. I. Bailey, Jr., and R. J. Lagow, *J. Chem. Soc., Chem. Commun.*, 1350 (1985).
- ¹⁴⁷ C. Gal and S. Rozen, *Tetrahedron Lett.*, **25**, 449 (1984).
- ¹⁴⁸ G. A. Russell, *J. Am. Chem. Soc.*, **78**, 1047 (1956).

Table 11.9. Relative Reactivities of Some Aromatic Hydrocarbons toward Oxygen

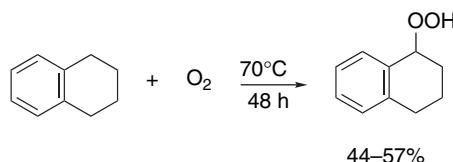
PhCH(CH ₃) ₂	1.0	PhCH ₂ CH ₃	0.18
PhCH ₂ CH=CH ₂	0.8	PhCH ₃	0.015
Ph ₂ CH ₂	0.35		

a. Data from G. A. Russell, *J. Am. Chem. Soc.*, **78**, 1047 (1956).

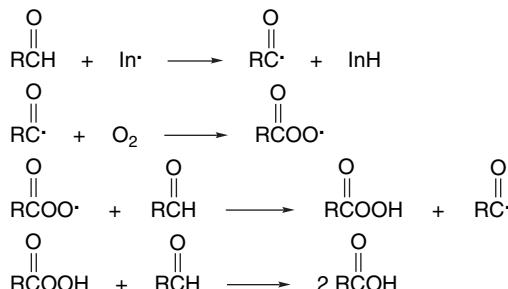
The best preparative results from autoxidation are obtained when only one relatively reactive hydrogen is available for abstraction. The oxidation of isopropylbenzene (cumene) is carried out on an industrial scale with the ultimate products being acetone and phenol.



The benzylic position in tetralin can be selectively oxidized to the hydroperoxide.¹⁴⁹



Functional groups that stabilize radicals are expected to increase susceptibility to autoxidation. This is illustrated by two cases that have been relatively well studied. Aldehydes, in which abstraction of the formyl hydrogen is facile, are easily autoxidized. The autoxidation initially forms a peroxy carboxylic acid, but usually the corresponding carboxylic acid is isolated because the peroxy acid oxidizes additional aldehyde in a parallel heterolytic reaction. The final step is an example of the Baeyer-Villiger reaction, which is discussed in Section 12.5.2.1 of Part B.



Similarly, the α -position in ethers is autoxidized quite readily to give α -hydroperoxy ethers.

¹⁴⁹ H. B. Knight and D. Swern, *Org. Synth.*, **IV**, 895 (1963).



This reaction is the cause of a widely recognized laboratory hazard. The peroxides formed from several commonly used ethers such as diethyl ether and tetrahydrofuran are explosive. Appreciable amounts of such peroxides can build up in ether samples that have been exposed to air. Since the hydroperoxides are less volatile than the ethers, they are concentrated by evaporation or distillation and the concentrated peroxide solutions may explode. For this reason, storage of ethers that have been exposed to oxygen is extremely hazardous.

11.4. Free Radical Addition Reactions

11.4.1. Addition of Hydrogen Halides

As with halogen substitution, thermochemical relationships impose limits on free radical chain addition reactions of the hydrogen halides. These relationships are summarized in Figure 11.13. There are significant endothermic steps for HF and HI and a slightly endothermic step for HCl. Radical chain additions of hydrogen fluoride and hydrogen iodide to alkenes are not observed. In the case of hydrogen iodide, the addition of an iodine atom to an alkene is an endothermic process and is too slow to permit a chain reaction, even though the hydrogen abstraction step is favorable. In the case of hydrogen fluoride, the abstraction of hydrogen from hydrogen fluoride is energetically prohibitive. Only in the case of HBr is the thermochemistry consistent with a radical chain process. The HBr addition has one thermal neutral step and an

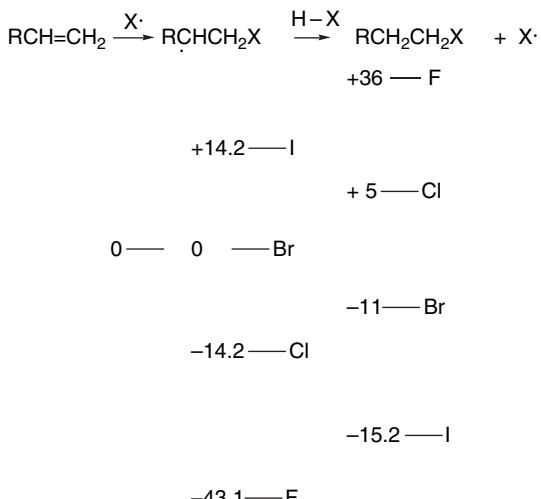
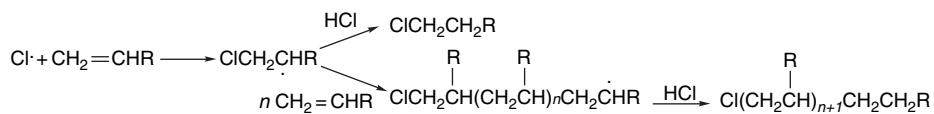
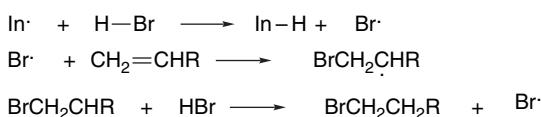


Fig. 11.13. Thermochemistry for the steps in radical chain additions of the hydrogen halides to alkenes. The C=C and C-H bond energies were taken as 70 and 98 kcal/mol, respectively, and primary C-X bond energies were used.

exothermic step. Because of the relatively slow second step, polymerization competes with addition of the hydrogen halide in the case of HCl.

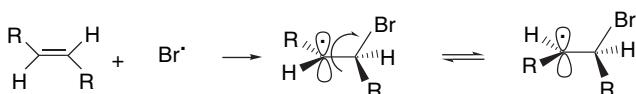


The reaction with HBr is also significant in terms of regiochemistry. The reaction results in the anti-Markovnikov orientation, with the bromine adding to the less-substituted carbon of the double bond. The anti-Markovnikov addition of HBr to alkenes was one of the earliest free radical reactions to be put on a firm mechanistic basis. In the presence of a suitable initiator, such as a peroxide, a radical chain mechanism becomes competitive with the ionic mechanism for addition of HBr.



The bromine atom adds to the less-substituted carbon of the double bond, generating the more stable radical intermediate. The regioselectivity of radical chain hydrobromination is opposite to that of ionic addition. (See Section 5.3 for discussion of the ionic mechanism.) The early work on the radical mechanism of addition of HBr was undertaken to understand why Markovnikov's rule was violated under certain circumstances. The cause was found to be conditions that initiated the radical chain process, such as peroxide impurities or light. Some examples of radical chain additions of hydrogen bromide to alkenes are discussed in Section 11.4.5.

The stereochemistry of radical addition of hydrogen bromide to alkenes has been studied with both acyclic and cyclic alkenes.¹⁵⁰ *Anti* addition is favored.^{151, 152} This is contrary to what would be expected if the sp^2 carbon of the radical intermediate was rapidly rotating or inverting with respect to the remainder of the molecule, which should result in stereorandomization and a mixture of *syn* and *anti* products.



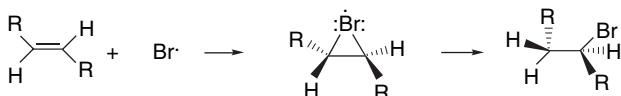
The stereoselectivity of the radical addition can be explained in terms of a bridged structure similar to that involved in ionic bromination of alkenes.¹⁵³

¹⁵⁰ B. A. Bohm and P. I. Abell, *Chem. Rev.*, **62**, 599 (1962).

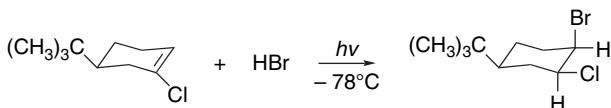
¹⁵¹ P. S. Skell and P. K. Freeman, *J. Org. Chem.*, **29**, 2524 (1964).

¹⁵² H. L. Goering and D. W. Larsen, *J. Am. Chem. Soc.*, **81**, 5937 (1959).

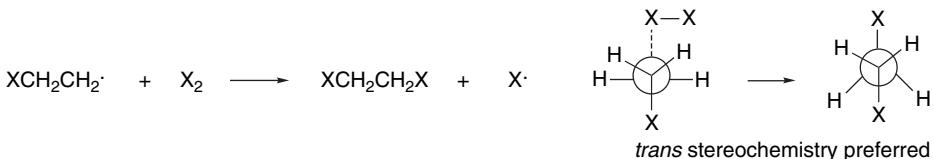
¹⁵³ P. S. Skell and J. G. Traynham, *Acc. Chem. Res.*, **17**, 160 (1984).



trans-Diaxial addition is the preferred stereochemical mode for addition to cyclohexene and its derivatives.¹⁵⁴ This stereochemistry, too, can be explained in terms of a bromine-bridged intermediate.



The issue of the role of bridged radicals in the stereochemistry of halogenation has recently been examined computationally and a new interpretation offered.¹⁵⁵ The structure, rotational barriers, and E_a for halogen atom abstraction for β -haloethyl radicals were studied. For the reactions where X=Cl or Br, the halogen atom abstraction reaction shows a preference for a *trans* TS.



The results also indicate that the chlorine and bromine abstraction steps are faster than rotational equilibration, so the stereochemistry can be explained without requiring a bridged radical.

The nature of bridging and migration involving chlorine has been explored computationally for the 3-chloro-2-butyl radical.¹⁵⁶ BHLYP/aug-cc-pVDZ calculations found an open radical to be the most stable form. The symmetrically bridged radical is a TS for chlorine atom migration. The energy of the TS varied from 2.4 to 7.0 kcal/mol, depending on the computational method. The methods also give differing values for the barrier to single-bond rotation. The chlorine has considerable negative charge ($-0.351e$) in the bridged radical, compared to the open radical ($-0.189e$) by NPA analysis. The spin density also increases at chlorine in the TS. These results suggest partial heterolytic character for the migration. The energy profile for rotation and migration derived from the BHLYP energies is given in Figure 11.14.

In contrast to the β -chloro radical, bromine-bridged radicals are calculated to be stable relative to open radicals at the MP2/6-31G** and B3LYP/6-31G** level of computation.¹⁵⁷ The 2-fluoroethyl radical shows no bridging and only a low barrier to single-bond rotation (<0.5 kcal/mol). Bridging was also found to be unfavorable for the other second-row substituents OH and NH₂.¹⁵⁸ These computational results suggest that significant bridging is to be expected in β -bromo radicals, whereas β -chloro radicals should be subject to facile 1,2-migration.

¹⁵⁴ H. L. Goering and L. L. Sims, *J. Am. Chem. Soc.*, **77**, 3465 (1955); N. A. LeBel, R. F. Czaja, and A. DeBoer, *J. Org. Chem.*, **34**, 3112 (1969); P. D. Readis and P. S. Skell, *J. Org. Chem.*, **31**, 753 (1966); H. L. Goering, P. I. Abell, and B. F. Aycock, *J. Am. Chem. Soc.*, **74**, 3588 (1952).

¹⁵⁵ Z.-H. Li, K.-N. Fan, and M. W. Wong, *J. Phys. Chem. A*, **105**, 10890 (2001).

¹⁵⁶ B. Neumann and H. Zipse, *Org. Biomol. Chem.*, **1**, 168 (2003).

¹⁵⁷ H. Ihee, A. H. Zewail, and W. A. Goddard, III, *J. Phys. Chem. A*, **103**, 6638 (1999).

¹⁵⁸ M. Guerra, *J. Am. Chem. Soc.*, **114**, 2077 (1992).

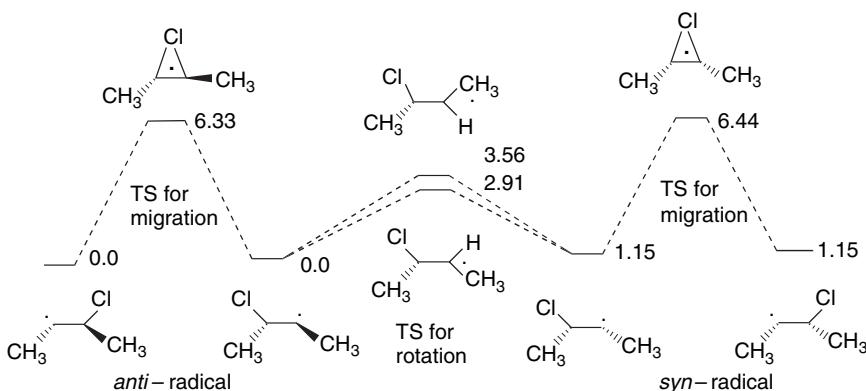
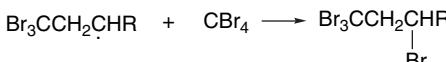


Fig. 11.14. Energy profile for chlorine migration and rotation in the 3-chloro-2-butyl radical.

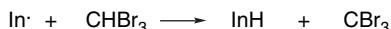
11.4.2. Addition of Halomethanes

One of the oldest preparative free radical reactions is the addition of polyhalomethanes to alkenes. Examples of addition of carbon tetrabromide, carbon tetrachloride, and bromoform have been recorded.¹⁵⁹ The reactions are chain processes that depend on facile abstraction of halogen or hydrogen from the halomethane.

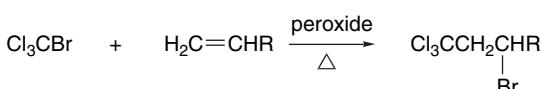
ADDITION OF TETRABROMOMETHANE



ADDITION OF TRIBROMOMETHANE

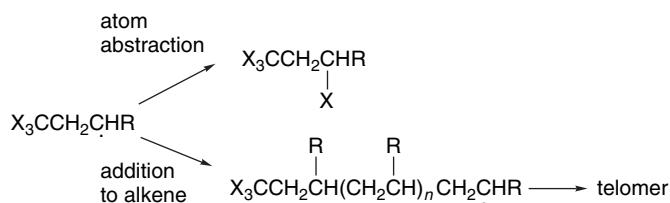


Bromotrichloromethane can also be used effectively in the addition reaction. Because of the preferential abstraction of bromine, a trichloromethyl unit is added to the less-substituted carbon atom of the alkene.

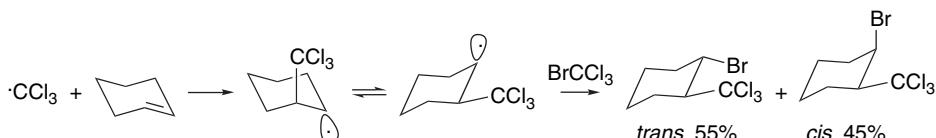


The order of reactivity of the halomethanes is $\text{CBr}_4 > \text{CBrCl}_3 > \text{CCl}_4 > \text{CH}_2\text{Cl}_2 > \text{CHCl}_3$. The efficiency of 1:1 addition for a given alkene also depends on the ease with which it undergoes radical chain polymerization, since polymerization can compete with the halogen atom abstraction step in the chain mechanism. Polymerization is usually most rapid for terminal alkenes bearing stabilizing substituents such as a phenyl or ester group.

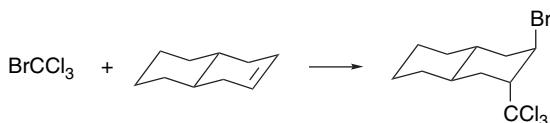
¹⁵⁹ E. Sosnovsky, *Free Radical Reactions in Preparative Organic Chemistry*, Macmillan, New York, 1964, Chap. 2.



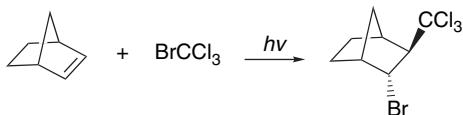
The addition of bromotrichloromethane to cyclohexene gives a nearly 1:1 mixture of the two possible stereoisomers.¹⁶⁰



This result indicates that the initially added trichloromethyl group has little influence on the stereochemistry of the subsequent bromine atom abstraction. The intermediate 2-(trichloromethyl)cyclohexyl radical presumably relaxes to the equatorial conformation faster than the occurrence of bromine atom abstraction, and there is little preference for axial or equatorial approach. In contrast, with $\Delta^{2,3}$ -octahydronaphthalene, the addition is exclusively *trans*-diaxial.



The *trans*-fused decalin system is conformationally rigid and the stereochemistry of the product indicates that the initial addition of the trichloromethyl radical is from an axial direction. This is expected on stereoelectronic grounds because the radical should initially interact with the π^* orbital. The axial trichloromethyl group then shields the adjacent radical position and directs the bromine abstraction in the *trans* sense. Addition of bromotrichloromethane to norbornene is also *anti*. This is again the result of steric shielding by the trichloromethyl group, which causes the bromine atom to be abstracted from the *endo* face of the intermediate radical.

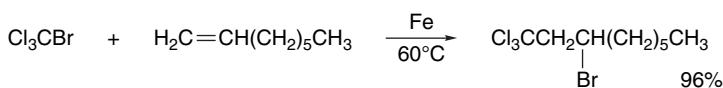


The addition of bromotrichloromethane to terminal alkenes occurs in reasonable yield in THF without the addition of a specific initiator.¹⁶¹ Bromotrichloromethane additions are effectively catalyzed by Fe(0), which acts as an initiator by one-electron reduction.¹⁶²

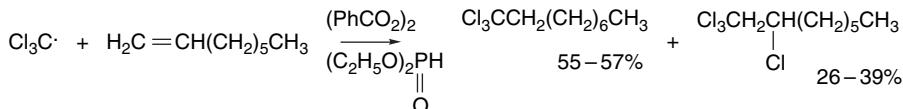
¹⁶⁰ J. G. Traynham, A. G. Lane, and N. S. Bhacca, *J. Org. Chem.*, **34**, 1302 (1969).

¹⁶¹ M. Heintz, G. L. Ny, and J. Y. Nedelec, *Tetrahedron Lett.*, **25**, 5767 (1984).

¹⁶² F. Bellesia, L. Forti, F. Ghelfi, and U. M. Pagnoni, *Synth. Commun.*, **27**, 961 (1997).

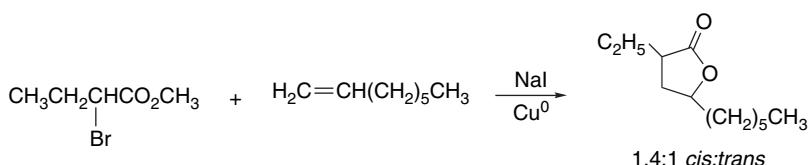


The combination of CCl_4 and diethyl phosphite with a peroxide initiator gives competitive addition of $\text{H}-\text{CCl}_3$. In this case the phosphite acts as a hydrogen donor.¹⁶³



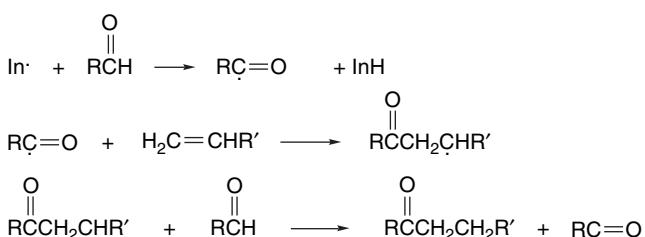
Section 11.4.5 provides some other examples of additions of tetrahalomethanes.

There are examples of other halomethanes that can undergo radical addition. α -Haloesters have been successfully added to alkenes in the presence of copper metal. The copper serves as an electron transfer initiator. The γ -haloester adduct cyclizes to a lactone. The reaction works best when NaI is also used to convert the bromide to the more reactive iodide.¹⁶⁴



11.4.3. Addition of Other Carbon Radicals

Other functional groups provide sufficient stabilization of radicals to permit successful chain additions to alkenes. Acyl radicals are formed by abstraction of the formyl hydrogen from aldehydes. As indicated in Table 3.17 (p. 315), the acyl radicals are somewhat stabilized. The C–H BDE for acetaldehyde, which is 88.3 kcal/mol, decreases slightly with additional substitution but increases for CF_3 .¹⁶⁵ The chain process results in formation of a ketone by addition of the aldehyde to an alkene



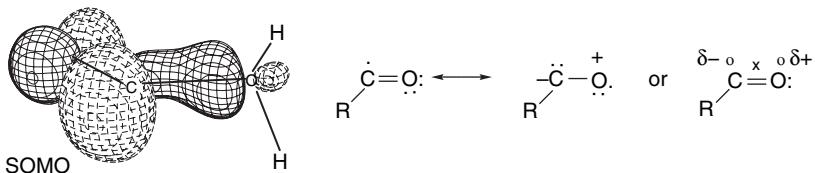
Acyl radicals are strongly bent with a nearly trigonal angle, according to MP2/6-31G* computations. The C=O bond length is just under 1.200 Å, somewhat shorter than a normal carbonyl bond. The SOMO orbital is in the plane of the molecule and

¹⁶³ J. M. Barks, B. C. Gilbert, A. F. Parsons, and B. Upendran, *Synlett*, 1719 (2001).

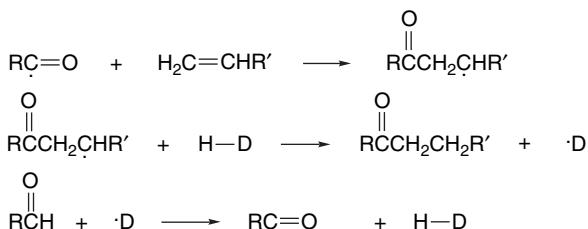
¹⁶⁴ J. O. Metzger, R. Mahler, and G. Franke, *Liebigs Ann. Recueil*, 2303 (1997).

¹⁶⁵ B. Viskolcz and T. Berces, *Phys. Chem. Chem. Phys.*, **2**, 5430 (2000); C. W. Bauschlicher, Jr., *J. Chem. Phys.*, **98**, 2564 (1994).

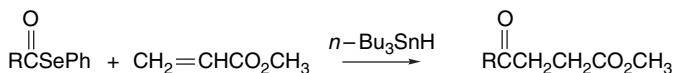
centered mainly on carbon, but also on the oxygen.¹⁶⁶ Acyl radicals are *nucleophilic*, based on their reactivity toward protonated heterocyclic molecules.¹⁶⁷ The acyl radical is isoelectronic with $\text{N}\dot{=}\text{O}$ and a similar Linnett structure can be drawn.



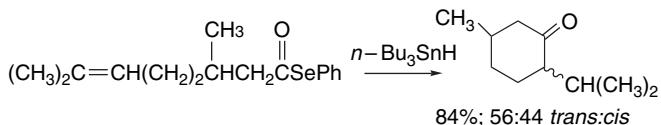
The efficiency of aldehyde additions can be improved by adding an alternative hydrogen atom donor, such as methyl thioglycolate or *N*-hydroxysuccinimide.¹⁶⁸



Acyl radicals can also be generated from acyl selenides and *tri-n*-butylstannane.¹⁶⁶



Intramolecular versions of this reaction have been used to form both common and macrocyclic rings.



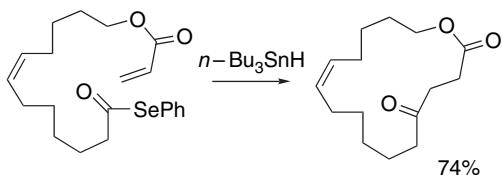
The latter reactions are carried out under high-dilution conditions and require an activating EWG substituent.¹⁶⁹

¹⁶⁶ D. L. Boger and R. J. Mathvink, *J. Org. Chem.*, **57**, 1429 (1992).

¹⁶⁷ M. Bellatti, T. Caronna, A. Citterio, and F. Minisci, *J. Chem. Soc., Perkin Trans. 2*, 1835 (1976); F. Minisci, *Top. Current Chem.*, **62**, 1 (1976).

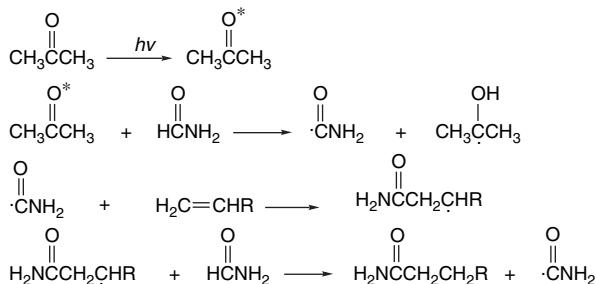
¹⁶⁸ V. Paul, B. P. Roberts, and C. R. Willis, *J. Chem. Soc., Perkin Trans. 2*, 1953 (1989); S. Tsujimoto, I. Iwahama, S. Sakaguchi, and Y. Ishii, *Chem. Commun.*, 2352 (2001); S. Tsujimoto, S. Sakaguchi, and Y. Ishii, *Tetrahedron Lett.*, **44**, 5601 (2003).

¹⁶⁹ D. L. Boger and R. J. Mathvink, *J. Am. Chem. Soc.*, **112**, 4008 (1990).



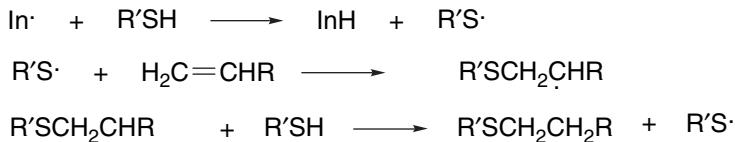
Some other examples of acyl radical additions are discussed in Section 11.4.5.

The chain addition of formamide to alkenes is a closely related reaction and results in the formation of primary amides.¹⁷⁰ The reaction is carried out with irradiation in acetone. The photoexcited acetone initiates the chain reaction by abstracting hydrogen from formamide.



11.4.4. Addition of Thiols and Thiocarboxylic Acids

The addition of S–H compounds to alkenes by a radical chain mechanism is a quite general and efficient reaction.¹⁷¹ The mechanism is analogous to that for hydrogen bromide addition. The energetics of both the hydrogen abstraction and addition steps are favorable. The reaction exhibits anti-Markovnikov regioselectivity.



The preferred stereochemistry of addition to cyclic alkenes is *anti*,¹⁷² but the additions are not as highly stereoselective as for hydrogen bromide addition.

11.4.5. Examples of Radical Addition Reactions

Scheme 11.5 gives some examples of these radical addition reactions. Entries 1 to 3 show anti-Markovnikov addition of HBr. The reaction in Entry 1 was carried out by passing HBr gas into the alkene, using benzoyl peroxide as the initiator, apparently near room temperature. Entry 2 is an example of anti-Markovnikov addition to

¹⁷⁰ D. Elad and J. Rokach, *J. Org. Chem.*, **29**, 1855 (1964).

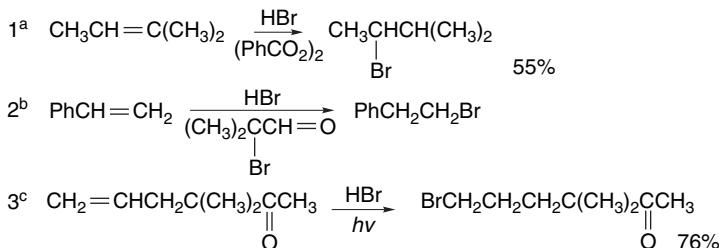
¹⁷¹ K. Griesbaum, *Angew. Chem. Int. Ed. Engl.*, **9**, 273 (1970).

¹⁷² N. A. LeBel, R. F. Czaja, and A. DeBoer, *J. Org. Chem.*, **34**, 3112 (1969); P. D. Readio and P. S. Skell, *J. Org. Chem.*, **31**, 759 (1966); F. G. Bordwell, P. S. Landis, and G. S. Whitney, *J. Org. Chem.*, **30**, 3764 (1965); E. S. Huyser, H. Benson, and H. J. Sinnige, *J. Org. Chem.*, **32**, 622 (1962).

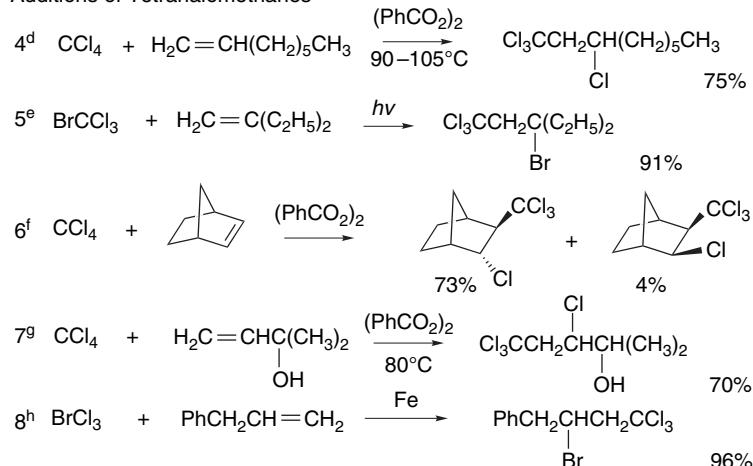
styrene. The α -bromoaldehyde additive was shown to increase the regioselectivity. A similar effect has been noted for PBr_3 ,¹⁷³ but the mechanistic basis is not established in either case. The reaction in Entry 3 was carried out under irradiation from

Scheme 11.5. Free Radical Additions to Alkenes

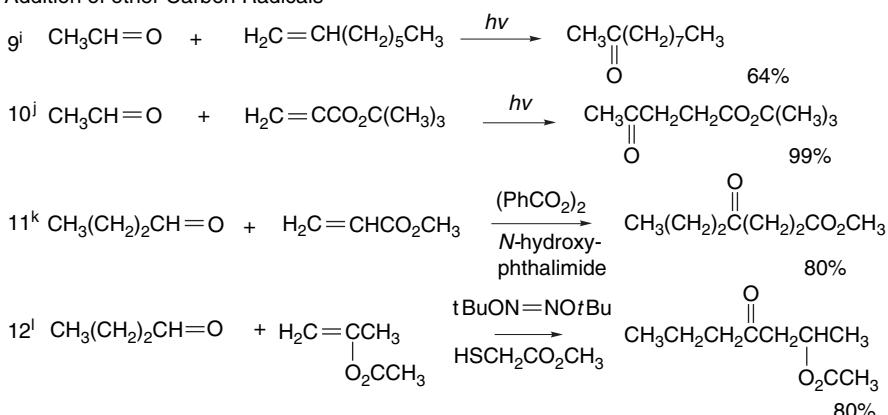
A. Addition of Hydrogen Bromide



B. Additions of Tetrahalomethanes

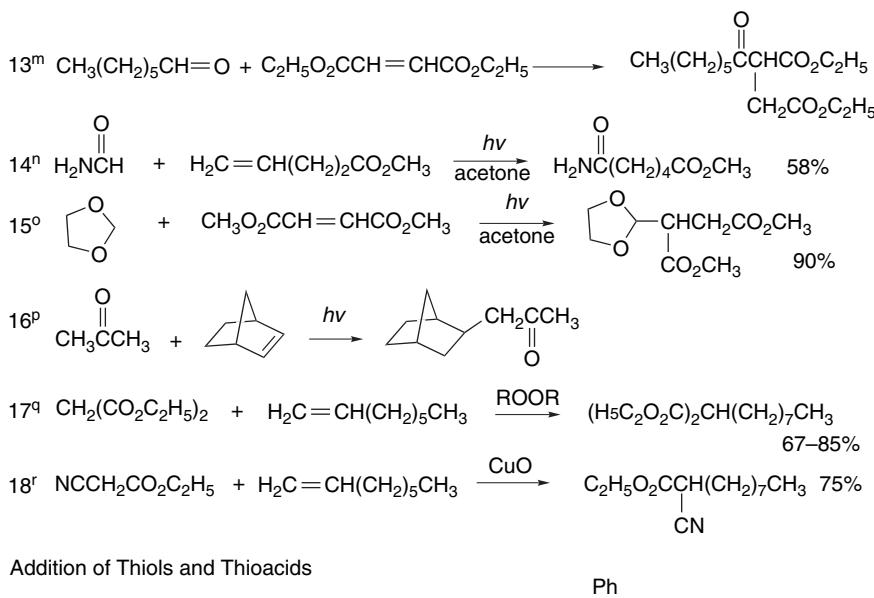


C. Addition of other Carbon Radicals

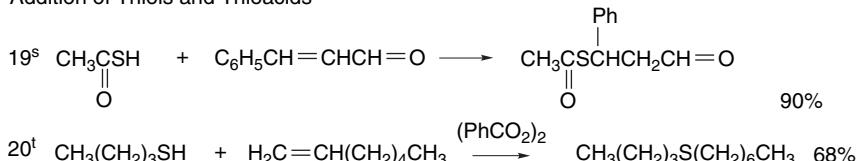


(Continued)

^{173.} G. A. Olah and T. R. Hockswender, Jr., *J. Org. Chem.*, **39**, 3478 (1974).



D. Addition of Thiols and Thioacids

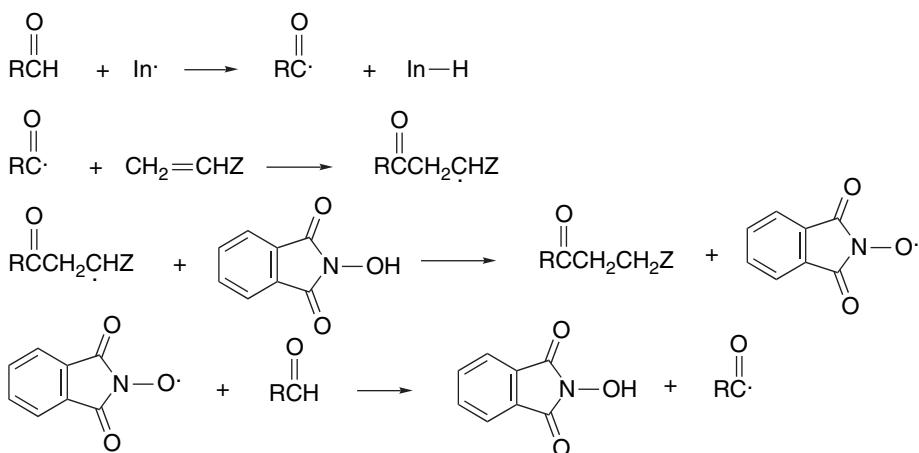


- a. W. J. Bailey and S. S. Hirsch, *J. Org. Chem.*, **28**, 2894 (1963).
 b. R. Neumann, F. de la Vega, and A. Bar-On, *J. Org. Chem.*, **60**, 1315 (1995).
 c. H. O. House, C.-Y. Chu, W. V. Phillips, T. S. B. Sayer, and C.-C. Yau, *J. Org. Chem.*, **42**, 1709 (1977).
 d. M. S. Kharasch, E. W. Jensen, and W. H. Urry, *J. Am. Chem. Soc.*, **69**, 1100 (1947).
 e. M. S. Kharasch and M. Sage, *J. Org. Chem.*, **14**, 537 (1949).
 f. C. L. Osborn, T. V. Van Auken, and D. J. Trecker, *J. Am. Chem. Soc.*, **90**, 5806 (1968).
 g. P. D. Klemmensen, H. Kolind-Andersen, H. B. Madsen, and A. Svendsen, *J. Org. Chem.*, **44**, 416 (1979).
 h. F. Bellesia, L. Forti, F. Ghelfi, and U. M. Pagnoni, *Synth. Commun.*, **27**, 961 (1997).
 i. M. S. Kharasch, W. H. Urry, and B. M. Kuderna, *J. Org. Chem.*, **14**, 248 (1949).
 j. E. C. Macias, J. M. G. Molinillo, G. M. Massanet, and F. Rodriguez-Luis, *Tetrahedron*, **48**, 3345 (1992).
 k. S. Tsushima, S. Sakaguchi, and Y. Ishii, *Tetrahedron Lett.*, **44**, 5601 (2003).
 l. H.-S. Dang and B. P. Roberts, *J. Chem. Soc. Perkin Trans. I*, 67 (1998).
 m. T. M. Patrick, Jr., and F. B. Erickson, *Org. Synth.*, **IV**, 430 (1963).
 n. D. Elad and J. Rokach, *J. Org. Chem.*, **29**, 1855 (1964).
 o. I. Rosenthal and D. Elad, *J. Org. Chem.*, **33**, 805 (1968).
 p. W. Reusch, *J. Org. Chem.*, **27**, 1882 (1962).
 q. J. C. Allen, J. I. G. Cadogan, B. W. Harris, and D. H. Hey, *J. Chem. Soc.*, 4468 (1962).
 r. A. Hajek and J. Malek, *Synthesis*, 454 (1977).
 s. R. Brown, W. E. Jones, and A. R. Pinder, *J. Chem. Soc.*, 2123 (1951).
 t. D. W. Grattan, J. M. Locke, and S. R. Wallis, *J. Chem. Soc., Perkin Trans. I*, 2264 (1973).

a mercury lamp. Entries 4 to 8 involve additions of tetrahalomethanes. In Entry 4 the ratio of reactants was 1.00 CCl_4 , 0.33 alkene, and 0.02 peroxide. Similar ratios were used in Entries 6 and 7. Entry 5 was done with irradiation from a mercury lamp. Entry 6 demonstrates the exclusive *exo* addition of the trichloromethyl radical and dominant *endo* abstraction of chlorine. Entry 8 is an example of a recently developed procedure in which iron powder acts both as an initiator and catalyst.

Entries 9 to 16 show additions of various carbon radicals. Entry 9 involves addition of acetaldehyde to a terminal alkene. The reaction was done under mercury

lamp irradiation and the conversion was rather low. Higher yields were obtained using heptanal. Entries 10 and 11 demonstrate that alkenes with EWG substituents are suitable reactants, which is consistent with the nucleophilic character of acyl radicals. The reaction in Entry 10 was carried out under irradiation from a mercury lamp. These reactions were found to be facilitated by O₂, which is thought to be involved in the initiation phase of the reaction. Entry 11 uses *N*-hydroxyphthalimide as the chain transfer agent in a process called *polarity reversal catalysis*. The adduct radical abstracts hydrogen from *N*-hydroxyphthalimide. The resulting radical is much more reactive toward hydrogen abstraction from the aldehyde than is the adduct radical. In the example cited, the ratio of reactants used was aldehyde 7.5, alkene 1.0, *N*-hydroxyphthalimide 0.1, benzoyl peroxide 0.1.



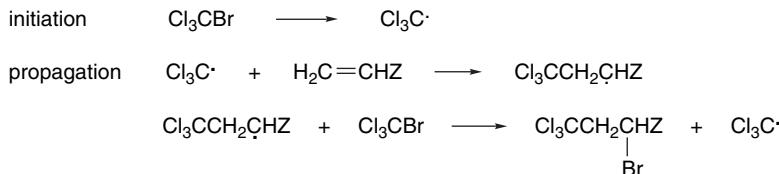
The reaction in Entry 12 is related and uses thioglycolate esters as a chain transfer agent. In this particular reaction involving an electron-rich alkene, the yield is only 8% in the absence of the thioglycolate. Entry 13 is another example of the addition of an acyl radical to relatively electrophilic alkene. Entry 14, involving the addition of formamide was done with acetone photosensitization. The 2-dioxolanyl radical involved in Entry 15 would be expected to be nucleophilic in character and higher yields were obtained with diethyl maleate than with typical terminal alkenes. The addition of 1,3-dioxolane to various enones has been done using benzophenone sensitization.¹⁷⁴ The radicals in Entries 17 and 18 are electrophilic in character. Entries 19 and 20 are examples of thiol additions.

Intramolecular addition reactions are quite common when radicals are generated in molecules with unsaturation in a sterically favorable position.¹⁷⁵ We will encounter several examples of intramolecular additions in the next section. Cyclization reactions based on intramolecular addition of radical intermediates are synthetically useful and several specific cases are considered in Section 10.3.3 of Part B.

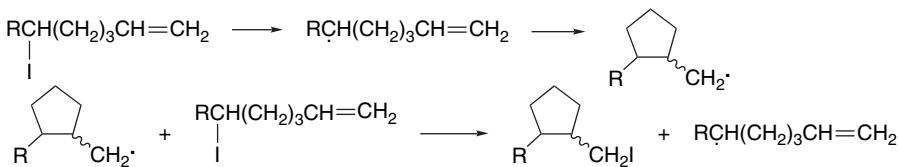
¹⁷⁴. C. Manfrotto, M. Mella, M. Freccero, M. Fagnoni, and A. Albini, *J. Org. Chem.*, **64**, 5024 (1999).

¹⁷⁵. A. L. J. Beckwith, *Tetrahedron*, **37**, 3073 (1981).

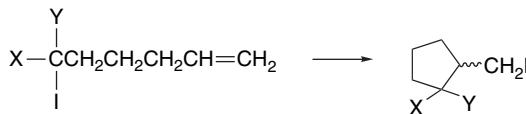
Other atoms and groups apart from hydrogen are susceptible to abstraction by free radicals. The most important from a synthetic point of view are bromine, iodine, sulfur, and selenium substituents.¹⁷⁶ Group transfer reactions can occur inter- or intramolecularly. Indeed, we have already encountered one example in the addition of polyhalogenated methanes to alkenes. The chain is propagated by a bromine atom transfer.



Cyclizations involving iodine atom transfers have been developed, and among the most effective examples are reactions involving the cyclization of 6-iodohexene derivatives.¹⁷⁷ The 6-hexenyl radical generated by iodine atom abstraction rapidly cyclizes to a cyclopentylmethyl radical. The chain is propagated by iodine atom transfer.



Various functionalized derivatives can be cyclized, including α -idoesters, α -iodoketones, and α -iodomalonates.¹⁷⁸ These substituents make the radical more electrophilic and reactive toward the alkene and also facilitate the iodine abstraction step.



Similarly, 6-iodoalkyne derivatives cyclize to iodomethylenecyclopentanes.¹⁷⁹ The chain is propagated by abstraction of iodine by the cyclized vinyl radical intermediate.

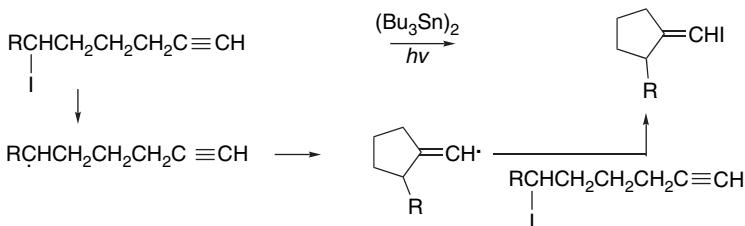
¹⁷⁶ J. Byers, in *Radicals in Organic Synthesis*, P. Renaud and M. P. Sibi, eds., Wiley-VCH, Weinheim, 2001, Vol. 1, Chap. 1.5.

¹⁷⁷ D. P. Curran and D. Kim, *Tetrahedron Lett.*, **27**, 5821 (1986).

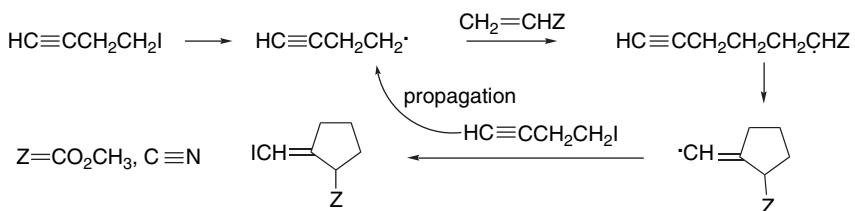
¹⁷⁸ D. P. Curran and C. T. Chang, *Tetrahedron Lett.*, **28**, 2477 (1987).

¹⁷⁹ D. P. Curran, M.-H. Chen, and D. Kim, *J. Am. Chem. Soc.*, **108**, 2489 (1986).

This sequence of reactions benefits from the high reactivity of the intermediate alkenyl reaction in the iodine transfer step.

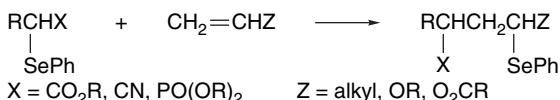


The hexabutyldistannane used in this reaction is not involved in the propagation sequence but may be involved in initiation or scavenging of potential chain termination radicals. With 4-iodobutyne, the intermediate radicals can be trapped by activated alkenes, which leads to cyclized products.¹⁸⁰



For all of these reactions, the reagents and reaction conditions must be chosen to meet the fundamental requirement for successful chain reactions. Each step in the sequence must be fast and exothermic to permit chain propagation.¹⁸¹

Aryl selenides have also proven to be excellent reagents in group transfer reactions.¹⁸² Photolysis of selenides in an inert solvent such as benzene can initiate chain reactions. Various substituted radicals can be generated in this manner by using α -selenenyl derivatives of esters,¹⁸³ nitriles,¹⁸⁴ malonates,¹⁸⁵ β -ketoesters,¹⁸³ α -methoxyesters,¹⁸⁶ and phosphonates.¹⁸⁷ The resulting radicals undergo addition to alkenes to generate γ -seleno derivatives.



¹⁸⁰ D. P. Curran and M.-H. Chen, *J. Am. Chem. Soc.*, **109**, 6558 (1987).

¹⁸¹ D. P. Curran, *Synthesis*, 417, 511 (1988); C. P. Jasperse, D. P. Curran, and T. L. Fervig, *Chem. Rev.*, **91**, 1237 (1991).

¹⁸² L. Castle and M. J. Perkins, in *The Chemistry of Organic Selenium and Tellurium Compounds*, Part 2, S. Patai, ed., Wiley, Chichester, 1987, Chap. 16.

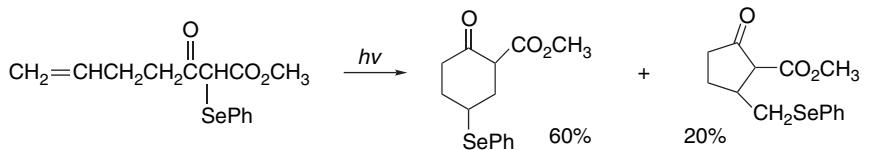
¹⁸³ J. H. Byers and B. C. Harper, *Tetrahedron Lett.*, **33**, 6953 (1992).

¹⁸⁴ D. P. Curran and G. Thoma, *J. Am. Chem. Soc.*, **114**, 4436 (1992).

¹⁸⁵ J. H. Byers and G. C. Lane, *J. Org. Chem.*, **58**, 3355 (1993).

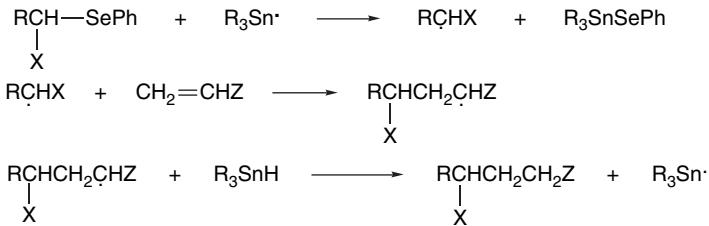
¹⁸⁶ P. Renaud and S. Abazi, *Synthesis*, 253 (1996).

¹⁸⁷ P. Balczewski, W. M. Pietrzykowski, and M. Mikolajczyk, *Tetrahedron*, **51**, 7727 (1995); J. H. Byers, J. G. Thissell, and M. A. Thomas, *Tetrahedron Lett.*, **36**, 6403 (1995).

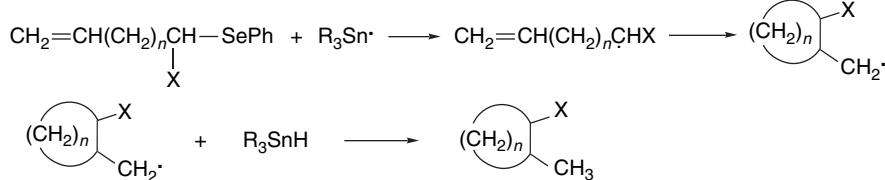


If selenide additions are carried out in the presence of tri-*n*-butylstannane, the radical generated by addition is reduced by hydrogen abstraction. The chain is then continued by selenide abstraction by the stanny radical, which leads to reduced addition and cyclization products.

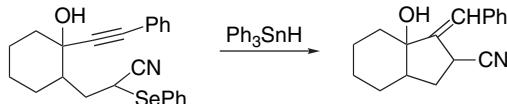
Intermolecular addition:



Intramolecular addition:

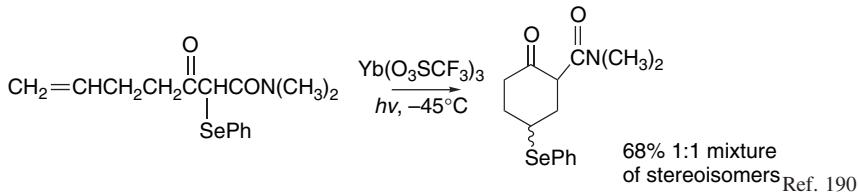


This reaction can also be applied to alkynes.



Ref. 189

Certain of these phenylselenenyl radical transfer reactions are catalyzed by Lewis acids. The regioselectivity depends on reactant structure, and related compounds give 5-*exo* and 7-*endo* products. The catalysis is believed to be the result of complexation at the carbonyl, which enhances the electrophilicity of the radical.



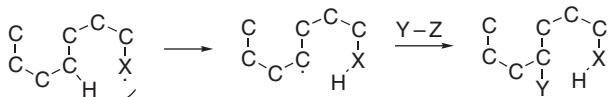
¹⁸⁸ J. H. Byers, T. G. Gleason, and K. S. Knight, *J. Chem. Soc., Chem. Commun.*, 354 (1991).

¹⁸⁹ D. J. L. Clive, T. L. B. Boivin, and A. G. Angoh, *J. Org. Chem.*, **52**, 4943 (1982).

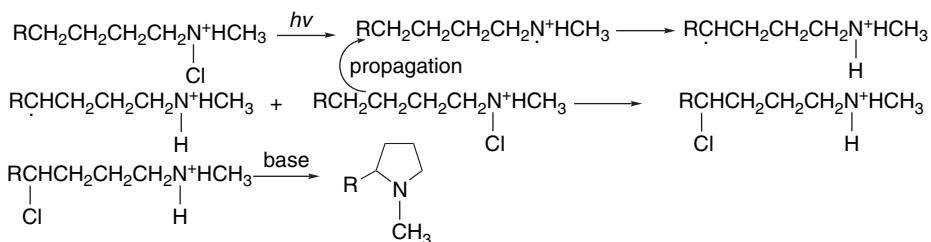
¹⁹⁰ D. Yang, Q. Gao, and O.-Y. Lee, *Org. Lett.*, **4**, 1239 (2002).

11.5.2. Intramolecular Hydrogen Atom Transfer Reactions

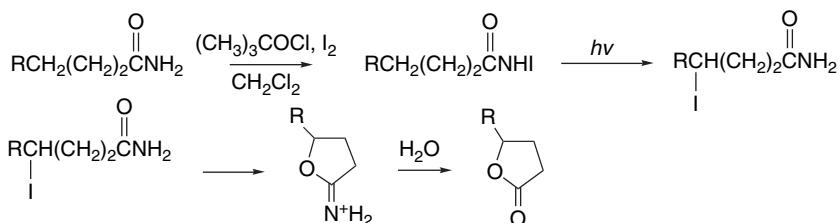
We have seen that substitution, addition, and group transfer reactions can occur intramolecularly. Intramolecular substitution reactions that involve hydrogen abstraction have some unique synthetic applications because they permit functionalization of carbon atoms relatively remote from the initial reaction site.¹⁹¹ The preference for a six-membered cyclic TS in the hydrogen abstraction step imparts position selectivity to the process.



There are several reaction sequences that involve such intramolecular hydrogen abstraction steps. One example is the photolytically initiated decomposition of *N*-haloamines in acidic solution, which is known as the *Hofmann-Loeffler reaction*.¹⁹² The reaction leads to γ -haloamines, but these are usually converted to pyrrolidines by intramolecular nucleophilic substitution.



There are related procedures involving *N*-haloamides that lead to lactones via iminolactone intermediates.¹⁹³



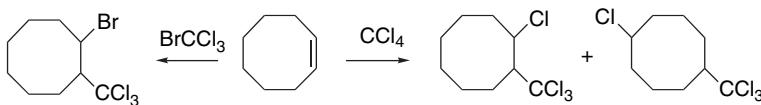
Intramolecular hydrogen abstraction reactions have also been observed in medium-sized rings. The reaction of cyclooctene with carbon tetrachloride and bromotrichloromethane is an interesting case. As shown in the equations below,

¹⁹¹ G. Majetich and K. Wheless, *Tetrahedron*, **51**, 7095 (1995).

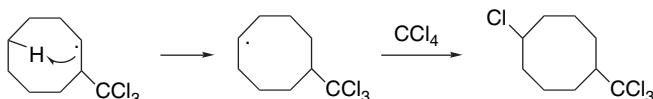
¹⁹² M. E. Wolff, *Chem. Rev.*, **63**, 55 (1963).

¹⁹³ D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, *J. Chem. Soc.*, 181 (1965); R. S. Neale, N. L. Marcus, and R. G. Schepers, *J. Am. Chem. Soc.*, **88**, 3051 (1966).

bromotrichloromethane adds in a completely normal manner, but carbon tetrachloride gives some 4-chloro-1-trichloromethylcyclooctane, as well as the expected product.¹⁹⁴



In the case of carbon tetrachloride, the radical intermediate undergoes two competing reactions; transannular hydrogen abstraction is competitive with abstraction of a chlorine atom from carbon tetrachloride. The former reaction leads to the 1,5-disubstituted product.

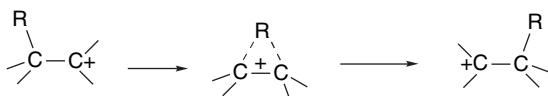


No product derived from the transannular hydrogen abstraction is observed in the addition of bromotrichloromethane because bromine atom transfer is sufficiently fast to prevent effective competition from the intramolecular hydrogen abstraction.

The selectivity observed in most intramolecular functionalizations depends on the preference for a six-membered TS in the hydrogen atom transfer step. Appropriate molecules can be constructed in which steric or conformational effects dictate a preference for selective abstraction of a hydrogen that is more remote from the reactive radical.

11.5.3. Rearrangement Reactions of Free Radicals

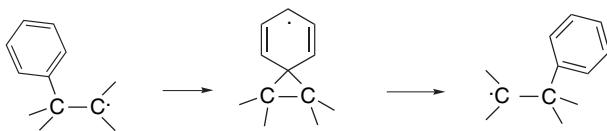
Compared with carbocations, rearrangements of radical intermediates are much less common. However, migrations can occur for specific structural types. The groups that are usually involved in migration in free radical intermediates include aryl, vinyl, acyl, and other unsaturated substituents. Migration of saturated groups is unusual and there is a simple structural reason for this. With carbocations, migration occurs through a bridged TS (or intermediate) that involves a three-center two-electron bond.



In a free radical, there is a third electron in the system that cannot occupy the same orbital as the other two electrons and must instead be in an antibonding level. As a result, the TS for migration is much less favorable than for the corresponding carbocation. The more facile migration of aryl and other unsaturated groups involves

¹⁹⁴ J. G. Traynham, T. M. Couvillon, and N. S. Bhacca, *J. Org. Chem.*, **32**, 529 (1967); J. G. Traynham and T. M. Couvillon, *J. Am. Chem. Soc.*, **87**, 5806 (1965); J. G. Traynham and T. M. Couvillon, *J. Am. Chem. Soc.*, **89**, 3205 (1967).

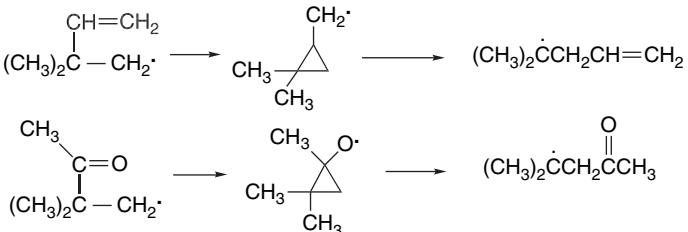
bridged radicals formed by an addition process. In the case of aryl migration, the bridged intermediate is a cyclohexadienyl radical.



It has been possible to measure absolute rates and E_a for rearrangement in a series of 2-substituted 2,2-dimethylethyl radicals. The rates at 25°C and the E_a for several substituents are as indicated below.¹⁹⁵

	X	k (s^{-1})	E_a (kcal/mol)
	Ph	7.6×10^2	11.8
	$\text{CH}_2=\text{CH}$	10^7	5.7
	$(\text{CH}_3)_3\text{CC}\equiv\text{C}$	9.3	12.8
	$(\text{CH}_3)_3\text{CC}=\text{O}$	1.5×10^5	7.8
	$\text{N}\equiv\text{C}$	9.0	16.4

The rapid rearrangement of vinyl and acyl substituents can be explained as proceeding through cyclopropyl intermediates.



The vinyl rearrangement is an example of reversible cyclopropylcarbinyl radical formation and ring opening. The acyl migration occurs through cyclopropanoxy radicals. The energy profile of the cyclopropanoxy radical has been compared computationally to that of the cyclopropylcarbinyl radical (see Section 11.1.3 and Figure 11.3). At the UMP3/6-31G* level, the cyclopropanoxy radical is a TS, rather than an intermediate.¹⁹⁶ The energy profile for the formation of the 2-oxocyclopentylmethyl radical and its rearrangement to the 3-oxocyclohexyl radical by acyl migration has been explored,¹⁹⁷ and the results are shown in Figure 11.15. The rearrangement is found to be exothermic and the calculated barrier for the rearrangement is 20.3 kcal/mol, which is slightly less than that for the initial cyclization. This calculation, too, indicates that the cyclopropanoxy radical fragments with no barrier.

Aryl migration is considerably slower because of the diminished susceptibility of the aryl ring to radical addition. Aryl migrations are promoted by steric crowding at the initial radical site. This trend is illustrated by data from the thermal decomposition

¹⁹⁵ D. A. Lindsay, J. Lusztyk, and K. U. Ingold, *J. Am. Chem. Soc.*, **106**, 7087 (1984).

¹⁹⁶ A. L. Cooksy, H. F. King, and W. H. Richardson, *J. Org. Chem.*, **68**, 9441 (2003).

¹⁹⁷ I. Ryu, H. Fukushima, T. Okuda, K. Matsu, N. Kombe, N. Sonoda, and M. Komatsu, *Synlett*, 1265 (1997).

	E_a	E_b	E_c	E_d	E_e
UMP3/6-31G*//UMP3/3-21G	30.7	20.3	17.0	16.4	-4.8

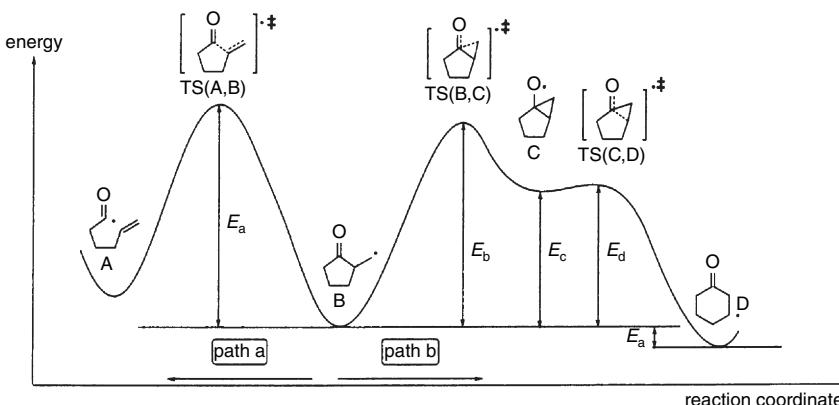


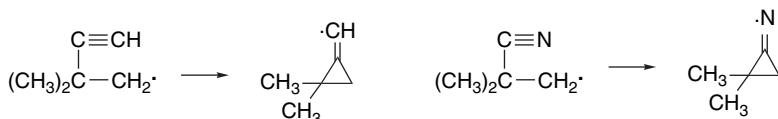
Fig. 11.15. Relative energies of the 5-hexenoyl, 2-oxocyclopentylmethyl, and 3-oxocyclohexyl radicals and the transition structures separating them. Reproduced from *Synlett*, 1265 (1997), by permission of G. Thieme Verlag.

of a series of diacyl peroxides. The amount of product derived from rearrangement increases with the size and number of the substituents.¹⁹⁸

$\begin{array}{c} R \\ \\ (\text{PhCCH}_2\text{CO}_2)_2 \\ \\ \text{R}' \end{array}$	$\xrightarrow{\Delta}$	$\begin{array}{c} R \\ \\ \cdot\text{CCH}_2\text{Ph} \\ \\ \text{R}' \end{array}$	R	R'	Rearrangement
			CH ₃	H	39%
			Ph	H	63%
			Ph	Ph	100%

The aryl migration has been modeled computationally at the UB3PW91/G-31G(*d,p*) level.¹⁹⁹ The bridged cyclohexadienyl radical is found to be a short-lived intermediate that is 10.1 kcal/mol above the open radical. The barrier for return to the open radical is 4.0 kcal/mol. The relative stability of the bridged radical is increased by most *para*-substituents, since they provide stabilization of the cyclohexadienyl radical.

The much slower rearrangement of alkynyl and cyano substituents can be attributed to the reduced stability of the intermediate derived by cyclization of the triply bound substituents.



Scheme 11.6 gives some examples of reactions in which free radical rearrangements have been observed. Entries 1 and 2 are phenyl group migrations in primary alkyl radicals generated by decarbonylation. The migration is competitive with the

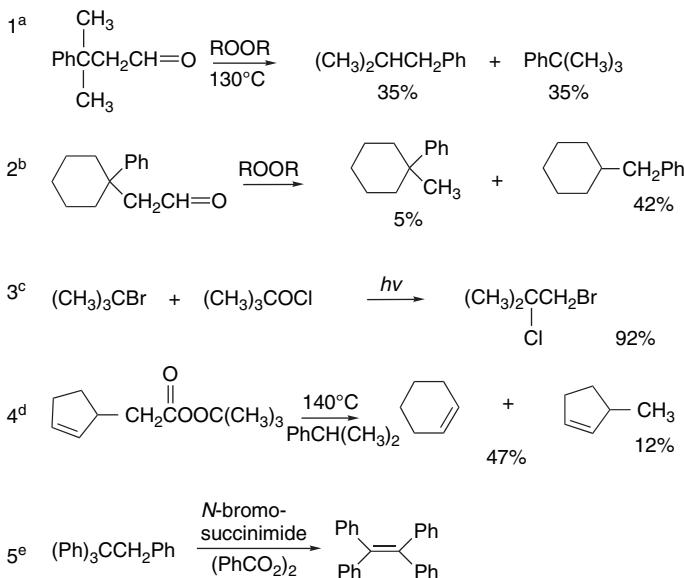
¹⁹⁸ W. Rickatson and T. S. Stevens, *J. Chem. Soc.*, 3960 (1963).

¹⁹⁹ A. Asensio and J. J. Dannenberg, *J. Org. Chem.*, **66**, 5996 (2001).

Scheme 11.6. Free Radical Rearrangements

CHAPTER 11

Free Radical Reactions



a. S. Winstein and F. H. Seibold, Jr., *J. Am. Chem. Soc.*, **69**, 2916 (1947).

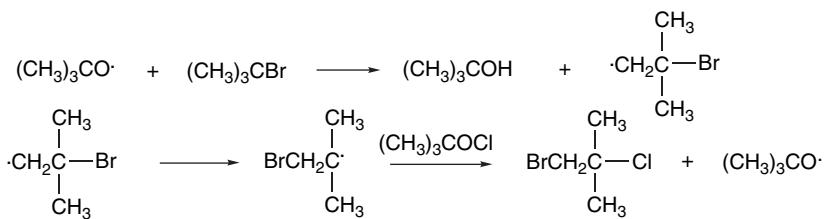
b. J. W. Wilt and H. P. Hogan, *J. Org. Chem.*, **24**, 441 (1959).

c. P. S. Skell, R. G. Allen, and N. D. Gilmour, *J. Am. Chem. Soc.*, **83**, 504 (1961).

d. L. H. Slaugh, *J. Am. Chem. Soc.*, **87**, 1522 (1965).

e. H. Meislisch, J. Constanza, and J. Strelitz, *J. Org. Chem.*, **33**, 3221 (1968).

hydrogen abstraction reaction that gives unarranged product. The reaction in Entry 3 occurs by hydrogen abstraction followed by bromine migration.



Entry 4 is an alkenyl migration that presumably occurs through a bicyclic radical.

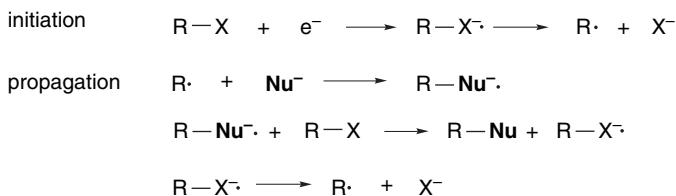


The reaction in Entry 5 involves a phenyl migration. The rearranged radical undergoes hydrogen atom elimination rather than the usual abstraction of bromine.

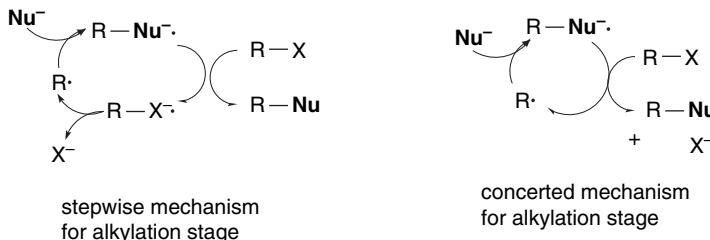
11.6. S_{RN}1 Substitution Processes

The mechanistic description S_{RN}1 refers to a nucleophilic substitution via a radical intermediate that proceeds by unimolecular decomposition of a radical anion derived from the reactant. There are two families of such reactions that have been developed

to a stage of solid mechanistic understanding as well as synthetic utility. The common mechanistic pattern of S_{RN}1 involves electron transfer to the reactant that generates a radical anion, which then expels the leaving group. A chain process occurs if the radical generated by expulsion of the leaving group can react with the nucleophile to give a radical anion capable of sustaining a chain reaction.



A key to the efficiency of S_{RN}1 reactions is the electron transfer to the alkylating reagent.²⁰⁰ This process can be stepwise if the radical anion that is formed is sufficiently stable, but can also be concerted. The concerted path is the most likely one for alkyl halides. The combination reaction between the radical and nucleophile is very fast.



The S_{RN}1 reaction was first discovered and developed for nitroalkane anions, but it is applicable to several other types of nucleophiles. The S_{RN}1 reaction is applicable to various aryl and tertiary alkyl halides and has also been extended to other leaving groups. The reaction has found a number of synthetic applications, especially in substitution of aryl and bridgehead alkyl halides that are resistant to other substitution mechanisms.²⁰¹

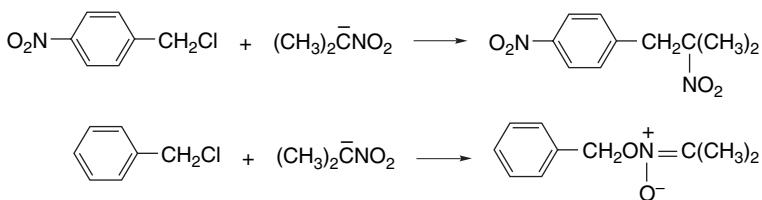
11.6.1. S_{RN}1 Substitution Reactions of Alkyl Nitro Compounds

The S_{RN}1 mechanism of this type permits substitution of certain aromatic and aliphatic nitro compounds by a variety of nucleophiles. These reactions were discovered as the result of efforts to understand the mechanistic basis for high-yield carbon alkylation of the 2-nitropropane anion by *p*-nitrobenzyl chloride. The corresponding

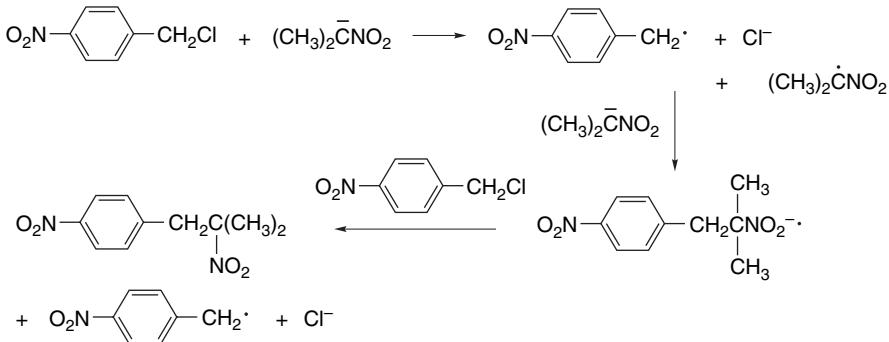
²⁰⁰. J.-M. Saveant, *J. Phys. Chem.*, **98**, 3716 (1994); R. A. Rossi, A. B. Pierini, and G. L. Borosky, *J. Chem. Soc., Perkin Trans. 2*, 2577 (1994).

²⁰¹. R. A. Rossi, *Current Org. Chem.*, **7**, 747 (2003); R. A. Rossi, A. B. Pierini, and A. N. Santiago, *Org. React.*, **54**, 1 (1999); R. A. Rossi, A. B. Pierini and A. B. Penenory, *Chem. Rev.*, **103**, 71 (2003).

bromide and iodide, as well as benzyl halides that do not contain a nitro substituent give mainly the unstable oxygen alkylation product with this ambident anion.²⁰²



A mixture of carbon and oxygen alkylation would be expected for an S_N2 substitution process. The high preference for carbon alkylation suggested that a different mechanism operates with *p*-nitrobenzyl chloride. This conclusion was further strengthened by the fact that the chloride is more reactive than would be predicted by application of the usual $\text{I} > \text{Br} > \text{Cl}$ reactivity trend for leaving groups in S_N2 reactions. The involvement of a free radical process was indicated by ESR studies and by demonstrating that typical free radical inhibitors decrease the rate of the carbon alkylation process. The mechanism proposed is a free radical chain process initiated by electron transfer from the nitronate anion to the nitroaromatic compound.²⁰³ This process is the dominant reaction only for the chloride, because, with the better leaving groups bromide and iodide, a direct S_N2 process is faster.

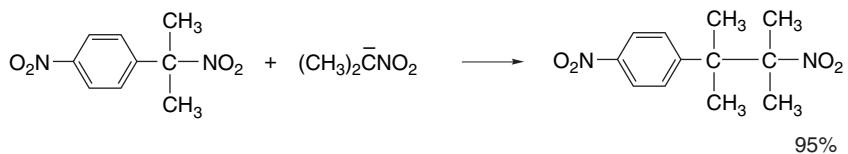


The absolute rate of dissociation of the *p*-nitrobenzyl chloride radical anion has been measured as $4 \times 10^3 \text{ s}^{-1}$. The *m*-nitro isomer does not undergo a corresponding reaction,²⁰⁴ owing to the fact that the *m*-nitro group does not provide any resonance stabilization of the benzylic radical. The kinetics of the overall reaction supports a concerted electron transfer involving dissociation at the stage of electron transfer from the nitronate to the benzylic halide.²⁰⁵



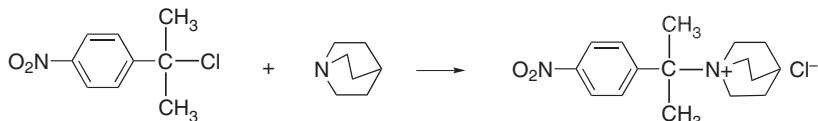
- ²⁰² N. Kornblum, *Angew. Chem. Int. Ed. Engl.*, **14**, 734 (1975); N. Kornblum, in *The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives*, S. Patai, ed., Interscience, New York, 1982, Chap. 10.
- ²⁰³ N. Kornblum, R. E. Michel, and R. C. Kerber, *J. Am. Chem. Soc.*, **88**, 5662 (1966); G. A. Russell and W. C. Danen, *J. Am. Chem. Soc.*, **88**, 5663 (1966).
- ²⁰⁴ R. K. Norris, S. D. Baker, and P. Neta, *J. Am. Chem. Soc.*, **106**, 3140 (1984).
- ²⁰⁵ C. Costentin, P. Hapiot, M. Medebielle, and J.-M. Saveant, *J. Am. Chem. Soc.*, **121**, 4451 (1999).

The synthetic value of the S_{RN}1 substitution reaction was developed from this mechanistic understanding. The reaction is capable of providing highly substituted carbon skeletons that would be inaccessible by normal S_N2 processes. For example, tertiary *p*-nitrocumyl halides can act as alkylating agents in high yield. The nucleophile need not be a nitroalkane anion, but can be anions such as thiolate, phenolate, or a carbanion such as those derived from malonate esters.²⁰⁶ The same mechanism operates as for the nitronate anion. Furthermore, the leaving group need not be a halide. Displacement of nitrite ion from α,p -nitrocumene occurs with good efficiency.²⁰⁷



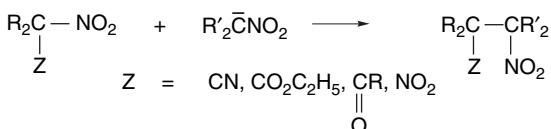
Azido, sulfonyl, and quaternary nitrogen groups can also be displaced by this mechanism.

An S_{RN}1 mechanism has been proposed for the alkylation of amines by *p*-nitrocumyl chloride.^{208, 209}



Clearly, the tertiary nature of the chloride would make a S_N2 mechanism highly unlikely. Furthermore, the nitro substituent is essential to the success of these reactions. Cumyl chloride itself undergoes elimination of HCl on reaction with amines.

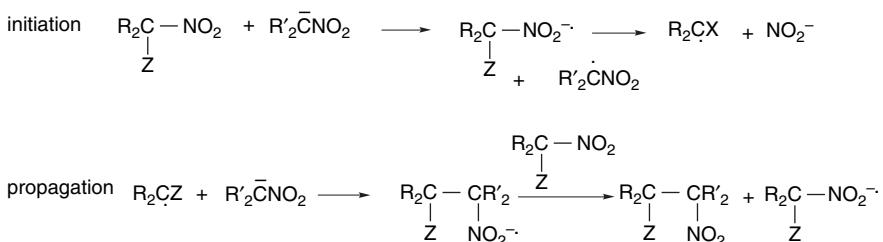
A related process constitutes a method of carrying out alkylation reactions to give highly branched alkyl chains that cannot easily be formed by an S_N2 mechanism. The alkylating agent must contain a nitro group and a second EWG. These compounds react with nitronate anions to effect displacement of the nitro group.²¹⁰



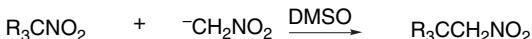
When radical scavengers are added, the reaction is greatly retarded, which indicates that a chain reaction is involved. The mechanism shown below indicates that one of the steps in the chain process is an electron transfer and that none of the steps involves

- ^{206.} N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.*, **89**, 725 (1967); N. Kornblum, L. Cheng, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. M. Kestner, J. W. Manthey, M. T. Musser, H. W. Pinnick, D. H. Snow, F. W. Stuchal, and R. T. Swiger, *J. Org. Chem.*, **52**, 196 (1987).
- ^{207.} N. Kornblum, T. M. Davis, G. W. Earl, G. S. Greene, N. L. Holy, R. C. Kerber, J. W. Manthey, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.*, **89**, 5714 (1967).
- ^{208.} N. Kornblum and F. W. Stuchal, *J. Am. Chem. Soc.*, **92**, 1804 (1970).
- ^{209.} W. R. Bowman, *Chem. Soc. Rev.*, **17**, 283 (1988).
- ^{210.} N. Kornblum and S. D. Boyd, *J. Am. Chem. Soc.*, **92**, 5784 (1970).

atom abstraction. The elimination of nitrite occurs as a unimolecular decomposition of the radical anion intermediate and the $S_{RN}1$ mechanistic designation applies.

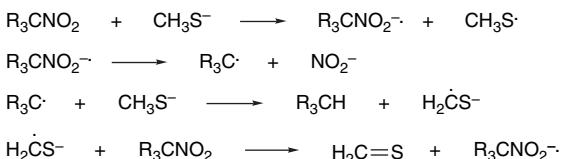


This reaction can also be applied to tertiary nitroalkanes lacking any additional other functional group. These reactions are carried out in dimethyl sulfoxide solution.²¹¹



These reactions also appear to be chain reactions that proceed through the $S_{RN}1$ mechanism. Dimethyl sulfoxide is a particularly favorable solvent for this reaction, probably because its conjugate base acts as an efficient chain initiator by transferring an electron to the nitroalkane.

Although the nitro group plays a crucial role in most of these $S_{RN}1$ reactions, they have synthetic application beyond the area of nitro compounds. The nitromethyl groups can be converted to other functional groups, including aldehydes and carboxylic acids.²¹² Nitro groups at tertiary positions can be reductively removed by reaction with the methanethiolate anion.²¹³ This reaction also appears to be of the electron-transfer type, with the thiolate anion acting as the electron donor.



A unique feature of the $S_{RN}1$ reactions of substituted alkyl nitro compounds is the facility with which carbon-carbon bonds between highly branched centers can be formed. This point is illustrated by several of the examples in Scheme 11.7.

11.6.2. $S_{RN}1$ Substitution Reactions of Aryl and Alkyl Halides

Aryl halides undergo substitution by certain nucleophiles by a chain mechanism of the $S_{RN}1$ class.²¹⁴ Many of the reactions are initiated photochemically and most have been conducted in liquid ammonia solution.

²¹¹ N. Kornblum and A. S. Erickson, *J. Org. Chem.*, **46**, 1037 (1981).

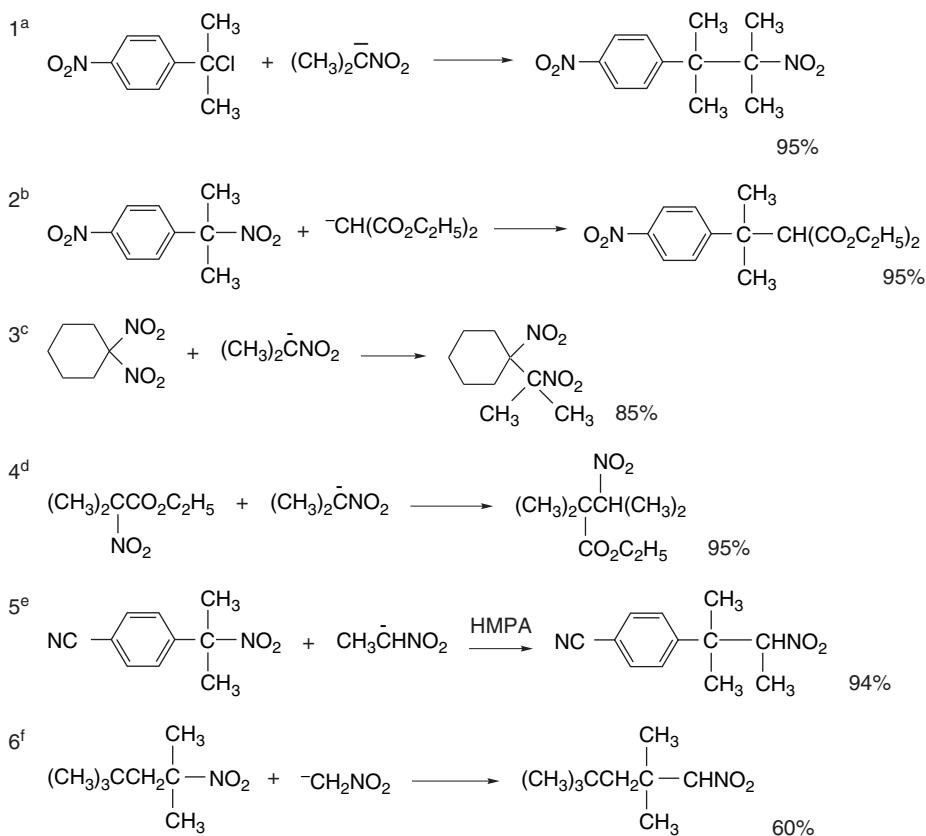
²¹² N. Kornblum, A. S. Erickson, W. J. Kelly, and B. Henggeler, *J. Org. Chem.*, **47**, 4534 (1982).

²¹³ N. Kornblum, S. C. Carlson, and R. G. Smith, *J. Am. Chem. Soc.*, **101**, 647 (1979).

²¹⁴ J. F. Bunnett, *Acc. Chem. Res.*, **11**, 413 (1978); R. A. Rossi and R. H. deRossi, *Aromatic Substitution by the $S_{RN}1$ Mechanism*, American Chemical Society Monograph # 178, Washington, 1983; J.-M. Saveant, *Adv. Phys. Org. Chem.*, **26**, 1 (1990).

Scheme 11.7. Alkylation of Carbanions by the S_{RN}1 Reaction

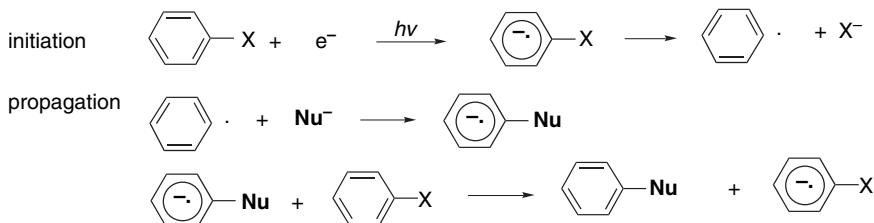
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SECTION 11.6

S_{RN}1 Substitution Processes

- a. N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.*, **89**, 725 (1967).
- b. N. Kornblum, T. M. Davies, G. W. Earl, G. S. Greene, N. L. Holy, R. C. Kerber, J. W. Manthey, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.*, **89**, 5714 (1967).
- c. N. Kornblum, S. D. Boyd, and F. W. Stuchal, *J. Am. Chem. Soc.*, **92**, 5783 (1970).
- d. N. Kornblum, S. C. Carlson, J. Widmer, N. Fifolt, B. N. Newton, and R. G. Smith, *J. Org. Chem.*, **43**, 1394 (1978).
- e. N. Kornblum and A. S. Erickson, *J. Org. Chem.*, **46**, 1037 (1984).

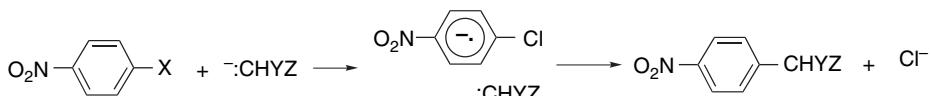


The reactions can also be initiated by a strong chemical reductant or electrochemically.²¹⁵ There are several lines of evidence that support the operation of a chain

²¹⁵. C. Amatore, J. Chaussard, J. Pinson, J.-M. Saveant, and A. Thiebault, *J. Am. Chem. Soc.*, **101**, 6012 (1979).

mechanism, one of the most general observations being that the reactions are stopped or greatly retarded by radical traps. The reactions are not particularly sensitive to the aromatic ring substituents. Both ERGs (such as methoxy) and EWGs (such as benzoyl) can be present.²¹⁶ Groups that easily undergo one electron reduction, especially the nitro group, cause the reaction to fail. The nucleophiles that have been used successfully include sulfide and phosphide anions, dialkyl phosphite anions, and certain enolates. Kinetic studies have shown that the enolate and phosphorus nucleophiles react at about the same rate.²¹⁷ This suggests that the step directly involving the nucleophile (Step 2 of the propagation sequence) occurs at essentially the diffusion-controlled rate, since there is little selectivity among the individual nucleophiles.²¹⁸ The combination of aryl radicals with diethyl phosphate anion has been measured at about $10^9 \text{ M}^{-1} \text{ s}^{-1}$.²¹⁹

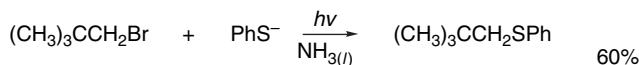
A related mechanism has been suggested for nitroarylation of enolates. An impetus for considering other mechanisms is the fact that the by-products that might be expected from aryl radicals, such as reduction products from hydrogen abstraction from the solvent or biaryls from coupling, are not observed. The alternative is that rather than being a chain process, the radicals may combine (*cage recombination*) more rapidly than they separate.



The kinetics of the reaction of *p*-nitrochlorobenzene with the sodium enolate of ethyl cyanoacetate is consistent with this mechanism. Moreover, radical scavengers have no effect on the reaction, contrary to what would be expected for a chain mechanism in which aryl radicals must encounter the enolate in a propagation step. However, the reactant, *p*-nitrophenyl chloride, is one that might also react by the addition-elimination mechanism (see Section 9.5) and the postulated mechanism is essentially the stepwise electron transfer version of the latter. The question then becomes whether the postulated radical pair is a distinct intermediate.

The synthetic value of the $S_{RN}1$ arylation lies in the fact that other substituents that activate the halide to substitution are not required, in contrast to aromatic nucleophilic substitution that proceeds by an addition-elimination mechanism (see Section 9.5). Scheme 11.8 illustrates some typical reactions.

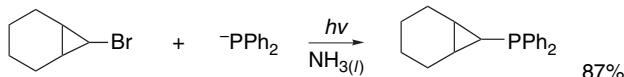
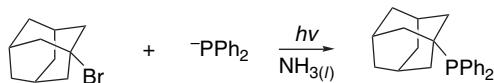
Substitution of hindered alkyl halides by the $S_{RN}1$ mechanism have also been documented.²²⁰ Some examples are shown below.



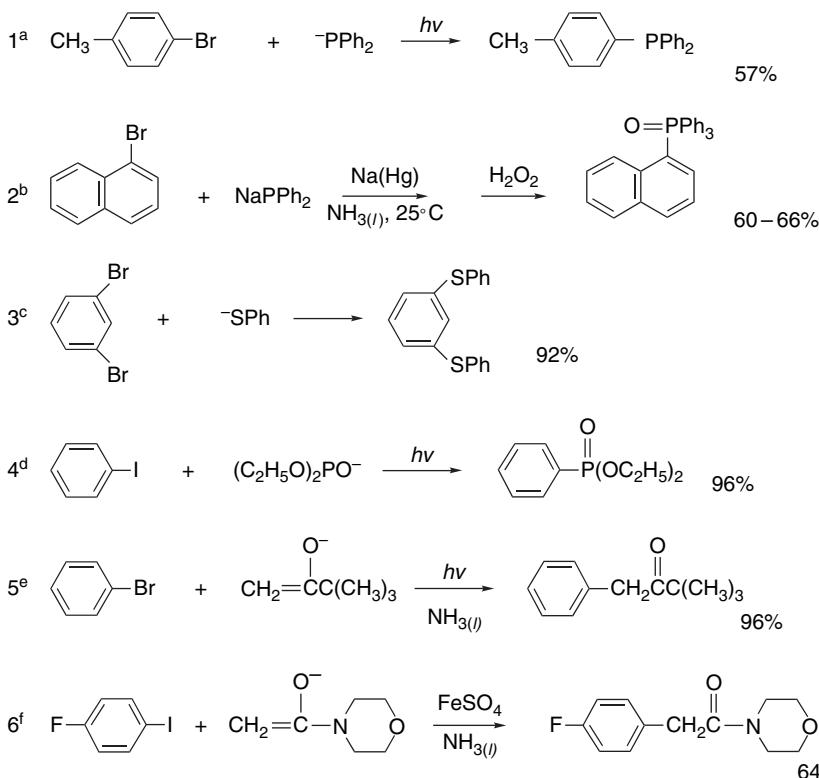
Ref. 221

- ²¹⁶ J. F. Bunnett and J. E. Sundberg, *Chem. Pharm. Bull.*, **23**, 2620 (1975); R. A. Rossi, R. H. deRossi, and A. F. Lopez, *J. Org. Chem.*, **41**, 3371 (1976).
- ²¹⁷ X.-M. Zhang, D.-L. Yang, X.-Q. Jia, and Y.-C. Liu, *J. Org. Chem.*, **58**, 7350 (1993).
- ²¹⁸ C. Galli and J. F. Bunnett, *J. Am. Chem. Soc.*, **103**, 7140 (1981); R. G. Scamehorn, J. M. Hardacre, J. M. Lukanich, and L. R. Sharpe, *J. Org. Chem.*, **49**, 4881 (1984).
- ²¹⁹ A. Annunziata, C. Galli, M. Marinelli, and T. Pau, *Eur. J. Org. Chem.*, 1323 (2001).
- ²²⁰ S. M. Palacios, A. N. Santiago, and R. A. Rossi, *J. Org. Chem.*, **49**, 4609 (1984).
- ²²¹ A. B. Pierini, A. B. Penenory, and R. A. Rossi, *J. Org. Chem.*, **50**, 2739 (1985).

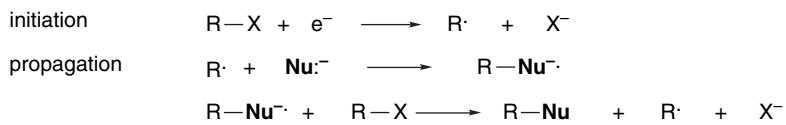
Ref. 222



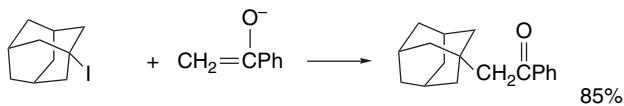
Ref. 223

Scheme 11.8. Aromatic Substitution by the S_{RN}1 Mechanisma. J. E. Swartz and J. F. Bunnett, *J. Org. Chem.*, **44**, 340 (1979).b. P. G. Mabzo, S. M. Palacios, R. A. Alonso, and R. A. Rossi, *Org. Prep. Proc. Int.*, **27**, 660 (1995).c. J. E. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3611 (1974).d. J. E. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3612 (1974).e. M. F. Semmelhack and T. Bargar, *J. Am. Chem. Soc.*, **102**, 7765 (1980).f. M. van Leeuwen and A. McKillop, *J. Chem. Soc., Perkin Trans. I*, 2433 (1993).²²² R. A. Rossi, S. M. Palacios, and A. N. Santiago, *J. Org. Chem.*, **47**, 4654 (1982).²²³ R. A. Rossi, A. N. Santiago, and S. M. Palacios, *J. Org. Chem.*, **49**, 3387 (1984).

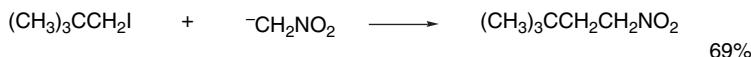
The mechanism is the same as for aryl halides, but the dissociation of the halide is probably concerted with the electron transfer.



Acetophenone enolate and nitromethane anions have also been used successfully in alkyl substitution.



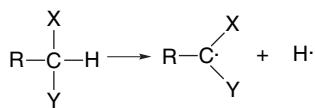
Ref. 224



Ref. 225

Topic 11.1. Relationships between Bond and Radical Stabilization Energies

In Section 3.4.3, we discussed substituent effects on radicals in terms of radical stabilization energies (RSE). These values are defined in terms of standard bond dissociation energies. These RSE values provide a numerical assessment of some well-recognized effects, such as increasing radical stability in the order methyl < primary < secondary < tertiary and the strong stabilization of benzylic and allylic radicals. However, there are some RSE values that are less consistent with chemical experience. For example, the $\text{CCl}_3\cdot$ radical is assigned a negative RSE of 13.79 kcal/mol, although it has a prominent place in radical chemistry. There is a general issue that pertains to radical stabilization energies from both thermochemical and computational BDE when they are defined as ΔH for the reaction



This formulation includes any stabilization of the reactant in the value of the BDE and resulting RSE. Thus the “inherent” strength of the C–H bond is considered to be decreased to the extent that the product radical is stabilized. Further interpretation requires subdividing the BDE into its “inherent” and “extra stabilization” factors. To

²²⁴ M. A. Nazareno and R. A. Rossi, *J. Org. Chem.*, **61**, 1645 (1996).

²²⁵ A. B. Peneo and R. A. Rossi, *Gazz. Chem. Ital.*, **125**, 605 (1995).

do this, structural features that strengthen or weaken the bond *in the reactant* must be accounted for. The AIM approach (see Section 1.4.3) provides the basis for one such scheme. The intrinsic bond energy BE_i was defined in terms of the AIM energy $E_i(r_{\text{BCP}})$ and charge density $\rho_i(r_{\text{BCP}})$:

$$\text{BE}_i = c_1^{\text{AB}} E_i(r_{\text{BCP}})/[c_2^{\text{AB}} + \rho_i(r_{\text{BCP}})] - c_3^{\text{AB}} \Delta R \quad (11.6)$$

where c_1^{AB} , c_2^{AB} , and c_3^{AB} are empirical characteristics of bond types and ΔR is the difference between the length of the AIM bond path and the internuclear distance.²²⁶

This concept of inherent bond energy was extended by Exner and Schleyer to a wider range of structures.²²⁷ The approach reproduced atomization energies for typical alkanes and alkenes with a standard deviation of about 4.6 kcal/mol, i.e., within about 1%, although some molecules, e.g., allene and cyclopropene, fell well outside those limits. The calculated intrinsic bond energies BE_i were then compared with BDE, the energy required for homolytic dissociation. This analysis suggested that most of the dependence of BDE on structure can be attributed to the “extra stabilization” of the radicals, rather than to inherent differences in bond strength. Table 11.10 includes experimental bond energies, computed (G2) bond dissociation energies, the BE_i resulting from application of Equation (11.6), and the resulting RSE.

The data conform to familiar qualitative trends. We see the methyl < *pri* < *sec* < *tert* trend for alkyl groups. The strong stabilization of allyl radicals is evident in the value C(3)–H bond energy for propene, whereas the positive RSE for ethene, ethyne, and benzene reflect the low stability of radicals at *sp*² and *sp* carbons. Also apparent in these data is the relative strength of C–H bonds in strained-ring compounds (cyclopropane). These results are also in accord with the concept of assigning most of the change in the BDE to radical stabilization or destabilization. The intrinsic bond energies, BE_i , show much less variation with substitution than the BDE.

Table 11.10. Comparison of Experimental, Computational, and Calculated C–H Bond Dissociation Energies (kcal/mol)^a

Compound	BDE (exp)	BDE (G2)	BE_i	RSE ^b
Methane	104.9	105.8	103.9	+1.0
Ethane	101.4	102.6	104.1	-2.7
Propane	98.6	100.3	100.3	-5.7
Isobutane	96.5	98.8	104.4	-7.9
Cyclopropane	106.3	113.0	105.8	+0.5
Cyclobutane	96.5	102.1	104.3	-7.8
Cyclopentane	94.5		103.9	-9.4
Cyclohexane	94.5		103.5	-9.0
Ethene	112.2	112.0	106.0	+5.2
Ethyne	132.8	135.0	110.4	+22.4
Propene	88.2	88.7	103.2	-15.0
Benzene	111.2		106.5	+4.7

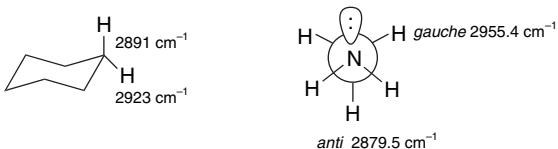
a. K. Exner and P. v. R. Schleyer, *J. Phys. Chem. A*, **105**, 3407 (2001).

b. Apparent radical stabilization from $\text{BDE}(\text{exp}) - \text{BE}_i$ [Equation (11.6)]

²²⁶. S. Grimme, *J. Am. Chem. Soc.*, **118**, 1529 (1996).

²²⁷. K. Exner and P. v. R. Schleyer, *J. Phys. Chem. A*, **105**, 3407 (2001)

Larson and Cremer have explored another approach to dissecting BDE into inherent and RSE effects.²²⁸ There is a relationship between C–H BDE and the vibrational frequencies of the bonds.²²⁹ Furthermore, the vibrations can be determined for C–H bonds in specific conformations, for example, the equatorial and axial bonds in cyclohexanes or the *anti* and *gauche* bonds in amines.



Ref. 230

Ref. 231

Variation in vibrational frequencies of stereochemically distinct bonds

The measurement of the vibrational frequencies provides a means to compare the relative stabilization in radicals with effects already present in the reactant molecules. Following up on experimental work that demonstrated that spectroscopic C–H-bond-stretching frequencies correlate with bond strength,²²⁹ Larson and Cremer developed reliable computation methods for calculating C–H frequencies and from them inherent (or ideal) bond energies. The difference is the radical stabilization (or destabilization energy), as indicated in Figure 11.16.

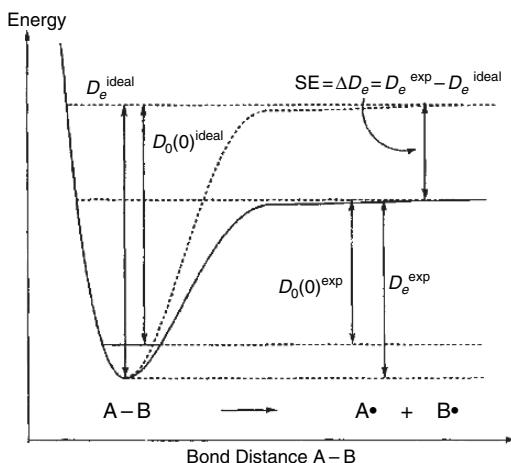


Fig. 11.16. Determination of fragment stabilization energy (SE) by comparison of D_e (exp) with D_e (ideal). D_0 includes correction for zero point energy. Reproduced from *J. Mol. Struct.*, **485/486**, 385 (1999), by permission of Elsevier.

²²⁸ J. A. Larson and D. Cremer, *J. Mol. Struct.*, **485/486**, 385 (1999).

²²⁹ D. C. McKean, *Chem. Soc. Rev.*, **7**, 399 (1978); D. C. McKean, *Int. J. Chem. Kinetics*, **21**, 445 (1989).

²³⁰ J. Caillod, O. Saur, and J.-C. Lavalle, *Spectrochim Acta*, **36A**, 185 (1980).

²³¹ J. L. Duncan, D. C. McKean, J. Torto, A. Brown, and A. M. Ferguson, *J. Chem. Soc., Faraday Trans. II*, **84**, 1423 (1988).

Table 11.11. Radical Stabilization Energy (SE) as Defined in Figure 11.16

Structure	BE_{exp}	BE_i	SE
$\text{CH}_3\text{--H}$	112.9	112.3	0.5
$\text{CH}_3\text{CH}_2\text{--H}$	109.0	109.2	-0.1
$\text{CH}_3\text{CH}_2\text{CH}_2\text{--H}$	105.6	108.5	-2.9
$(\text{CH}_3)_2\text{CH--H}$	102.9	106.4	-3.4
$\text{FCH}_2\text{--H}$	107.5	110.0	-3.4
$\text{HOCH}_2\text{--H}$	101.2	103.6	-2.3
$\text{H}_2\text{NCH}_2\text{--H}$	103.3	96.0	7.3
$\text{ClCH}_2\text{--H}$	108.6	113.4	-4.7
$\text{O}=\text{CH--H}$	95.1	95.4	-0.2
$\text{O}=\text{CHCH}_2\text{--H}$	101.2	107.2	-6.0
$\text{CH}_3\text{C}(=\text{O})\text{--H}$	95.6	95.9	-0.3
$\text{NCCH}_2\text{--H}$	102.3	112.1	-9.8
$\text{H}_2\text{C}=\text{CH--H}$	118.8	118.2	0.5
$\text{HC}\equiv\text{C--H}$	140.1	140.2	-0.1
$\text{HC}\equiv\text{CCH}_2\text{--H}$	97.0	110.9	-13.9
$\text{C}_6\text{H}_5\text{--H}$	118.0	118.6	-0.6
$\text{H}_2\text{C}=\text{CHC}(=\text{O})\text{--H}$	93.4	93.7	-0.3
$\text{O}=\text{C}=\text{CH--H}$	111.9	123.7	-11.7

TOPIC 11.1

Relationships between Bond and Radical Stabilization Energies

The RSEs found for several groups by this approach are given in Table 11.11. Among the noteworthy features of this analysis is the disappearance of the “negative stabilization energies” associated with phenyl, ethenyl, and ethynyl radicals. Nearly all the observed high BDEs in these compounds is attributed to the inherent strength of the C–H bond in the reactant. On the other hand, the stabilization of acyl radicals (see $\text{H}_2\text{C}=\text{O}$ and $\text{CH}_3\text{CH}=\text{O}$) also disappear, because in this case the bonds in the reactant are inherently weaker. The various π -conjugating substituents such as propargyl, cyanomethyl, and the α -acyl radicals show significant stabilization (a negative number by this definition). The halogens and hydroxyl groups have modest stabilizing effects according to this analysis, but an α -amino group has a destabilizing effect. This is because the C–H bond in the reactant is particularly weak, not because the aminoalkyl radicals are unstable. The ketene ($\cdot\text{CH}=\text{C}=\text{O}$) radical shows a large stabilization, but only because the reactant bond is strong and the BDE is high, so one would not expect facile reaction, despite the apparent stabilization.

Where does this leave us in terms of understanding substituent effects on radicals? The most general statement to be made is that the BDE, not the RSE, is the best indicator of reactivity of the C–H bond. This is evident in the relationship allyl \sim benzyl $<$ *tert* $<$ *sec* $<$ *pri* $<$ methyl \sim ethenyl \sim phenyl $<$ ethynyl bonds to hydrogen. We also note that the statement “all substituents weaken adjacent C–H bonds” is generally true. The traditional RSE values, however, result from two substituent effects, those in the reactant and those in the radical, and ultimately depend on the definition of the inherent bond strength. The clearest guide to reactivity is the experimental BDE or its computational equivalent. We discuss the *rates of hydrogen abstraction reactions* in more detail in Topic 11.2.

Topic 11.2. Structure-Reactivity Relationships in Hydrogen Abstraction Reactions

Hydrogen abstraction reactions are of considerable importance in several contexts. They play a role in determining the kinetics of combustion, which determines fuel characteristics, e.g., octane number. The rates of hydrogen abstraction reactions are also important in understanding the role of hydrocarbons and halogenated hydrocarbons in such environmental issues such as air pollution and polar ozone depletion. Hydrogen abstraction reactions are also of importance in understanding the relationship between bond dissociation energies and reactivity. The order allyl \sim benzyl $>$ *tert* $>$ *sec* $>$ *pri* $>$ aryl \sim vinyl for C–H bond reactivity is one of the fundamental structure-reactivity relationships that is developed in introductory organic chemistry. In this section we explore the empirical relationship between the rates and E_a for some hydrogen abstraction reactions from small hydrocarbons and halogenated hydrocarbons by some radicals of fundamental importance, such as the halogen atoms and hydroxyl radical. We consider some empirical, analytical, and computational approaches to understanding hydrogen atom abstraction reactions.

Owing to the importance of hydrogen abstraction reactions, there have been several approaches to developing empirical relationships that can be used to predict activation energies. These efforts are kinetic analogs of the group equivalent approach to thermodynamic properties, in that experimental data are taken as the base and predictive relationships are derived from the data. An example of an empirical approach has been reported by Ranzi et al.²³² From thermodynamic and kinetic data pertaining to radicals such as alkyl, hydroxyl, hydroperoxyl, methoxyl, and chlorine atoms, characteristic values corresponding to the A and E_a components of the Arrhenius equation were tabulated. Each reactant species was also assigned a correction factor. These characteristic values are then put into an equation that uses the reference Arrhenius parameters and correction factors to compute E_a :

$$E_a = E_{x^{\cdot}}^o + E_{R-H}^C \left(\frac{E_x^o}{13500} \right)^{0.333} - \left[1 - \left(\frac{E_R^o}{13500} \right)^{0.333} \right] E_{X-H} \quad (11.7)$$

where E_x^o and E_R^o are the tabulated energy terms and E^C is the correction term. This equation has no theoretical basis beyond the Arrhenius equation and essentially assumes that each reactant and radical has transferable characteristics. The relative simplicity of the hydrogen atom transition state perhaps contributes to the existence of transferability. Figure 11.17 shows the correlation between calculated and experimental rate constants.

Roberts and Steel investigated the applicability of an extended Bell-Evans-Polyani relationship to a series of hydrogen abstraction reactions. They developed a correlation equation that incorporated additional terms for electronegativity differences and for radical stabilization effects:

$$E_a = E_o f + \alpha \Delta H^o (1 - d) + \beta \Delta \chi_{AB}^2 + \gamma (s_A + s_B) \quad (11.8)$$

where $f = (\text{BDE}_{AH} \times \text{BDE}_{BH}) / \text{BDE}_{H_2}$, d is a parameter added for delocalized radicals, β and γ are parameters derived from the correlation, χ is electronegativity, and s is a parameter that is characteristic of the atoms A and B. The inclusion of the various

²³² E. Ranzi, M. Dente, T. Faravelli, and G. Pennati, *Combust. Sci. and Tech.*, **95**, 1 (1994).

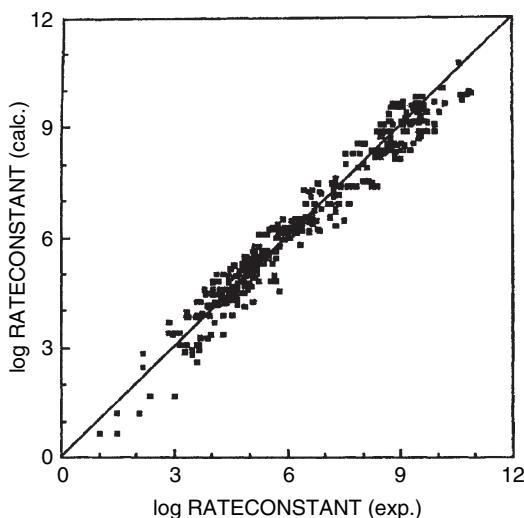
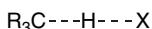


Fig. 11.17. Correlation of experimental hydrogen abstraction rates with rates calculated by Equation (11.7). Reproduced from *Combust. Sci. and Tech.*, **95**, 1 (1994) by permission of Taylor and Francis

terms has conceptual justifications; for example, the electronegativity term accounts for the increased strength of bonds between elements of differing electronegativity and the parameter d is related to the stabilization associated with delocalized radicals. For the set of 65 reactions examined, the E_a averaged to within 0.5 kcal/mol of the experimental value. The value of such an approach is that it provides for prediction of relative reactivity (in the form of E_a) on the basis of existing BDE and electronegativity data. The numerical values of the parameters are determined by the correlation equation.²³³

Another kind of approach is based on estimates from first principles. The fundamental concept of these approaches is that the E_a of a hydrogen abstraction reaction will be determined mainly by the strength of the C–H and H–X bonds and by repulsions between R_3C and X in the transition state.



The problem is to formulate these relationships quantitatively. One approach, called the *interacting state model* (ISM) uses the Morse curves for the C–H and H–X bonds as the starting point and describes the TSs in terms of the length of the C–H and C–X bonds at the TS.²³⁴ The total bond order is taken to be 1.0 unless one of the radicals has extra (e.g., resonance) stabilization, in which case a parameter is added to the formulation. These assumptions lead to a formula that gives the TS energy from the bond lengths and force constants of the C–H and H–X bonds. These structural characteristics are available from experiment or computation. There are other methods

²³³. B. P. Roberts and A. J. Steel, *J. Chem. Soc., Perkin Trans. 2*, 2155 (1994); B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 2719 (1996).

²³⁴. L. G. Arnaut, A. A. C. C. Pais, and S. J. Formosinho, *J. Mol. Struct.*, **563**, 1 (2001).

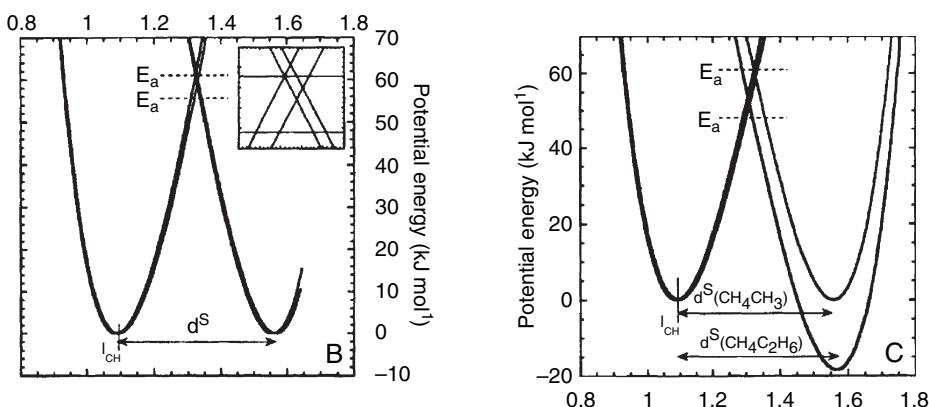


Fig. 11.18. Comparison of Morse curves from: (a) $\text{CH}_3\cdot + \text{CH}_4$ and $\text{C}_2\text{H}_5\cdot + \text{C}_2\text{H}_6$ thermoneutral; and (b) $\text{CH}_3\cdot + \text{C}_2\text{H}_6$ exothermic hydrogen atom transfer reactions. Reproduced from *J. Mol. Struct.*, **563**, 1 (2001), by permission of Elsevier.

of estimating or calculating E_a that use the C–H and H–X bond energies as the principal determinant of E_a .²³⁵

The qualitative interpretation of the ISM method can be illustrated by Figure 11.18. Figure 11.18a shows the equi-energy curves that pertain to the transfer of H between methyl and methane and ethyl and ethane. The curves nearly overlap, but the slightly weaker C–H bond in ethane is characterized by a smaller force constant and leads to a somewhat smaller barrier. The calculated barriers are 14.6 and 14.3 kcal/mol, respectively. The methyl-ethane reaction, shown in Figure 11.18b, is exothermic and there is a much more substantial shift in the curves. The calculated barrier is 12.4 kcal, compared with the experimental value of 11.5. Thus, the calculation moves the barriers in the right direction, although it does not reproduce the entire effect that is observed experimentally.

There have also been computational approaches using both semiempirical and ab initio MO and DFT methods. As in the treatment of isolated radicals, computational methods applied to radical transition states must use methods that are applicable for systems having unpaired electrons.²³⁶ In one study, reactant, product, and TS energies were calculated using the PM3 method.²³⁷ These were then compared with the corresponding experimental data. Figure 11.19 shows the PM3 representation of the SOMO distribution for the TS for hydrogen abstraction from propene (allylic hydrogen) by ethyl radical. Note that there is some delocalization of the SOMO distribution into the propene double bond, which is consistent with the idea that the stabilization of the allylic radical will contribute to the TS structure and lower the E_a . When the PM3 computations were applied to about 40 hydrocarbons, including some 10 benzylic and related conjugated structures, a good linear correlation was found between experimental and calculated E_a . The calculated E_a values tended to be too high by several kcal, but calibration of the linear correlation provided an average deviation of 1.5 kcal. The correlation was even better if the hydrocarbons were subdivided into structurally related groups.

²³⁵ H. S. Johnston and C. Parr, *J. Am. Chem. Soc.*, **85**, 2544 (1963); N. Agmon and R. D. Levine, *Chem. Phys. Lett.*, **52**, 197 (1977); R. D. Gilliom, *J. Am. Chem. Soc.*, **99**, 8399 (1977); A. A. Zavitsas and C. Chatgilialoglu, *J. Am. Chem. Soc.*, **117**, 10645 (1995).

²³⁶ Y. Y. Chuang, E. L. Coitino, and D. G. Truhlar, *J. Phys. Chem. A*, **104**, 446 (2000).

²³⁷ X. Ma and H. H. Schobert, *Ind. Eng. Chem. Res.*, **40**, 743 (2001).

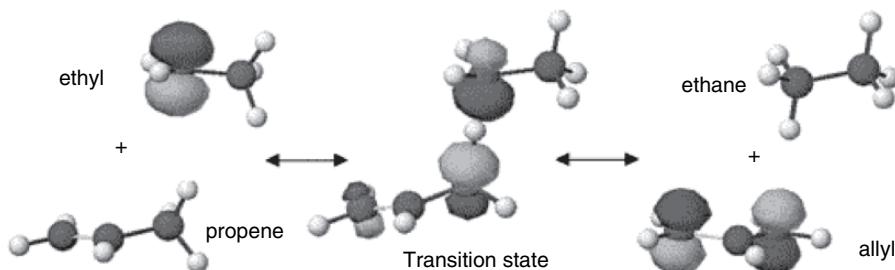


Fig. 11.19. PM3 representation of reactants, transition state, and products showing optimal geometry and distribution of SOMO orbital. Reproduced from *Int. Eng. Chem. Res.*, **40**, 743 (2001), by permission of the American Chemical Society.

These results extend those of an earlier study using AM1 and PM3 computations that showed excellent correlations within structurally similar groups, e.g., *tert*, *sec*, *pri*, and conjugated.²³⁸ These studies also showed that the barrier for identity hydrogen atom transfers (e.g., ethyl/ethane) *increased* with conjugation. This result, which at first might seem surprising, reflects the fact that there is greater conjugative stabilization in the radicals than in the transition state. Table 11.12 lists some of the computed barriers. The trend toward an increased barrier with conjugation should not be confused with the *greater* reactivity of allylic and benzylic C–H toward more reactive alkyl radicals. For example, the data for hydrogen atom abstraction from toluene and propene by the methyl radical in Table 11.5 show barriers of 9.5 and 7.7 kcal/mol, respectively.

There has been a good deal of study of the polyhalogenated methanes in hydrogen atom abstraction reactions toward hydroxyl (HO^\cdot) and chlorine radicals.²³⁹ These reactions are involved in both the atmospheric destruction of such compounds as well as their involvement in ozone depletion. Information is needed about these reactions to model the environmental impact of the compounds.

The reactions of halogenated methanes with HO^\cdot are characterized by a low activation barrier and early TS. In one study the reactants, products, and TS were calculated at the 6-311G(2d,2p) level using the PMP4(SDTQ) method to remove spin contamination.²⁴⁰ Table 11.13 gives the calculated rates, E_a , and the derived atmospheric lifetimes for the halogenated methanes based on the reaction with HO^\cdot . The atmospheric lifetimes are computed in relation to the known rate for CH_3CCl_3 .

Table 11.12. Computed Barriers for Identity Hydrogen Atom Abstraction Reactions

Saturated		Conjugated	
R	E_a	R	E_a
$\text{CH}_3\cdot$	15.8	$\text{CH}_2=\text{CHCH}_2\cdot$	15.7
$\text{CH}_3\text{CH}_2\cdot$	10.1	$(\text{CH}_2=\text{CH})_2\text{CH}\cdot$	20.0
$(\text{CH}_3)_2\text{CH}\cdot$	8.3	$\text{PhCH}_2\cdot$	15.7
$(\text{CH}_3)_3\text{C}\cdot$	10.9 ^a	$\text{Ph}_2\text{CH}\cdot$	19.3

a. This value is believed to be overestimated by the PM3 method.

²³⁸ D. M. Camioni, S. T. Autrey, T. B. Salinas, and J. A. Franz, *J. Am. Chem. Soc.*, **118**, 2013 (1996).

²³⁹ R. Atkinson, *Chem. Rev.*, **86**, 69 (1986).

²⁴⁰ F. Louis, C. A. Gonzalez, R. E. Huie, and M. J. Kurylo, *J. Phys. Chem. A*, **105**, 1599 (2001).

Table 11.13. Computed Rates, E_a , and Atmospheric Lifetimes for Halomethanes^a

Compound	Number	$k_{298} \times 10^{-15}$	E_a/R	Lifetime (years)
CH ₃ F	2	21	1340	6.37
CH ₃ Cl	5	189	1015	1.55
CH ₃ Br	8	100	1190	2.47
CH ₂ F ₂	3	23	1595	3.59
CH ₂ FCl	11	80	1160	1.68
CH ₂ Cl ₂	6	433	510	0.43
CH ₂ ClBr	16	304	590	0.54
CH ₂ Br ₂	8	247	690	0.57
CHF ₃	4	0.28	2640	397
CHF ₂ Cl	12	9.1	1540	13.16
CHF ₂ Br	15	15	1375	6.03
CHFCl ₂	13	115	765	1.18
CHCl ₃	7	870	10	0.15
CH ₂ FBr	17	30	1440	1.88
CHFBr ₂	17	100	825	0.49
CHFClBr	20	68	920	0.73
CHCl ₂ Br	18	264	330	0.16
CHClBr ₂	19	346	250	0.12

a. F. Louis, C. A. Gonzalez, R. E. Huie, and M. J. Kurylo, *J. Phys. Chem. A*, **105**, 1599 (2001).

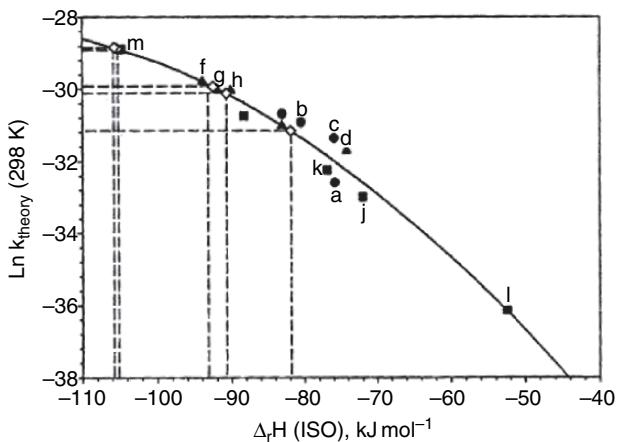


Fig. 11.20. Quadratic Evans-Polanyi relationship $\ln k(298) = -1.368 \times 10^{-3} \Delta H_r^2 - 0.354 \Delta H_r - 50.96$: (a) CH₃F, (b) CH₃Cl, (c) CH₃Br, (d) CH₂F₂, (e) CH₂FCl, (f) CH₂Cl₂, (g) CH₂ClBr, (h) CH₂Br₂, (i) CHF₃, (j) CHF₂Cl, (k) CHF₂Br, (l) CHFCl₂, (m) CHCl₃. From *J. Phys. Chem. A*, **105**, 1599 (2001).

Table 11.14. Comparison of Computed and Observed E_a (kcal/mol) for Reaction of Halomethanes with Cl.

Compound	E_a (MP4/6-31G**)	E_a (observed)
CH ₃ F	3.4	1.54 ± 1.0
CH ₂ F ₂	3.7	3.26 ± 1.0
CHF ₃	9.7	7.62 ± .16
CH ₃ Cl	3.9	2.50 ± 0.4
CH ₂ Cl ₂	1.6	2.7 ± 1.0
CHCl ₃	0.6	2.48 ± 1.0
CH ₂ CF	2.6	2.78 ± 1.0
CHClF ₂	5.4	4.51 ± 1.0
CHCl ₂ F	2.3	

The purpose of this study was to test the reliability of theoretical rate calculations to predict the atmospheric lifetime, an important property of these compounds:



These kinetic data lead to a quadratic rather than linear Bell-Evans-Polyani relationship:

$$\ln k_{298} = 1.368 \times 10^{-3} \Delta H^2 - 0.354 \Delta H - 50.96$$

The corresponding plot is shown in Figure 11.20.

A quadratic relationship between E_a and ΔH was also noted for the reactions of Cl· and some of the same halomethanes.²⁴¹ Table 11.14 shows the computed and experimental E_a and Figure 11.21 shows the Evans-Polyani relationship. The

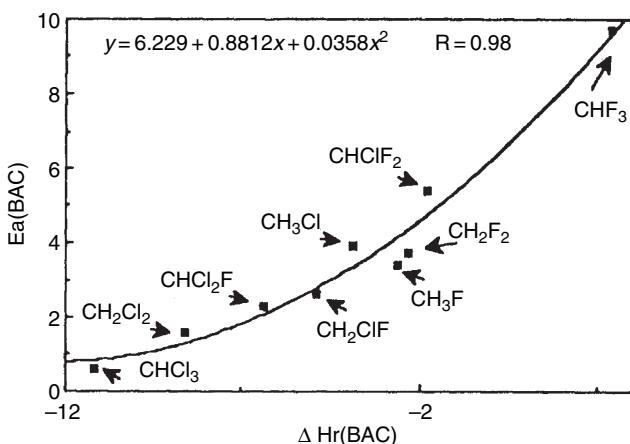


Fig. 11.21. Quadratic Evans Polyani relationship between E_a and BDE for Cl· and halomethanes. From *J. Phys. Chem.*, **98**, 111342 (1994).

²⁴¹ M.-T. Rayez, J.-C. Rayez, and J.-P. Sawerysyn, *J. Phys. Chem.*, **98**, 111342 (1994).

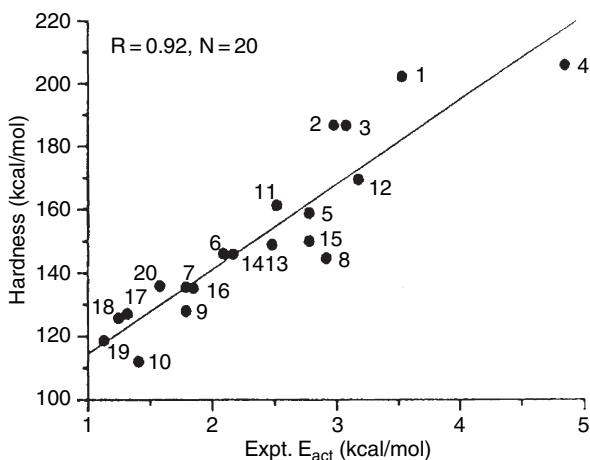


Fig. 11.22. Correlation between hardness and E_a for reaction of halomethanes with hydroxyl radical. Compounds are identified in Table 11.13. Reproduced from *Chem. Phys. Lett.*, **318**, 69 (2000), by permission of Elsevier.

observation of quadratic relationships is related to the concept of intrinsic barriers as formulated in the Marcus theory (see Section 3.3.2.3).

Chandra et al. considered the reactivity trends of the halomethanes toward HO· in the DFT/hardness context.²⁴² There is a good correlation with the global hardness parameter. For X=Cl or Br, hardness decreases as more Cl and Br substituents are added. For fluorine the hardness trend is CH₃F=CH₂F₂ < CH₄ < CHF₃. This is in qualitative agreement with the rate data shown in Table 11.14. For the halomethanes, electron transfer to ·OH is exothermic, and ·OH is expected to be electrophilic in its reactions with the halomethanes. The trend of decreased reactivity with increased hardness can then be interpreted as decreased electron donation in the TS. Figure 11.22 shows the correlation between global hardness and the E_a .

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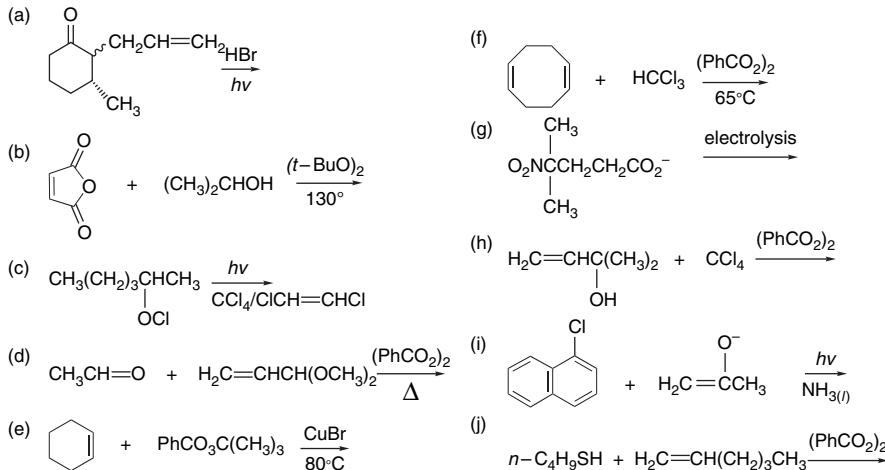
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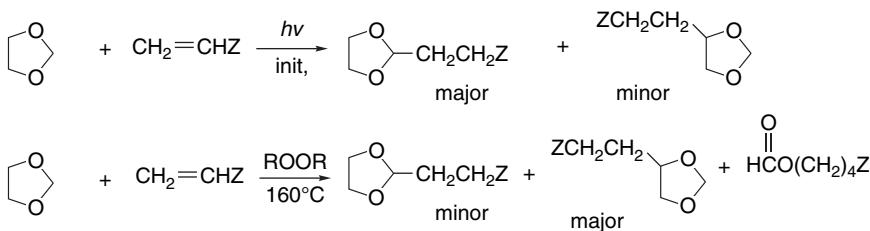
Problems

(References for these problems will be found on page 1167.)

- 11.1. Predict the structure of the products of the following reactions.

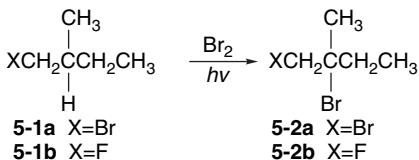


- 11.2. Using the data in Table III of Problem ref 11.2, calculate the expected product composition from gas phase chlorination and bromination of 3-methylpentane under conditions (excess hydrocarbon) that minimize polyhalogenation.
- 11.3. A careful study of the photoinitiated addition of HBr to 1-hexene established the following facts: (1) The chain length is about 400. (2) The products are 1-bromohexane, 2-bromohexane, and 3-bromohexane. The amounts of 2- and 3-bromohexane formed are always nearly identical and increase from about 8% at 4°C to about 22% at 63°C. (3) During the course of the reaction, a small amount of 2-hexene can be detected. Write a mechanism that is consistent with these results.
- 11.4. The irradiation of 1,3-dioxolane in the presence of alkenes and an initiator leads to 2-alkyldioxolanes along with small amounts of 4-alkyldioxolanes. The reaction is particularly effective with EWG-substituted alkenes such as diethyl maleate. When the reaction is done thermally with a peroxide initiator at 160°C, the product mixture is more complex and more of the 4-substituted dioxolane is formed. Account for the change in product ratio with increasing temperature.

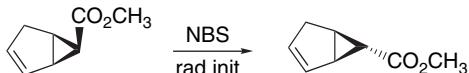


11.5. Provide a detailed mechanistic explanation for the following results.

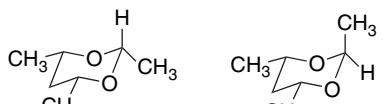
- a. Photochemically initiated bromination of resolved **5-1a**, $\alpha_D + 4.21$, affords **5-2a** which retains optical activity, $\alpha_D - 3.23$, but **5-1b** under the same conditions gives racemic **5-2b**.



- b. The stereoisomerization shown below proceeds efficiently, with no other chemical change occurring at a comparable rate, when the compound is warmed with *N*-bromosuccinimide and a radical chain initiator.



- c. There is a substantial difference in the reactivity of the two stereoisomeric compounds shown below toward abstraction of the hydrogen atom at C(2) by the *t*-butoxy radical.

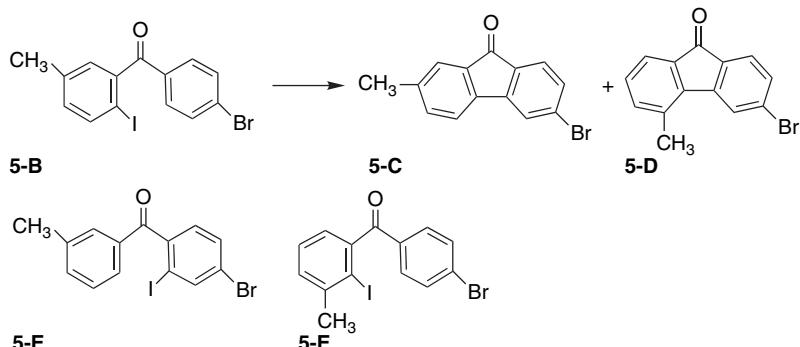


The eq-CH₃ isomer is 7–10 times more reactive than the ax CH₃ isomer.

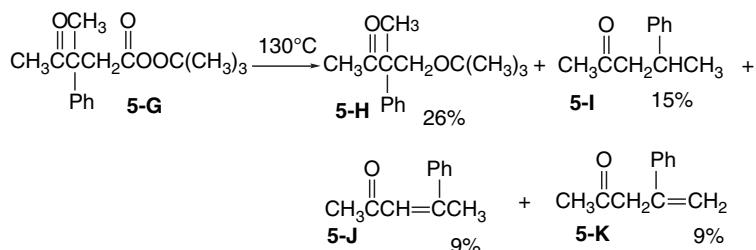
- d. Free radical chain chlorination of enantiomerically resolved 1-chloro-2-methylbutane yields six dichloro derivatives, of which four are optically active and two are not. Identify the products that are expected to fall in each group. Indicate the mechanistic significance of the identity of the optically active and inactive compounds.
- e. Irradiation of the hydrocarbon **5-A** in the presence of di-*t*-butyl peroxide generates a radical that can be identified as the 2-phenylethyl radical by its ESR spectrum. This is the only radical identified, even when the photolysis is carried out at -173°C .



- f. Among the products from heating 1,6-heptadiene with 1-iodoperfluoropropane in the presence of AIBN are two saturated 1:1 adducts. Both adducts give the same product on dehydroiodination, and it can be shown by spectroscopic means to contain a $=\text{CH}_2$ unit. Indicate structures for the two adducts and propose a mechanism for their formation.
- g. Photolysis of the iodide **5-B** gives not only the expected cyclization product **5-C** but also **5-D**. During the course of the photolysis halides **5-E** and **5-F** are also formed.

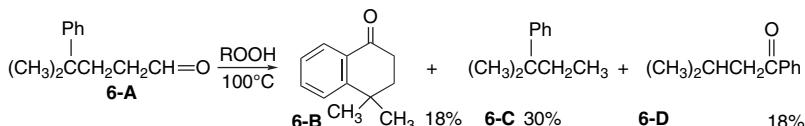


- h. Thermal decomposition of **5-G** gives products **5-H** to **5-K**:

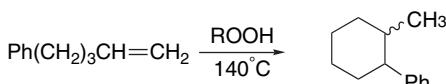


11.6. Write mechanisms for the following reactions:

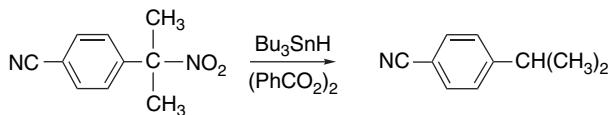
a.



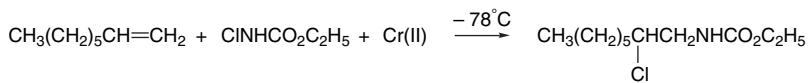
b.



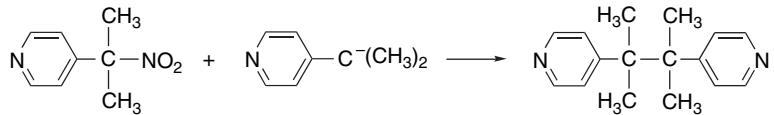
c.



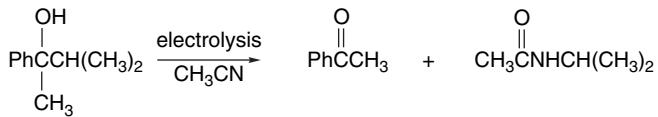
d.



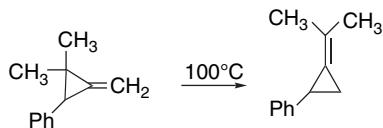
e.



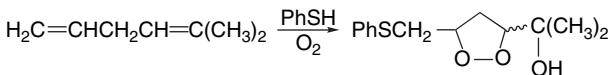
f.



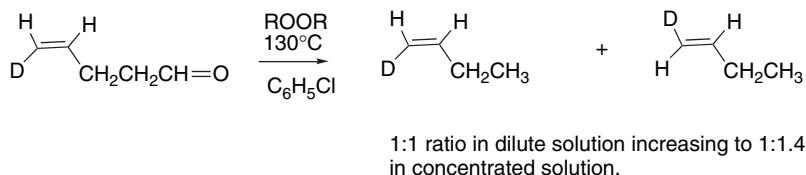
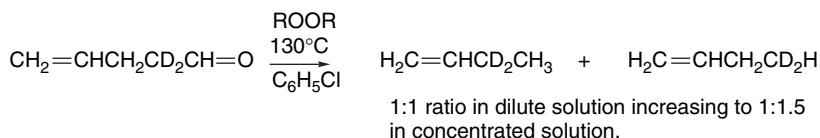
g.



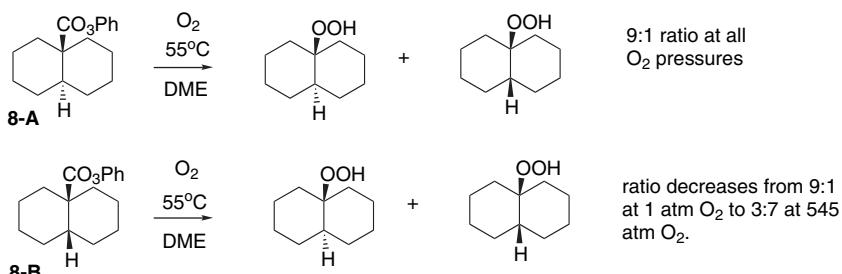
h.



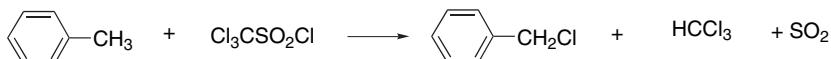
- 11.7. The decarbonylation of the two isotopically labeled pentenals shown below have been studied. Explain why the distribution of deuterium found in the products is affected by solution concentration.



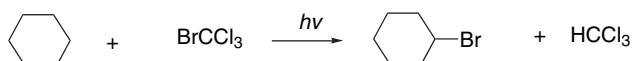
- 11.8. Decomposition of the *trans*-decaryl peroxyester **8-A** gives a 9:1 ratio of *trans*- and *cis*-hydroperoxides at all the oxygen pressures studied. The product ratio from the *cis*-peroxyester **8-B** is dependent on oxygen pressure. At 1 atm O₂ it is 9:1 *trans:cis*, identical to the *trans* isomer, but the ratio decreases and eventually inverts with increasing O₂ pressure. At 545 atm, the ratio is 7:3, favoring the *cis*-hydroperoxide. What deductions about the stereochemistry of the 9-decaryl radical can be made from these observations?



- 11.9 a. Trichloromethanesulfonyl chloride can chlorinate hydrocarbons as described in the stoichiometric equation below. The reaction occurs by a free radical chain process. Write at least two possible sequences for chain propagation.

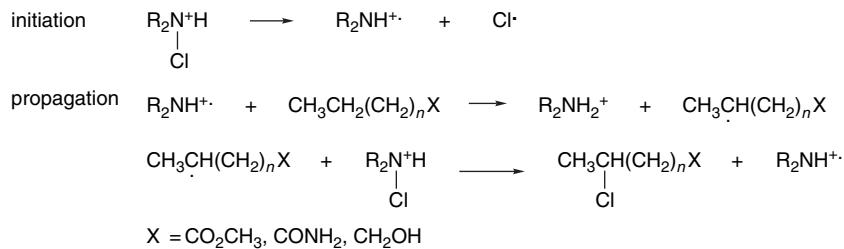


- b. The chlorination has been compared with bromination by BrCCl₃ carried out under radical chain conditions. In this reaction, cyclohexane is about one-fifth as reactive as toluene, but in the chlorination by trichloromethanesulfonyl chloride, cyclohexane is about three times more reactive than toluene. Does this information permit a choice between the chain sequences you have written in part (a)?



- 11.10. A highly selective photochemical chlorination of esters, amides, and alcohols can be carried out in 70–90% H₂SO₄ using *N*-chlorodialkylamines as the

chlorinating agents. Mechanistic study indicates that the reaction occurs by the following chain sequence:



A very interesting feature of the reaction is that the chlorine is introduced with high selectivity at the *next-to-terminal position* for molecules with $n = 4$ to 6. In contrast, chlorination in nonpolar solvents does not show comparable selectivity. Rationalize these observations.

- 11.11. a. Analyze the hyperfine coupling of the spectrum of the butadiene radical anion given in Figure 11.P11a. What is the spin density on each carbon atom according to the McConnell equation?
- b. The ESR of the allyl radical is given in Figure 11.P11b. Derive the splitting pattern and determine the values of the hyperfine splitting constants.

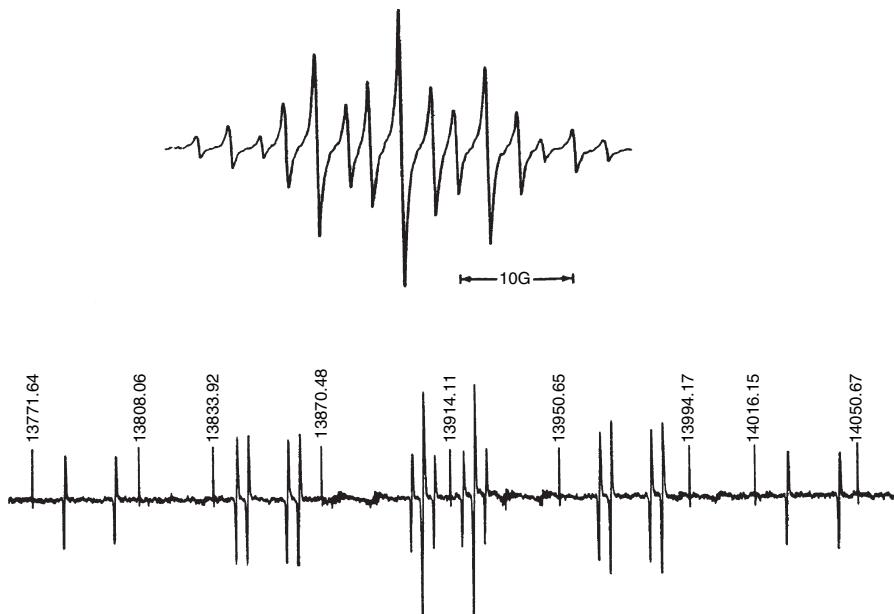
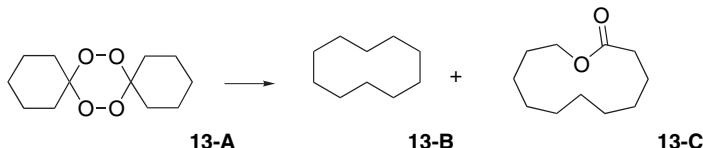


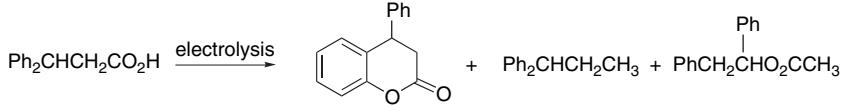
Fig. 11.P11. (a) ESR spectrum of butadiene radical anion from *J. Chem. Phys.* **41**, 1062 (1964); (b) ESR spectrum of allyl radical from *J. Am. Chem. Soc.*, **90**, 7157 (1968).

- 11.12. Write a stepwise mechanism for each of the radical rearrangement reactions listed in Scheme 11.6.

- 11.13. The *spiro* peroxide **13-A**, which is readily prepared from cyclohexanone and hydrogen peroxide, decomposes thermally to give substantial amounts of cyclodecane (**13-B**) and 11-undecanolactone (**13-C**). Account for the efficient formation of these macrocyclic compounds.

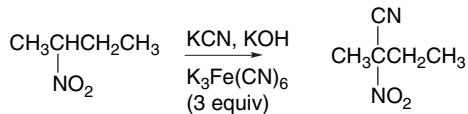


- 11.14. Methylcyclopropane shows strikingly different reactivity toward chlorine and bromine under radical chain conditions in CH_2Cl_2 solution. The main product with chlorine is chloromethylcyclopropane (56%), along with smaller amounts of 1,3-dichlorobutane and 1,3-dichloro-2-methylpropane. Bromine gives only 1,3-dibromobutane. Offer a mechanistic explanation.
- 11.15. Electrolysis of 3,3-diphenylpropanoic acid in acetic acid–sodium acetate solution gives the products shown below. Propose mechanisms for the formation of each product.

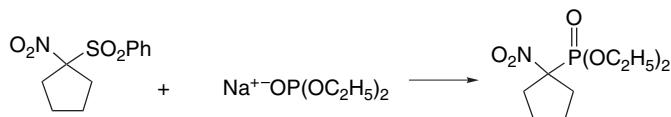


- 11.16. Write a mechanism to account for the observed product of each of the following reactions:

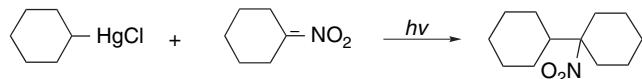
a.



b.

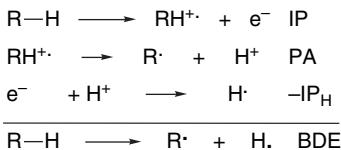


c.



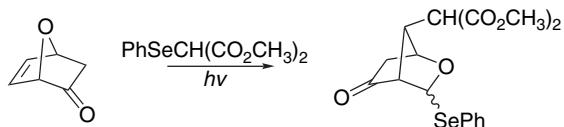
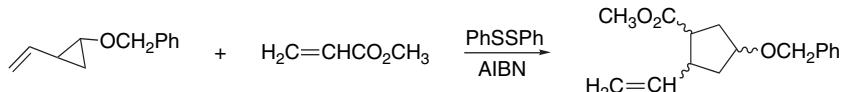
- 11.17. The *N*-benzoyl methyl esters of the amino acids glycine, alanine, and valine have been shown to react with *N*-bromosuccinimide to give the α -bromo derivatives. The order of reactivity is glycine > alanine > valine in the ratio 23:8:1. Account for the formation of the products and the order of the reactivity.

- 11.18. By measurement in an ion cyclotron resonance mass spectrometer, it is possible to measure the proton affinity (PA) of free radicals. These data can be combined with ionization potential (IP) data according to the scheme below to determine the bond dissociation energy (BDE) of the corresponding C–H bond. The ionization potential of the H atom is 313.6 kcal/mol. Use the data given below to determine the relative stabilization of the various radicals relative to methyl, for which the BDE is 104 kcal/mol. Compare the BDE determined in this way with the comparable values given in Table 3.20.



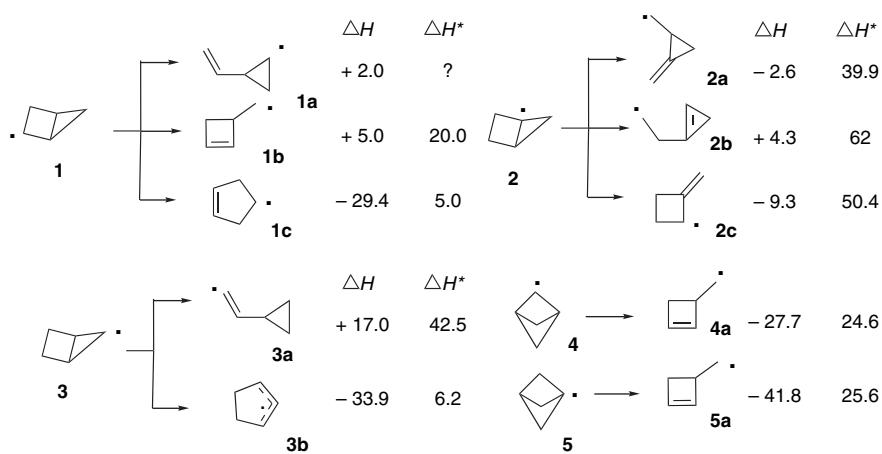
	IP	PA
PhCH ₂ —H	203	198
	190	200
	198	199
	224	180
CH ₂ =CHCH ₂ —H	224	180
	232	187
CH ₂ =CH—H	242	183

- 11.19. Provide stepwise mechanisms for the following reactions:

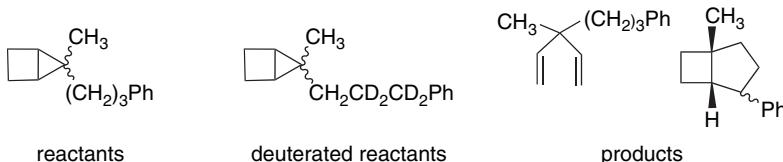


- 11.20. The energy of some free radicals derived from small strained hydrocarbons has been calculated at the MINDO/3 level. The ΔH and ΔH^\ddagger were calculated for several possible fragmentations and are given below. Consider the stereoelectronic and steric

factors involved in the various fragmentations. Explain the large variations in ΔH and ΔH^\ddagger and identify structural features that lead to facile fragmentation.



- 11.21. The pyrolysis of a mixture of the two stereoisomers of 5-methyl-5-(3-phenylpropyl)bicyclo[2.1.0]pentane leads to a mixture of three products. The two reactants equilibrate under the reaction conditions at a rate that exceeds product formation. When deuterium is introduced into the propyl side chain, there is no intermolecular deuterium scrambling. Write a mechanism for formation of each product and indicate how the deuterium results help to define the mechanism. What can be said about the lifetime of the intermediates in your mechanism?



Photochemistry

Introduction

The photochemical reactions of organic compounds attracted great interest beginning in the 1960s. As a result, many useful and fascinating reactions were uncovered and photochemistry is now an important synthetic tool in organic chemistry. A firm basis for mechanistic descriptions of many photochemical reactions has been developed. Some of the more general types of photochemical reactions are discussed in the present chapter. In Section 12.2, the photochemistry of alkenes, dienes, and polyenes is considered, including the relationship of photochemical reactions to orbital symmetry principles. Important reaction types include *cis-trans* isomerization, electrocyclic reactions, photocycloadditions, and rearrangements. In subsequent sections, characteristic photochemical reactions of carbonyl compounds and aromatic rings are introduced.

12.1. General Principles

We begin by summarizing the basic elements of photochemical reactions. The first condition that must be met is that the reactant absorb light emitted by the source. For light to be absorbed, the compound must have an energy level that corresponds to the energy of the radiation. Organic photochemical reactions usually involve excited electronic states. Depending on functionality, organic compounds can have electronic absorption bands in the ultraviolet and/or the visible region of the spectrum. Most of the photochemistry we discuss involves unsaturated groups, mainly alkenes, carbonyl compounds, and arenes, in which an electron is promoted to an antibonding π^* orbital. These excited states involve promotion of electrons in valence shell orbitals. The excited states can be singlets or triplets. In a *singlet excited state* the excited electrons retain opposite spins, whereas in *triplet excited states* they have parallel spins. The photoexcitation of organic molecules can also involve *Rydberg states*, which involve excitation of an electron from the valence level to a higher shell, typically 3s and 3p for organic molecules. The Rydberg states are similar to a radical cation in the

valence shell but with an additional diffuse distribution of the excited electron. In many molecules, there is mixing of character of valence shell excited states with Rydberg states, and the latter can decay to valence shell excited states.

Table 12.1 lists the general regions of absorption for the classes of organic molecules that are discussed in this chapter. A number of light sources can be used, the most common for preparative scale work being mercury vapor lamps, which emit mainly at 214, 254, 313, and 366 nm. The composition of the radiation reaching the sample can be controlled by filters. For example, if the system is constructed so that light passes through standard glass, only wavelengths longer than 300–310 nm reach the sample because the glass absorbs below this wavelength. Pure fused quartz, which transmits down to 200 nm, must be used if the 254-nm radiation is desired. Other glasses have cutoff points between those of quartz and standard glass. Filter solutions that absorb in specific wavelength ranges can also be used to control the energy of the light reaching the sample.¹ Mechanistic studies are frequently done using lasers, which permits intense radiation at specific wavelengths and for brief periods of time.

The energy supplied by a particular wavelength of light can be calculated from the fundamental equation

$$E = h\nu \quad (12.1)$$

The energy in kcal/mole is

$$E = 2.86 \times 10^4 / \lambda$$

where λ is wavelength in nm. Thus, light of $\lambda = 254$ nm equals 112.6 kcal/mol, an energy sufficient to rupture most single bonds. The energy is also often expressed in terms of the frequency of the light:

$$E(\text{cm}^{-1}) = 349.8 \text{ cm}^{-1} / \text{kcal/mol}$$

Energy is also sometimes expressed in eV, where $1 \text{ eV} = 23.14 \text{ kcal/mol}$.

When a quantum of light is absorbed, the electronic configuration changes to correspond to an excited state. Three general points about this process should be emphasized:

Table 12.1. Approximate Wavelength Ranges for Lowest-Energy Absorption Band of Representative Organic Compounds

Reactant	Absorption maxima (nm)
Monoalkenes	190–200
Acyclic dienes	220–250
Cyclic dienes	250–270
Aryl-substituted alkenes	270–300
Saturated ketones	270–280
α, β -Unsaturated ketones	310–330
Benzene derivatives	250–280
Aromatic ketones and aldehydes	280–300

¹. Detailed information on the emission characteristics of various sources and the transmission properties of glasses and filter solutions can be found in A. J. Gordon and R. A. Ford, *The Chemist's Companion*, Wiley-Interscience, New York, 1972, pp. 348–368 and in S. L. Murov, I. Carmichael, and G. L. Hug, *Handbook of Photochemistry*, 2nd Edition, Marcel Dekker, New York, 1993.

1. The excitation promotes an electron from a filled orbital to an empty one. In many cases, the promotion is from the HOMO to the LUMO, which is usually an antibonding orbital. Higher excited states, can also be populated. In any case, photoexcitation involves *unpairing of electrons* but at the instant of excitation they still have opposite spins.
2. At the instant of excitation, only electrons are reorganized. The nuclei retain their ground state geometry. The excitation is called a *vertical transition*, and the statement of this condition is referred to as the *Frank-Condon principle*. A consequence is that the initial excited state is in a nonminimal energy geometry. The excited state then attains its minimum energy structure extremely rapidly, with release of excess energy.
3. The electrons do not undergo spin inversion at the instant of excitation. Inversion is forbidden by quantum mechanical selection rules, which require that there be conservation of spin during the excitation process. Although a subsequent spin state change may occur, it is a separate step from excitation. In the initial excited state the unpaired electrons have opposite spins in a *singlet state*.

Thus, in the very short time (10^{-15} s) required for excitation, the molecule does not undergo changes in nuclear position or in the spin state of the promoted electron. After the excitation, however, these changes can occur very rapidly. There may be a minimum, usually shallow, close to the initial Franck-Condon geometry. Such states are attained very rapidly (<50 ps). The ultimate minimum energy geometry associated with the excited state is rapidly achieved by vibrational processes that transfer thermal energy to the solvent. This process, called *internal conversion*, results in formation of the minimum energy structure of the singlet excited state. The rate of transformation between different excited states depends on their similarity in structure and energy.² The more similar in structure and energy, the faster the transition. Often, the excited state attains its minimum energy without passing any barrier. Sometimes, chemical reactions of the excited molecule are fast relative to this vibrational relaxation, but this is unusual in solution. When reaction proceeds more rapidly than vibrational relaxation, the reaction is said to involve a *hot excited state*, that is, one with excess vibrational energy. The excited state can also undergo *intersystem crossing*, the inversion of spin of an electron in a half-filled orbital to give a *triplet state*, in which both unpaired electrons have the same spin. The triplet state also adopts a new minimum energy molecular geometry. Photochemical transitions can also be described as *diabatic* and *adiabatic*. A diabatic process involves a shift from one energy surface to another without a geometric change. An adiabatic process occurs on one energy surface by geometric reorganization.

Intersystem crossing must also occur when triplet excited states return to singlet ground states. A prominent factor in the rate of such processes is *spin-orbit coupling*, which depends on the structure of the triplet state and strongly affects the rate of intersystem crossing. The extent of spin-orbit coupling and the rate of intersystem crossing decrease with increasing separation of the orbitals containing the unpaired electrons.³ There is also a preference for perpendicular orientation of the orbitals.

². L. Landau, *Phys.Z. Sowjet.*, **2**, 46 (1932); L. Zener, *Proc. Royal Soc. London*, **A137**, 696 (1932).

³. L. Salem and C. Rowland, *Angew. Chem. Int. Ed. Engl.*, **11**, 92 (1972); L. Carlacci, C. Doubleday, Jr., T. R. Furlani, H. F. King, and J. W. McIver, Jr., *J. Am. Chem. Soc.*, **109**, 5323 (1987); C. Doubleday, Jr., N. J. Turro, and J.-F. Wang, *Acc. Chem. Res.*, **22**, 199 (1989); M. Klessinger, *Theor. Org. Chem.*, **5**, 581 (1998).

Spin-orbit coupling also increases with the degree of ionic character of the singlet state. The presence of a heavy element, e.g., bromine, also promotes intersystem crossing.

The overall situation can be represented for a hypothetical molecule using a potential energy diagram. The designations S and T are used for singlet and triplet states, respectively. The excitation is a vertical transition; that is, it involves no distortion of the molecular geometry. Horizontal displacement on the diagram corresponds to motion of the atoms relative to one another. Since the potential energy surfaces of the excited states are displaced from that of the ground state, the species formed by excitation is excited both electronically and vibrationally. The energy wells corresponding to the triplet states also correspond to a different minimum energy molecular geometry. *Nonradiative decay*, also called *internal conversion*, results in dissipation of the vibrational energy as the molecule moves to the bottom of any particular energy well. One of the central issues in the description of any photochemical reaction is the question of whether a singlet or triplet excited state is involved, and this depends on the rate of intersystem crossing in comparison with the rate of chemical reaction of the singlet excited state. If intersystem crossing is fast relative to reaction, reaction will occur through the triplet excited state. If reaction is faster than intersystem crossing, the reaction will occur from the singlet state. The processes that can occur after photochemical excitation are summarized in Figure 12.1.

Photosensitization is an important alternative to direct excitation of molecules and this method usually results in reaction occurring via a triplet excited state. If a reaction is to be carried out by photosensitization, a substance known as the *sensitizer* is included in the system. Each sensitizer has a characteristic energy, E_T , that it can transfer to a reactant. The sensitizer is chosen to meet the following criteria: (1) It must be excited by the irradiation to be used. (2) It must be present in sufficient concentration and absorb more strongly than the other reactants under the conditions

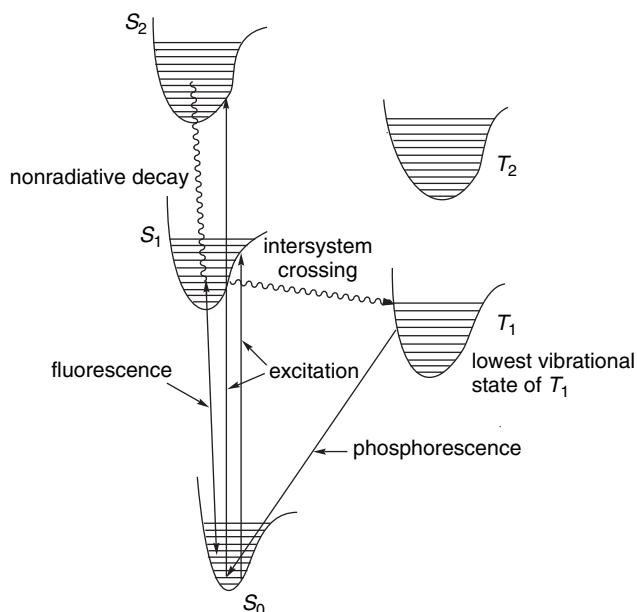
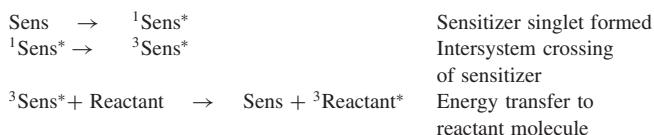


Fig. 12.1. Energy level diagram and summary of photochemical processes.

of the experiment so that it is the major light absorber. (3) Its intersystem crossing rate must be faster than energy transfer to the reactant or solvent from the singlet excited state. (4) The energy of its triplet state must be greater than that of the reactant; if this condition is not met, the energy transfer becomes endothermic and cannot compete with other transformations. (5) The triplet excited sensitizer must be able to transfer energy to the desired reactant.

The transfer of energy proceeds with net conservation of spin. In the usual case, the reactant molecule is a ground state singlet, and its reaction with the triplet excited state of the sensitizer produces a triplet state of the reactant. The mechanism for triplet photosensitization is as follows:



Sensitization can occur from singlet excited states, but for most cases we discuss, triplet sensitization operates.

When an excited state of the reactant has been formed, either by direct or sensitized energy transfer, the stage is set for a photochemical reaction. There are, however, competitive processes that can occur and result in the return of unreacted starting material. The excited state can decay to the ground state by emission of light, a *radiative transition*. The rate of emission can be very fast ($k = 10^5 - 10^9 \text{ s}^{-1}$) for transitions between electronic states of the same multiplicity, but is somewhat slower ($k = 10^3 - 10^5 \text{ s}^{-1}$) between states of different multiplicities. The two processes are known as *fluorescence* and *phosphorescence*, respectively. When energy has been emitted as light, the reactant is no longer excited, of course, and a photochemical reaction does not occur. Excited states can also be *quenched*. Quenching is the same physical process as sensitization, but the term “quenched” is used when a photoexcited state of the reactant is deactivated by transferring its energy to another molecule in solution. This substance is called a *quencher*. Finally, *nonradiative decay* can occur. In this process, the energy of the excited state is transferred to the surrounding molecules as vibrational (thermal) energy without light emission.

Owing to the existence of these competing processes, not every molecule that is excited undergoes a photochemical reaction. The fraction of molecules that react relative to those that are excited is called the *quantum yield*, Φ , which is a measure of the efficiency of the absorption of light in producing reaction product. A quantum yield of 1 means that each molecule excited (which equals the number of quanta of light absorbed) goes to product. If the quantum yield is 0.01, then only 1 out of 100 of the molecules that are excited undergoes photochemical reaction. The quantum yield can vary widely, depending on the structure of the reactants and the reaction conditions. The quantum yield can be greater than 1 in a chain reaction, in which a single photoexcitation initiates a series of repeating reactions leading to many molecules of product per initiation step.

As photochemical processes are very fast, special techniques are required to obtain rate measurements. One method is flash photolysis, in which the excitation is effected by a short pulse of light in an apparatus designed to monitor very fast spectroscopic

changes. The rate characteristics of the reactions following radiation can be determined from these spectroscopic changes. Various other techniques have been developed to follow the exceedingly fast changes that occur immediately after excitation. Some of them can detect changes that occur over 10–100 fs (10^{-15} s).

A useful technique for indirectly determining the rates of certain reactions involves measuring the quantum yield as a function of quencher concentration. A plot of the inverse of the quantum yield versus quencher concentration is then made (*Stern-Volmer plot*). As the quantum yield indicates the fraction of excited molecules that go on to product, it is a function of the rates of the processes that result in other fates for the excited molecule. These processes are described by the rate constants k_q (quenching) and k_n (other nonproductive decay to ground state):

$$\Phi = \frac{k_r}{k_r + k_q[Q] + k_n} \quad (12.2)$$

A plot of $1/\Phi$ versus $[Q]$ then gives a line with the slope k_q/k_r . It is often possible to assume that quenching is diffusion controlled, permitting assignment of a value to k_q . The rate of photoreaction, k_r , for the excited intermediate can then be calculated.

In the sections that follow, the discussion centers on the reactions of excited states, rather than on the other routes available for dissipation of excitation energy. The chemical reactions of photoexcited molecules are of interest for several reasons:

1. Excited states have excess energy and can therefore undergo reactions that would be highly endothermic if initiated from the ground state. For example, from the relationship $E = h\nu$ we can calculate that excitation by 350-nm light corresponds to 82 kcal/mol in energy transfer.
2. The population of one or more antibonding orbitals in the excited state allows the occurrence of chemical transformations that are electronically forbidden to ground state species.
3. Both singlet and triplet excited states have unpaired electrons, whereas closed-shell species are involved in most thermal processes (free radical reaction being an exception). This permits the formation of intermediates that are unavailable under thermal conditions.

Another important distinction between ground state and excited state reactions involves the relative rates of conformational interconversion. In thermal reactions, as stated by the Curtin Hammett principle (p. 296) conformers are normally in equilibrium, but the position of the equilibrium does not determine the reaction pathway. Many steps in photochemical reactions occur sufficiently rapidly that various conformers are not in equilibrium. This is the principle of *nonequilibrium of excited rotamers* (NEER).⁴ Thus in analyses of photochemical reactions, it is often necessary to consider conformational issues in order to interpret the reaction. *Reaction dynamics* refers to the conformational and other geometrical aspects of the reactions.

As we describe photochemical reactions, we note repeatedly that photochemical reactions involve unpairing and re-pairing of electrons. Frequently, atom and group migrations occur prior to the final electron re-pairing. Although discerning these unpairing/re-pairing schemes is a first step in understanding photochemical mechanisms, we also want to consider the structure of excited states and reaction intermediates. As is the case for transition structures in thermal reactions, computational approaches have provided a new level of insight.

⁴. H. J. C. Jacobs and E. Havinga, *Adv. Photochem.*, **11**, 305 (1979).

The mechanisms of photochemical reactions can be presented at several levels of detail. The most basic level is to recognize the unpairing/re-pairing sequence that is associated with bond breaking and bond forming. These processes can be further described by depicting the orbitals that are involved. Just as in thermal reactions, orbital symmetry and/or stereoelectronic effects can be recognized in this way. Photochemical reactions can also be described by potential energy diagrams, similar to those we have used for thermal reactions. For a photochemical reaction, the diagram represents transitions between the excited structures and aims to trace the path from excitation to photoproduct. As for thermal reactions, the path depicted is the minimum energy path across a potential energy surface. Photochemical reactions, however, can involve several excited states, each with its own potential energy surface, so there are several energy plots representing these surfaces. Two-dimensional representations can depict progress in one structural change, such as a twist about a bond or a bond breaking. Alternatively, the reaction progress may be viewed as a composite of all the structural changes that take place among reactant, excited state, and product. Figure 12.2 is such a diagram, depicting transitions between excited states and, eventually, the ground state surface of the products. The diagram shows excitation to both S_1 and S_2 , the first and second singlet excited states. Molecules drop to the S_1 surface at point C. Singlet excited molecules return to the ground state at point A and may return to reactant or proceed to product P_1 . Intersystem crossing occurs at points B or D and provides the triplet excited state, which gives product P_2 .

Reactions in which structural change is simultaneously occurring in more than one structural parameter can be depicted as interaction between surfaces with coordinates described by the structural parameters. For many photochemical reactions it has been found that transfer from an excited to a ground state involves a *conical intersection* (CI), which can be thought of as a funnel that permits transition from one energy surface (state) to another. The efficiency of the transformation depends on the structural similarity between the excited state and the corresponding ground state molecular ensemble. There can be a number of CIs for the excited states of a typical polyatomic molecule. The transition occurs without luminescence. Conical

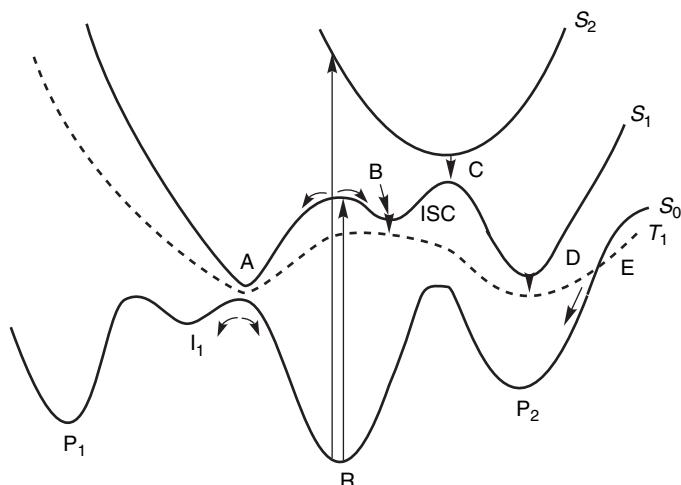


Fig. 12.2. A schematic representation of several transitions between excited states leading to photochemical reaction products.

intersections are analogous to transition states in thermal reactions in that they are points at which the electronic transition from the excited to the ground state is very fast.⁵ In a transition structure there is an imaginary vibrational frequency corresponding to the reaction coordinate (Section 3.2.1). Conical intersections can proceed along any direction in a plane and can reach more than one minimum (product). The ultimate outcome of the reaction is influenced by dynamic factors at the CI. Thus motion toward a particular product may be associated with dynamic factors, e.g., direction of rotation at a preceding stage of the reaction. As in the case of thermal TSs, the structure of a CI can be described on the basis of computation.⁶ Figure 12.3 is a representation of a conical intersection showing divergent paths to two different products, P_1 and P_2 , resulting from different components of motion along the X_1 and X_2 coordinates.

We discuss some prototypical reactions, such as *cis-trans* isomerization, electrocyclic reactions, and cycloadditions in terms of the structures of excited states and conical intersections. For most other reactions, we represent the reaction changes in terms of structures that depict the unpairing and re-pairing events. Such representations identify key structural features that influence the outcome of the reaction, even though they may leave much uncertainty about the detailed structure of the excited states and intermediates. For several reactions, the mechanism is discussed in terms of the structure and reaction paths for CIs. Structures of specific CIs derived from computation are depicted. At this time, it is perhaps too early to fully judge the accuracy of these structural representations. However, just as for depiction of TS structures, visualization of the CI can help understand the course of a photochemical reaction.

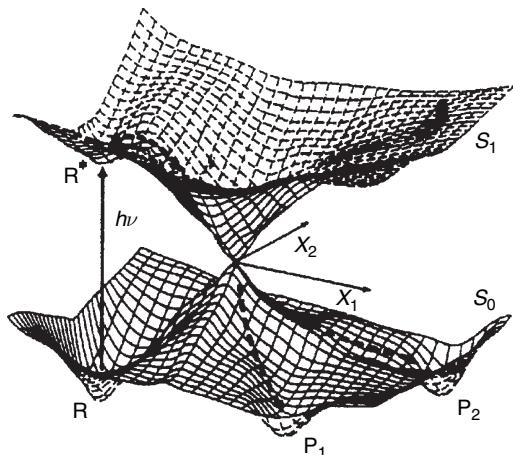


Fig. 12.3. Schematic representation of the potential energy surfaces of the ground (S_0) and excited (S_1) state in a nonadiabatic photochemical reaction. Two reaction channels lead from the conical intersection to products P_1 and P_2 . The trajectories entering the conical intersection determine which reaction channel is followed. Reproduced from *Angew. Chem. Int. Ed. Engl.*, **34**, 549 (1995), by permission of Wiley-VCH.

⁵ Y. Haas and S. Zilberg, *J. Photochem. Photobiol.*, **144**, 221 (2001); M. Klessinger, *Angew. Chem. Int. Ed. Engl.*, **34**, 549 (1995).

⁶ F. Bernardi, M. Olivucci, and M. A. Robb, *J. Photochem. Photobiol. A*, **105**, 365 (1997).

SECTION 12.2

Photochemistry of
Alkenes, Dienes, and
Polyenes

We begin by discussing two fundamental types of photochemical reactions of alkenes and dienes. One is *cis-trans* isomerization and the others fall into the category of pericyclic reactions, including electrocyclic reactions and cycloadditions. As indicated in Chapter 10, there is a broad dichotomy between thermal and photochemical pericyclic reactions. Thermally forbidden processes are typically allowed photochemically and vice versa. Although the interpretation and prediction of the stereoselectivity of pericyclic thermal reactions is generally possible within the framework of the Woodward-Hoffmann rules, we will find several complicating factors when we consider photochemical reactions. We also examine a number of unimolecular photochemical rearrangements of alkenes and polyenes. Cycloadditions are considered further, from a synthetic viewpoint, in Section 6.3.2 of Part B.

12.2.1. *cis-trans* Isomerization

Interconversion of *cis* and *trans* isomers is a characteristic photochemical reaction of alkenes. Usually, the *trans* isomer is thermodynamically more stable, but photolysis can establish a mixture that is richer in the *cis* isomer. Irradiation therefore provides a means of converting a *trans* alkene to the *cis* isomer. The composition of the photostationary state depends on the absorption spectra of the isomeric alkenes. A hypothetical case is illustrated in Figure 12.4. Assume that the vertical line at 265 nm is the lower limit for light reaching the system. This wavelength can be controlled by use of appropriate sources and filters. Because of the shift of its spectrum toward longer wavelengths and higher extinction coefficients, the *trans* isomer absorbs substantially more light than the *cis* isomer. The relative amount of light absorbed at any wavelength is proportional to the extinction

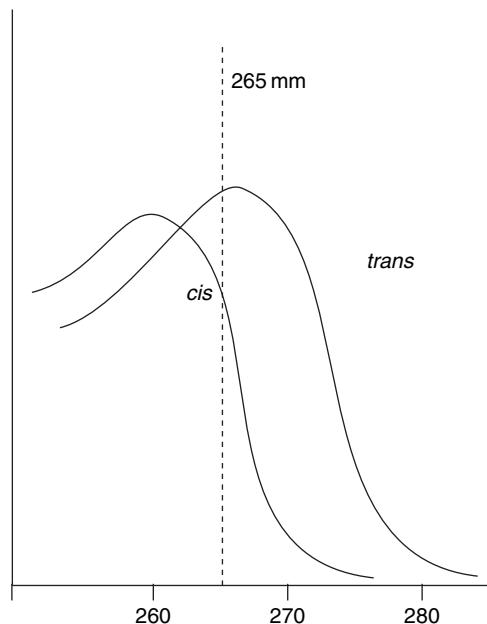


Fig. 12.4. Absorption spectra of a *cis-trans* isomer pair.

coefficients at that wavelength. If we assume that the quantum yield for conversion of *cis*→*trans* is approximately equal to that for *trans*→*cis*, the conversion of *trans* alkene to *cis* will occur faster than the converse process when the two isomers are in equal concentrations. On continued photolysis, a photostationary state will be achieved when the rate of *trans*→*cis* is equal to that of *cis*→*trans*. At this point the concentration of the *cis* isomer will be greater than that of the *trans* isomer. The relationship can be expressed quantitatively for monochromatic light as

$$\frac{[\text{trans}]}{[\text{cis}]} = \left(\frac{\varepsilon_c}{\varepsilon_t} \right) \left(\frac{\Phi_{c \rightarrow t}}{\Phi_{t \rightarrow c}} \right) \quad (12.3)$$

The *cis*-*trans* isomerization of alkenes is believed to take place via an excited state in which the two sp^2 carbons are twisted by about 90° with respect to one another. This twisted geometry is believed to be the minimum energy geometry for both the singlet and triplet excited states. The twisted geometry is an *energy maximum* on the ground state surface. The twisted geometry for the excited state permits the possibility of returning to either the *cis* or *trans* configuration of the ground state. The return from the singlet excited state to the ground state involves re-pairing of the electrons by a nonradiative process. Return from the triplet state requires intersystem crossing.

12.2.1.1. Photoisomerization of Ethene and Styrene We consider the excited states of ethene and styrene in some detail. These molecules do not exist as *cis* and *trans* isomers unless they are isotopically labeled. However, they are prototypes of isolated and conjugated alkenes and have been studied extensively. The excited states of ethene have been studied both by experiment and computation. The S_1 and T_1 excited states have been described by MP4(SDTQ)/6-311G** computations.⁷ At this level of computation the energy of T_1 is 2.92 eV and S_1 is 5.68 eV. The T_1 state is calculated to have a perpendicular structure with extension of the C–C bond to 1.455 Å. The S_1 state is also twisted and is very strongly pyramidalized at one carbon. The C–C bond distance is 1.360 Å. This state is believed to have a large degree of zwitterionic character, with the negative charge at the pyramidalized carbon. These structures are depicted in Figure 12.5.

The excited state lifetime of ethene is very short ($<10^{-13}$ s). Both the valence and Rydberg excited states return to the ground state through a conical intersection. The CIs of the S_1 state have been examined using quantum dynamics calculations.^{8,9} Return from an excited state to the ground state involves both twisting at the C–C bond and pyramidalization. Another conical intersection, which is similar in structure to the carbene ethylidene, occurs at a similar energy. These structures are shown in Figure 12.6. As we explore alkene photochemistry, we will see that the excited states and CIs depicted in Figures 12.5 and 12.6 are prototypical of the structures that are involved in the photochemistry of alkenes. The triplet T_1 state of alkenes can be represented as a twisted triplet diradical. The S_1 state is often referred to as a zwitterionic state and can be thought of as having cationic character at one carbon and carbanionic character at the other. The S_1 excited state is quite similar to the strongly

⁷. S. El-Taher, P. Hilal, and T. A. Albright, *Int. J. Quantum Chem.*, **82**, 242 (2001); V. Molina, M. Merchan, B. O. Roos, and P.-A. Malmqvist, *Phys. Chem. Chem. Phys.*, **2**, 2211 (2000).

⁸. M. Ben-Nun and T. J. Martinez, *Chem. Phys. Lett.*, **298**, 57 (1998); M. Ben-Nun, J. Quenneville, and T. J. Martinez, *J. Chem. Phys. A*, **104**, 5161 (2000); J. Quenneville, M. Ben-Nun, and T. J. Martinez, *J. Photochem. Photobiol.*, **144**, 229 (2001).

⁹. M. Ben-Nun and T. J. Martinez, *Chem. Phys.*, **259**, 237 (2000).

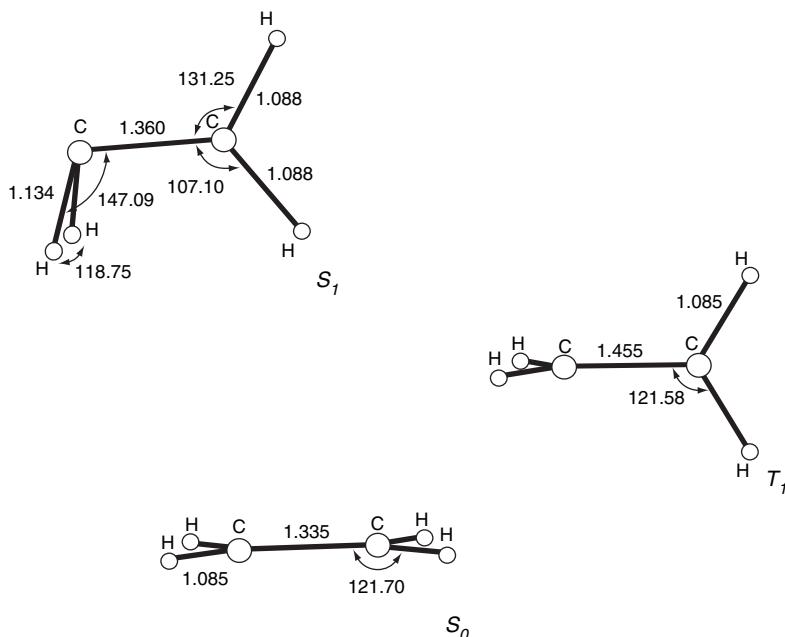
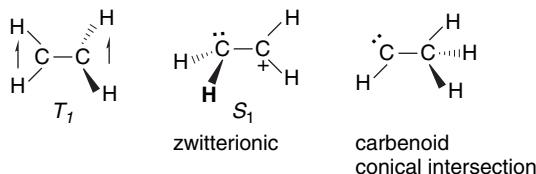


Fig. 12.5. Minimum energy structures (MP2/6-31G*) for S_0 , S_1 , and T_1 states of ethene. Reproduced from *Int. J. Quantum Chem.*, **82**, 242 (2001), by permission of Wiley-VCH.

pyramidalized CI in Figure 12.6. The CI with carbene character is also a common feature of alkene chemistry and can be considered to form by hydride migration from the zwitterionic excited state. Similar structures involving carbon migration are also found for substituted alkenes.



There are two relatively low-lying singlet states for styrene. S_1 is associated primarily with the benzene ring, whereas S_2 is a singlet quinoid structure. The S_1 state

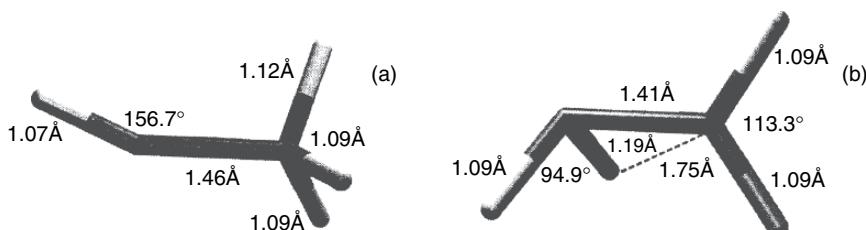
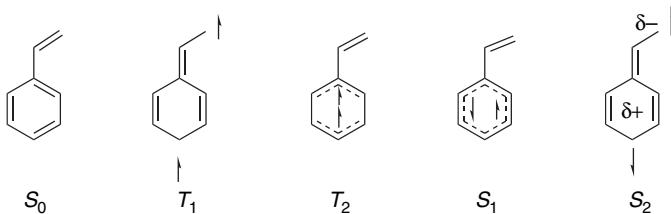


Fig. 12.6. Structures of lowest-energy conical intersections for the singlet excited state of ethene: (a) ethylidene-like structure; (b) twisted and pyramidalized structure. Reproduced from *Chem. Phys.*, **259**, 237 (2000), by permission of Elsevier.

is believed to be planar with a barrier to rotation of the double bond with respect to the ring of at least 3–4 kcal/mol.¹⁰ The decay time for the S_1 styrene is in the nanosecond range, which is considerably longer than for ethene.¹¹ The S_2 excited state of styrene is a zwitterionic structure similar to the S_1 state for ethene. In this case, as might be expected, the terminal methylene group is pyramidalized, with the cationic character associated with the phenyl-substituted carbon. The T_1 state is quinoid in character with a shortened bond between the benzene ring and the double bond. T_2 involves a triplet configuration of the benzene π electrons. Valence bond representations are shown below.



Valence Bond Representation of Excited States of Styrene

The geometries and energetics of the styrene excited states have been calculated at the CAS-SCF/6-31G* level using all the π orbitals of styrene and are given in Figure 12.7.¹² The changes in bond length relative to the ground state indicate the nature of the excited states. Figure 12.7 shows the computed structures and energies of the excited states and indicates the singlet-singlet and singlet-triplet intersections. The $T_2 \rightarrow T_1$ internal conversion, which involves transfer of triplet character from the benzene ring to the ethylene bond, is efficient. The $T_1 \rightarrow S_0$ intersection, labeled ISC_c , is considered to be inefficient because of small spin-orbit coupling. This conversion is believed to occur in time range 20–100 ns.¹³ This appears to be the slowest step in the decay sequence from the triplet excited state. Return to the ground state in the singlet manifold can occur from the ISC_b intersection. The styrene conical intersection appears to be similar to that for ethene and to involve both twisting and pyramidalization.¹⁴ As Figure 12.7 suggests, there is considerable complexity to the styrene excited state surface. The introduction of the second chromophore, the benzene ring, introduces new issues

- ¹⁰. J. I. Seeman, V. H. Grassian, and E. R. Bernstein, *J. Am. Chem. Soc.*, **110**, 8542 (1988); V. H. Grassian, E. R. Bernstein, H. V. Secor, and J. I. Seeman, *J. Phys. Chem.*, **93**, 3470 (1989); J. A. Syage, F. Al Adel, and A. H. Zewail, *Chem. Phys. Lett.*, **103**, 15 (1983).
- ¹¹. D. A. Condirston and J. D. Laposa, *Chem. Phys. Lett.*, **63**, 313 (1979).
- ¹². M. J. Bearpack, M. Olivucci, S. Wilsey, F. Bernardi, and M. A. Robb, *J. Am. Chem. Soc.*, **117**, 6944 (1995).
- ¹³. R. Bonneau, *J. Photochem.*, **10**, 439 (1979); R. A. Caldwell, L. D. Jacobs, T. R. Furlani, E. A. Nalley, and J. Laboy, *J. Am. Chem. Soc.*, **114**, 1623 (1992).
- ¹⁴. V. Molina, M. Merchan, B. O. Roos, and P.-A. Malmqvist, *Phys. Chem. Chem. Phys.*, **2**, 2211 (2000).

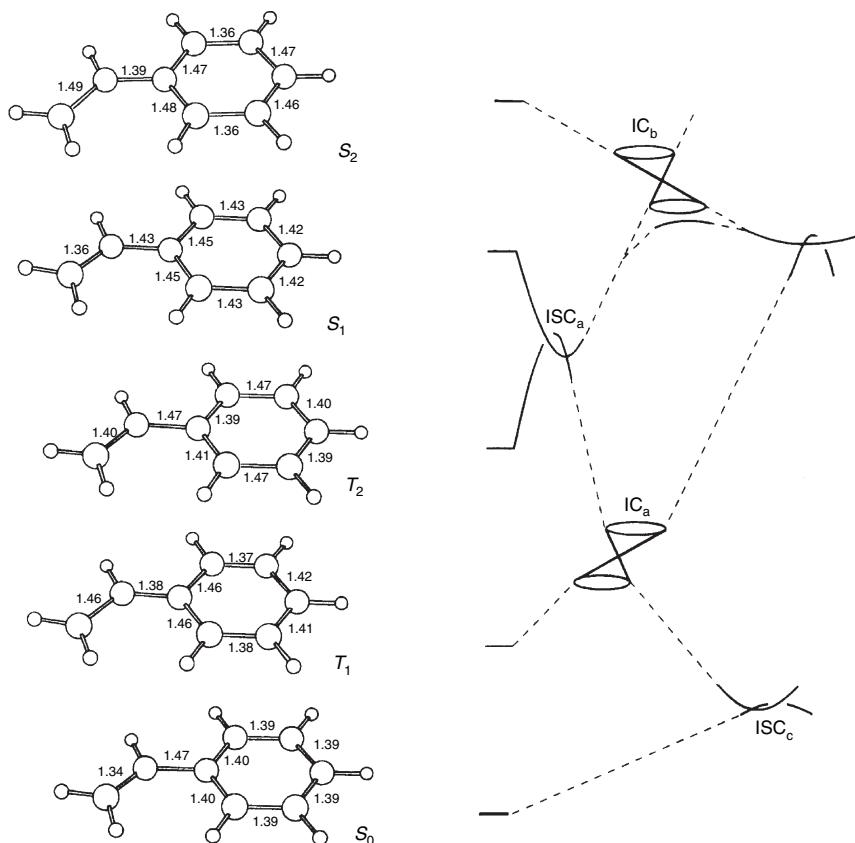


Fig. 12.7. Structures for the excited states T_1 , T_2 , S_1 , and S_2 of styrene. Singlet-singlet conical intersections are labeled IC (internal conversion). Singlet-triplet intersections are labeled ISC (inter-system crossing). Adapted from *J. Am. Chem. Soc.*, **117**, 6944 (1995), by permission of the American Chemical Society.

concerning energy transfer between the chromophores. However, the fundamental aspects of the double-bond rotation seem to be structurally similar to those for ethene.

12.2.1.2. Photoisomerization of Stilbene Especially detailed study of the mechanism of photochemical configurational isomerism has been done on *Z*- and *E*-stilbene.¹⁵ The isomerization involves a twisted singlet state that can be attained from either the *Z*- or the *E*-isomer. Spectroscopic data have established the energies of the singlet and triplet states of both *Z*- and *E*-stilbene and of the twisted excited states that are formed from both isomers. Some features of the potential energy diagram are due to structural

¹⁵. J. Saltiel, J. T. D'Agostino, E. D. Megarity, L. Metts, K. R. Neuberger, M. Wrighton, and O. C. Zafiriou, *Org. Photochem.*, **3**, 1 (1973); J. Saltiel and J. L. Charlton, in *Rearrangements in Ground and Excited States*, Vol. 3, P. de Mayo, ed., Academic Press, New York, 1980, Chap. 14; D. H. Waldeck, *Chem. Rev.*, **91**, 415 (1991); U. Mazzucato, G. A. Aloisi, G. Bartocci, F. Elisei, G. Galiazzo, and A. Spalletti, *Med. Biol. Environ.*, **23**, 69 (1995); H. Gorner and H. J. Kuhn, *Adv. Photochem.*, **19**, 1 (1995).

differences in the ground state molecules.¹⁶ Although the double bond in *E*-stilbene can be assumed to be planar, the phenyl groups can rotate with respect to the plane of the double bond. In the solid state, the molecule is nearly planar, but in solution or gas phase the molecule is probably somewhat twisted. For the *Z*-isomer, steric interactions between the phenyl rings require their rotation from coplanarity. A rotation of 43° has been found in the gas phase. This steric effect makes the *Z*-isomer somewhat less stable than the *E*-isomer. Computed minimum energy ground state structures are shown in Figure 12.8.¹⁷

As shown in Figure 12.9, the absorption spectra of *Z*- and *E*-stilbene differ substantially, with the *E*-isomer absorbing more strongly at $\lambda > 260$ nm. Thus the

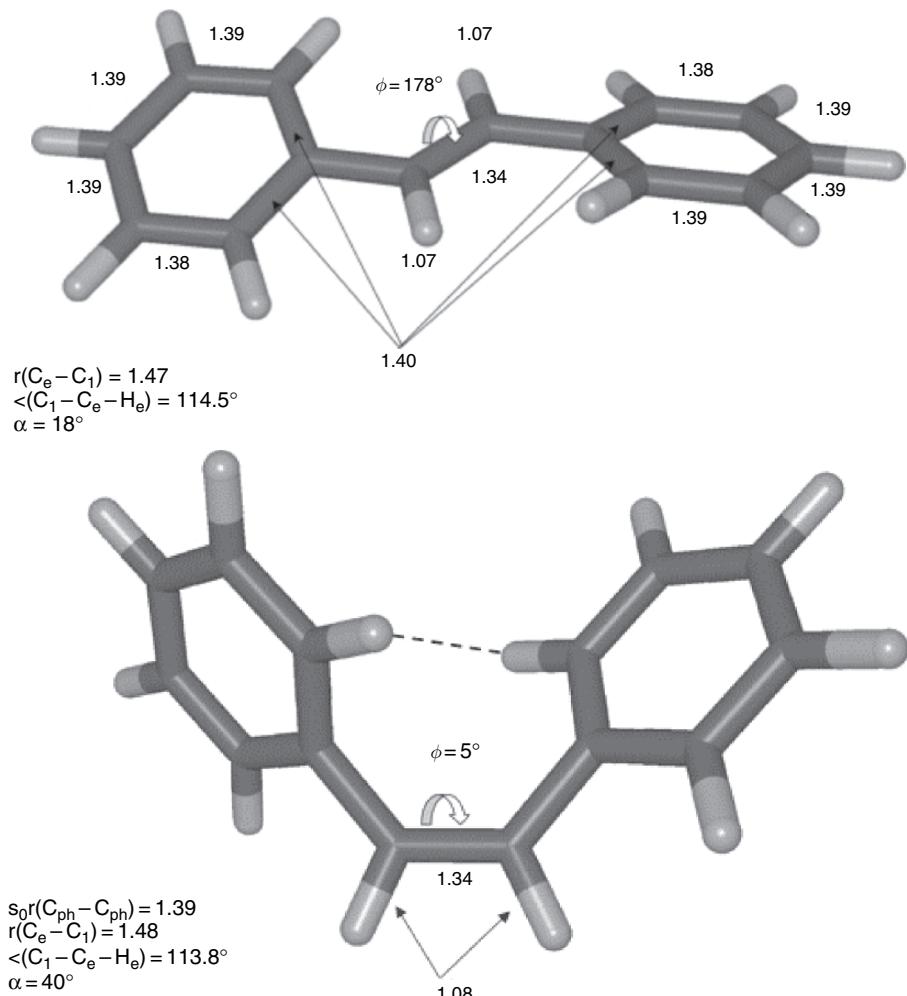


Fig. 12.8. Computed ground state geometries of *E*- and *Z*-stilbene. Reproduced from *J. Phys. Chem. A.*, **107**, 829 (2003), by permission of the American Chemical Society.

¹⁶ H. Meier, *Angew. Chem. Int. Ed. Engl.*, **31**, 1399 (1992).

¹⁷ J. Quenneville and T. J. Martinez, *J. Phys. Chem. A.*, **107**, 829 (2003).

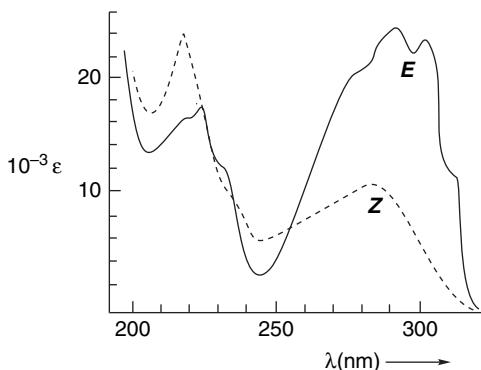


Fig. 12.9. UV spectra of *E*- and *Z*-stilbene in hexane at room temperature. Reproduced from *Angew. Chem. Int. Ed. Engl.*, **31**, 1399 (1992), by permission of Wiley-VCH.

photostationary state composition can be controlled by the wavelength of the irradiation, as indicated by the general examples and Equation (12.3) on p. 1082.¹⁸

Direct irradiation leads to isomerization via singlet state intermediates.¹⁹ This involves a HOMO→LUMO excitation that involves primarily the ethylenic bond. Among the pieces of evidence indicating that a triplet intermediate is not involved in direct irradiation is the fact that azulene, which is known to intercept stilbene triplets, has only a minor effect on the efficiency of the direct photoisomerization.²⁰ Some aspects of this process can be described in terms of the two-dimensional energy diagram shown in Figure 12.10, which shows the relative energies and shapes of the S_0 , T_1 , S_1 , and S_2 states with respect to twisting at the double bond. The temperature dependence of the isomerization reveals that the process of formation of the twisted state from S_1 involves a small activation energy. This energy is required for conversion of the initial excited state to the twisted geometry associated with the S_1 state. The energy barrier is greater from the *E*-isomer than from the *Z*-isomer. Note, however, that the large energy gap between the twisted excited and ground states implies a low probability of direct interconversion.

The photoisomerization can also be carried out by photosensitization. Under these conditions, the composition of the photostationary state depends on the triplet energy of the sensitizer. With sensitizers having triplet energies above 60 kcal/mol, $[Z]/[E]$ is slightly more than 1, but a range of sensitizers having triplet energies of 52–58 kcal/mol affords much higher *Z*:*E* ratios in the photostationary state.²¹ The high *Z*:*E* ratio in this region results from the fact that the energy required for excitation of *E*-stilbene is less than for *Z*-stilbene. Thus sensitizers in the range 52–58 kcal/mol selectively excite the *E*-isomer. Since the rate of conversion of $E \rightarrow Z$ is increased, the composition of the photostationary state is enriched in *Z*-isomer.

- ¹⁸. J. Saltiel, A. Marinari, D. W.-L. Chang, J. C. Mitchener, and E. D. Megarity, *J. Am. Chem. Soc.*, **101**, 2982 (1979).
- ¹⁹. J. Saltiel, *J. Am. Chem. Soc.*, **89**, 1036 (1967); **90**, 6394 (1968).
- ²⁰. J. Saltiel, E. D. Megarity, and K. G. Kneipp, *J. Am. Chem. Soc.*, **88**, 2336 (1966); J. Saltiel and E. D. Megarity, *J. Am. Chem. Soc.*, **91**, 1265 (1969).
- ²¹. G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. S. Bradshaw, D. O. Cowan, R. C. Counsell, V. Vogt, and C. Dalton, *J. Am. Chem. Soc.*, **86**, 3197 (1964); S. Yamauchi and T. Azumi, *J. Am. Chem. Soc.*, **95**, 2709 (1973).

Photosensitizer ^a	E_T	[Z:E]
Acetophenone	73.6	1.2
Benzophenone	68.5	1.2
2-Acetyl naphthalene	59.3	2.6
1-Naphthyl phenyl ketone	57.5	2.8
Benzil	53.7	4.6
Fluorenone	52.3	8.3
Pyrene	48.7	4.6
3-Acetylpyrene	45	2.8

a. From *J. Am. Chem. Soc.*, **86**, 3197 (1964).

Further insight into the stilbene $E \rightarrow Z$ photoisomerization has been obtained by computational studies. The S_1 state is considered to be a $\pi \rightarrow \pi^*$ state with considerable zwitterionic character. The transfer from the singlet photoexcited state of stilbene to the ground state is observed to be very fast and involves a CI. There have been two computational studies aimed at characterization of the CI. A CAS-SCF(STDQ-CI) study examined five filled and seven vacant π orbitals.²² The CI was characterized by considering primarily the singlet and doublet HOMO \rightarrow LUMO excitations. The CI is described as two PhCH fragments that are twisted with respect to one another. The structure of the CI has also been investigated by CAS-SCF-CASPT2 methods,¹⁷ and is shown in Figure 12.11. The qualitative characteristics of the CI are very similar to

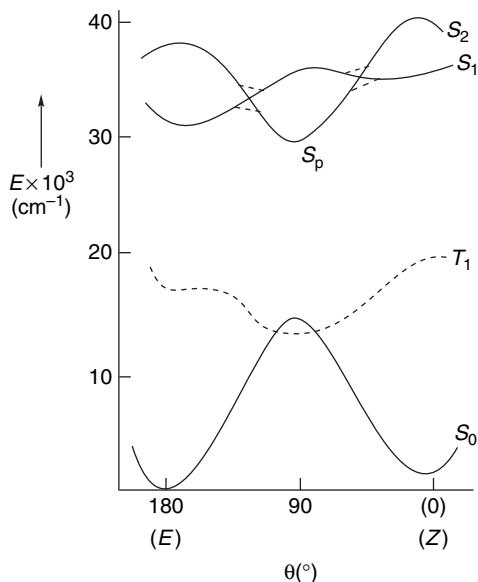


Fig. 12.10. Schematic potential energy profile for the $E \rightarrow Z$ isomerization of stilbene. The reaction coordinate is the torsion angle θ about the double bond. Reproduced from *Angew. Chem. Int. Ed. Engl.*, **31**, 1399 (1992), by permission of Wiley-VCH.

²². V. Molina, M. Merchan, and B. O. Roos, *J. Phys. Chem. A*, **101**, 3478 (1997); V. Molina, M. Merchan, and B. O. Roos, *Spectrochim Acta A*, **55**, 433 (1999).

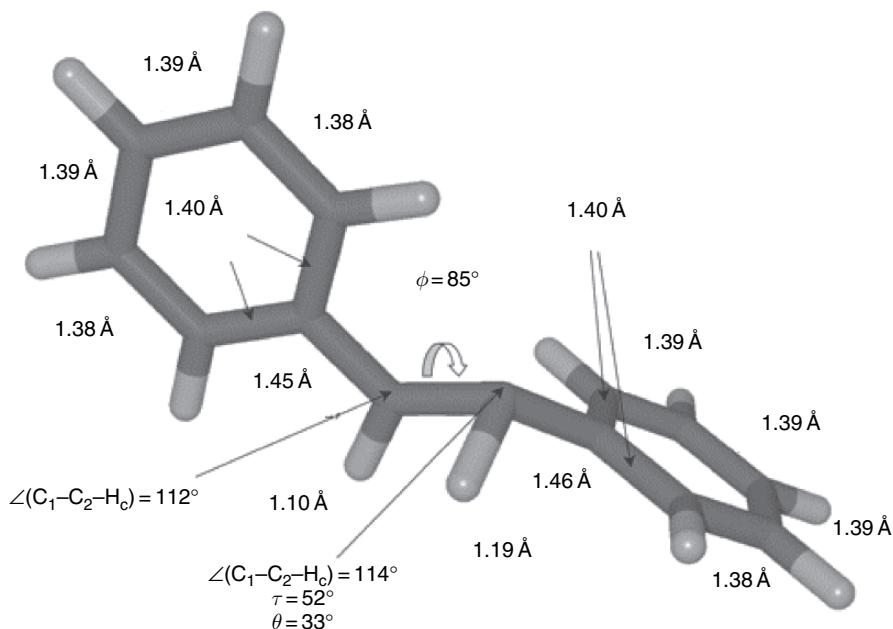


Fig. 12.11. The minimum energy structure for the S_0/S_1 conical intersection for stilbene. The geometrical parameters are from SA-2-CAS(2/2) level computations. Reproduced from *J. Phys. Chem. A*, **107**, 829 (2003), by permission of the American Chemical Society.

those described earlier for ethene and styrene. The structure is both twisted and pyramidalized, and is a mix of zwitterionic and (singlet) diradical character. Figure 12.12 depicts the singlet energy surface for stilbene as a function of both torsion at the ethylenic bond and pyramidalization.

The common feature of the ethene, styrene, and stilbene $S_1 \rightarrow S_0$ transformations is that double-bond isomerization involves not only twisting at the double bond but also pyramidalization. The pyramidalization modifies the energies that are depicted in Figure 12.10, which considers only the bond rotation, and lowers the energy of the S_p state sufficiently to permit rapid internal conversion.

The stilbene *cis-trans* isomerization has also been explored using DFT calculations.²³ The potential energy as a function of rotation of the single bond for the S_0 , T_1 , S_1 , and S_2 states is as shown in Figure 12.13. The S_0 maximum at 90° is characterized as a singlet diradical with the electrons delocalized in the adjacent phenyl ring, *i.e.*, two benzylic radicals. The central bond is essentially a single bond. This structure is 44.9 kcal/mol above the ground state *trans* (180°) minimum. The rotational potential for T_1 is very flat and nearly intersects the S_0 curve near 90° , at an energy of 46.5 kcal/mol. There is essentially no barrier to rotation at the T_1 surface. This structure is a triplet diradical. The vertical energy to the T_1 state is slightly higher for *cis*-stilbene than for *E*-stilbene, and proceeds without a barrier to the twisted minimum. The S_1 state shows a small maximum near 90° . There is a very shallow minimum slightly displaced from the vertical 180° (*trans*) structure. There is also a shallow minimum

²³ W.-G. Han, T. Lovell, T. Liu, and L. Noddeman, *Chem. Phys. Chem.*, **3**, 167 (2002).

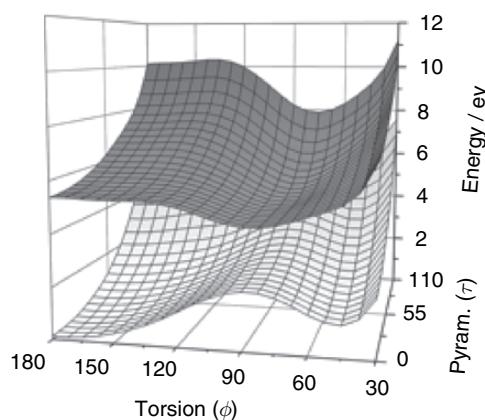


Fig. 12.12. Potential energy surfaces for S_0 and S_1 for stilbene computed at the SA-2-CAS(2/2) level as a function of C=C twist and pyramidalization τ with other dimensions held constant. The S_0 minima correspond to the *E*-isomer (180°) and *Z*-isomer (45°). Reproduced from *J. Phys. Chem. A*, **107**, 829 (2003), by permission of the American Chemical Society.

on S_1 at about 45° beginning from the *Z*-vertical state. At 90° , the S_1 state is about 70 kcal/mol above ground state *E*-stilbene. The twisted structure is a neutral diradical, but in contrast to T_1 and the S_0 maximum, there is nearly equal distribution of each

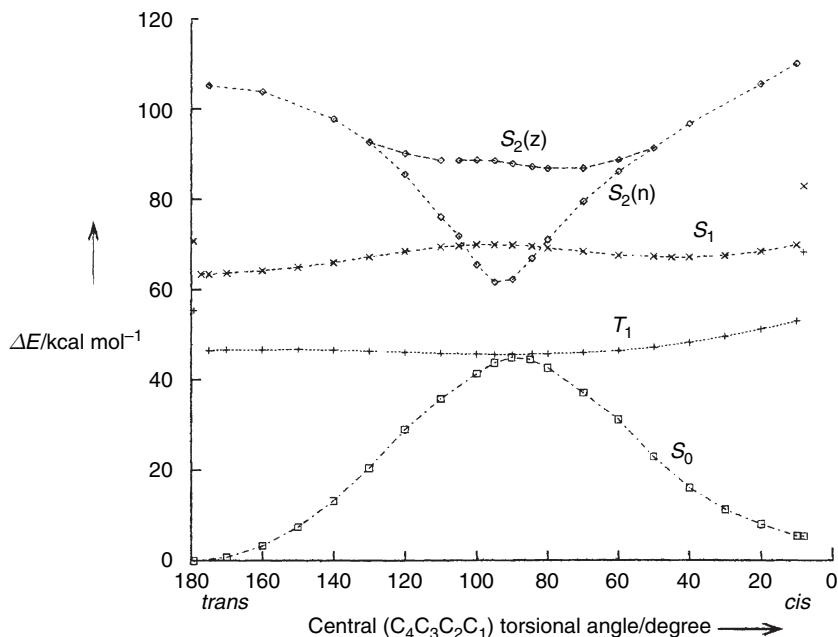
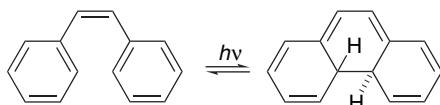


Fig. 12.13. DFT computation of the rotational energy profile of stilbene, beginning at the *trans* (180°) and *cis* (0°) geometries. Both neutral (*n*) and zwitterionic (*z*) versions of S_2 were computed. Reproduced from *Chem. Phys. Chem.*, **3**, 167 (2002), by permission of the Royal Society of Chemistry.

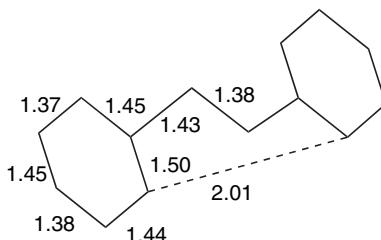
electron over both rings. The S_2 state shows a minimum at 90° , about 18 kcal above T_1 and S_0 at this geometry. The S_2 curve encounters small barriers from the vertical transitions (6.6 kcal/mol for *trans* and 2.2 for *cis*), in agreement with experimental conclusions. The main difference between the DFT and MO calculations is that the DFT computation describes the S_2 minimum as primarily a singlet diradical, rather than a zwitterionic, structure.

In addition to *cis-trans* isomerization, *Z*-stilbene also undergoes photocyclization to 4a,4b-dihydrophenanthrene via an electrocyclization.²⁴



The cyclization product is thermally unstable relative to *cis*-stilbene and reverts to starting material unless trapped by an oxidizing agent.²⁵ The extent of cyclization is solvent dependent, with nonpolar solvents favoring cyclization more than polar ones.²⁶ The quantum yield for *cis-trans* isomerization is nearly constant at about 0.35, but the cyclization quantum yield is in the range of 0.15–0.18 in hydrocarbons, as compared with 0.05–0.08 in acetonitrile or methanol. The detailed interpretation of the system involves the effect of solvent on the lifetime and dynamics of the excited states.²⁷ Figure 12.14 incorporates the reaction coordinate for cyclization into the *cis-trans* energy diagram.

The cyclization has been investigated by computation and can be described in terms of a CI involving interaction between the two phenyl rings.²⁸ The structural features are similar to the CI involved in electrocyclization of *Z*-1,3,5-hexatrienes to cyclohexadienes described on p. 1142.



12.2.2. Photoreactions of Other Alkenes

Direct photochemical excitation of unconjugated alkenes requires light with $\lambda < 220\text{ nm}$. A study of *Z*- and *E*-2-butene diluted with neopentane demonstrated that *cis-trans* isomerization was competitive with the photochemical $[2\pi + 2\pi]$

²⁴. T. Wismonski-Knittel, G. Fischer, and E. Fischer, *J. Chem. Soc., Perkin Trans. 2*, 1930 (1974).

²⁵. L. Liu, B. Yang, T. J. Katz, and M. K. Poindexter, *J. Org. Chem.*, **56**, 3769 (1991).

²⁶. J.-M. Rodier and A. B. Myers, *J. Am. Chem. Soc.*, **115**, 10791 (1993).

²⁷. R. J. Sension, S. T. Repinec, A. Z. Szarka, and R. M. Hochstrasser, *J. Phys. Chem.*, **98**, 6291 (1993).

²⁸. M. J. Bearpark, F. Bernardi, S. Clifford, M. Olivucci, M. A. Robb, and T. Vreven, *J. Phys. Chem. A*, **101**, 3841 (1997).

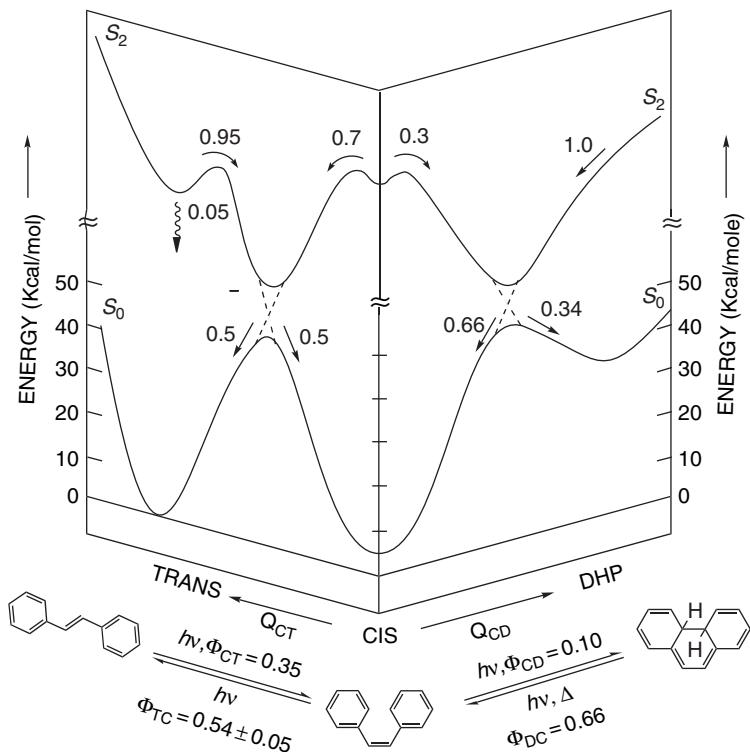
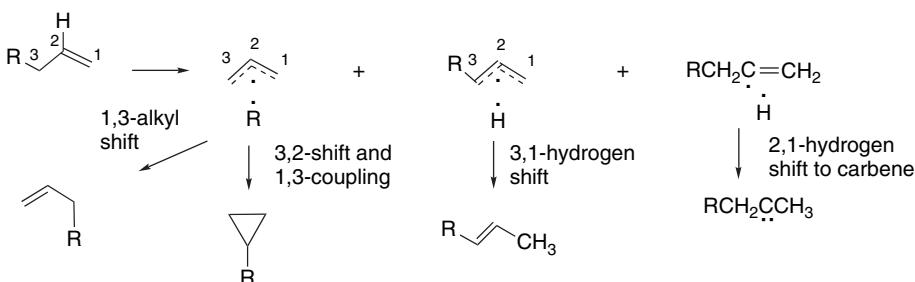


Fig. 12.14. Schematic representation of the potential energy surface for S_2 and S_0 of stilbene including the photocyclization reaction. Approximate branching ratios and quantum yields are indicated. Reproduced from *J. Phys. Chem.*, **98**, 6291 (1993), by permission of the American Chemical Society.

cycloaddition that occurs in pure liquid alkene.²⁹ We discuss the cycloaddition further in the next section. As the ratio of neopentane to butene increased, the amount of cycloaddition decreased, relative to *cis-trans* isomerization. This effect presumably is the result of the very short lifetime of the intermediate responsible for cycloaddition. When the alkene is diluted by inert hydrocarbon, the rate of encounter of a second alkene molecule is reduced, and the unimolecular isomerization becomes the dominant reaction. Rearrangement reactions are also observed, including 1,2-hydrogen shifts (to carbenes), 1,3-hydrogen and alkyl shifts, and cyclopropane formation. These reactions can occur from CIs that have the character of hydrogen or alkyl groups associated with an allyl or vinyl radical.³⁰ The vertical excitation energy for unconjugated alkenes is in the range of 150 kcal/mol, and these CIs are at 100 ± 20 kcal/mol. This is similar to the energy required for the dissociation of allylic C–H and C–C bonds, and dissociation is one of the pathways open to excited state alkenes.

²⁹. H. Yamazaki and R. J. Cvetanovic, *J. Am. Chem. Soc.*, **91**, 520 (1969); H. Yamazaki, R. J. Cvetanovic, and R. S. Irwin, *J. Am. Chem. Soc.*, **98**, 2198 (1976).

³⁰. F. Bernardi, M. Olivucci, M. A. Robb, and G. Tonachini, *J. Am. Chem. Soc.*, **114**, 5805 (1992); S. Wilsey and K. N. Houk, *J. Am. Chem. Soc.*, **122**, 2651 (2000).



Simple alkenes can be isomerized using triplet sensitizers and this often avoids the competing rearrangement reactions. Aromatic compounds such as benzene, toluene, xylene, and phenol can photosensitize *cis-trans* interconversion of simple alkenes.³¹ This is a case where the sensitization process must be somewhat endothermic because of the energy relationships between the excited states of the alkene and the sensitizers. The photostationary state obtained under these conditions favors the less strained of the alkene isomers. The explanation for this effect can be summarized with reference to Figure 12.15. Isomerization takes place through a twisted triplet state that is achieved by a combination of energy transfer from the sensitizer and thermal activation. Because the *cis* isomer is somewhat higher in energy, its requirement for activation to the excited state is somewhat less than for the *trans* isomer. If it is also assumed that the excited state forms the *cis* and *trans* isomers with equal ease, the rate of *cis* \rightarrow *trans* exceeds that for *trans* \rightarrow *cis* conversion ($k_{\text{c} \rightarrow \text{t}} > k_{\text{t} \rightarrow \text{c}}$) at the photostationary state and therefore $[\text{trans}] > [\text{cis}]$.³²

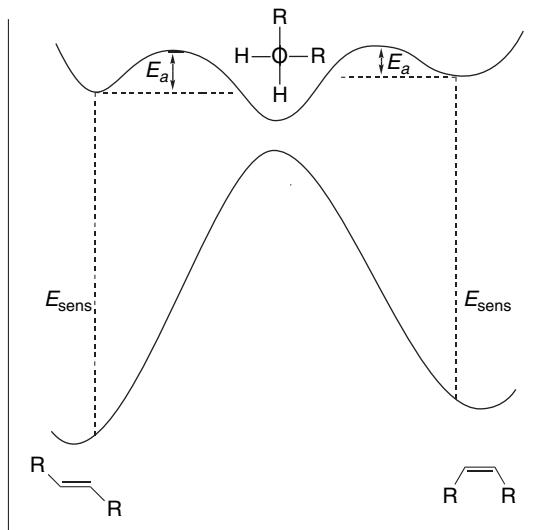
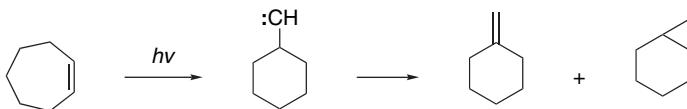


Fig. 12.15. Schematic potential energy diagram illustrating differential in energy required for triplet-sensitized photoisomerization of *cis* and *trans* isomers.

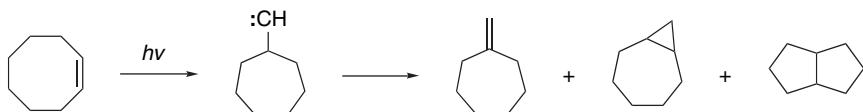
³¹ M. Tonaka, T. Terao, and S. Sato, *Bull. Chem. Soc. Jpn.*, **38**, 1645 (1965); G. A. Haninger and E. K. C. Lee, *J. Phys. Chem.*, **71**, 3104 (1967).

³² J. J. Snyder, F. P. Tise, R. D. Davis, and P. J. Kropf, *J. Org. Chem.*, **46**, 3609 (1981).

Photoexcitation of cycloalkenes introduces additional features because the ring limits the extent to which the double bond can twist. Cyclohexene, cycloheptene, and cyclooctene give rise to ring contraction and carbene insertion products.



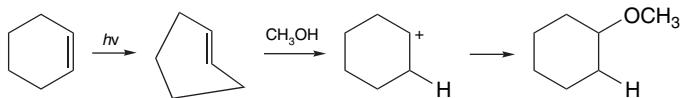
Ref. 33



Ref. 34

It has been possible to observe the processes that occur within 100 fs after excitation of cyclohexene to the $\pi-\pi^*$ and $\pi, 3s(R)$ states (200 nm). This time scale is too short to allow for intermolecular reactions, even in solution. The products are methylenecyclopentane and bicyclo[3.1.0]hexane. The processes are summarized in Figure 12.16.³⁵ The process designated τ_1 (20 fs) is believed to follow the relaxation of the vertical $\pi-\pi^*$ and $\pi, 3s(R)$ states to the equilibrium geometry on the $\pi-\pi^*$ surface. The process designated τ_2 represents the start of 1,3-H migration. At τ_3 the isomerization to the carbeneoid structure is complete. The C–C bond shift corresponds to τ_4 . The carbene can then return to the ground state surface by forming cyclohexene, bicyclo[3.1.0]hexane, or methylenecyclopentane. Some *E*-cyclohexene is formed and can be trapped by hydroxylic solvents.³⁶

The reaction course taken by photoexcited cycloalkenes in hydroxylic solvents depends on ring size.³⁷ Cyclohexene, cycloheptene, cyclooctene, 1-methylcyclohexene, 1-methylcycloheptene, and 1-methylcyclooctene all add methanol, but neither 1-methylcyclopentene nor norbornene does so. The key intermediate in the addition reaction is believed to be the highly reactive *E*-isomer of the cycloalkene. The *E*-cycloalkenes can be protonated exceptionally easily because of the enormous relief of strain that accompanies protonation.^{36,38}



The *E*-cycloheptene and cyclooctene isomers can be observed and *E*-cyclooctene can be isolated.

³³ Y. Inoue, S. Takamuka, and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 577 (1975).

³⁴ P. J. Kropp, J. D. Mason, and G. F. H. Smith, *Can. J. Chem.*, **63**, 1845 (1985).

³⁵ W. Fuss, W. E. Schmid, and S. A. Trushin, *J. Am. Chem. Soc.*, **123**, 7101 (2001).

³⁶ P. J. Kropp, E. J. Reardon, Jr., Z. L. F. Gaibel, K. F. Williard, and J. H. Hattaway, Jr., *J. Am. Chem. Soc.*, **95**, 7058 (1973).

³⁷ T. Mori and Y. Inoue, *CRC Handbook of Photochemistry and Photobiology*, W. Horspool and F. Lenci, ed., CRC Press, Boca Raton, FL, 2004, Section 16.

³⁸ J. A. Marshall, *Acc. Chem. Res.*, **2**, 33 (1969).

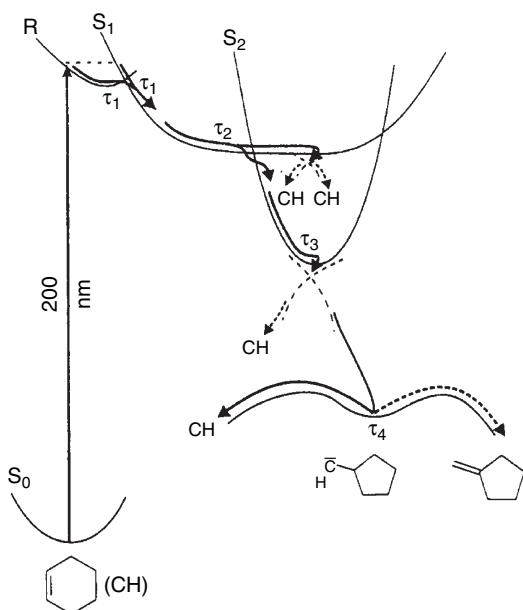
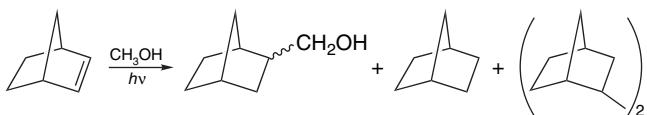
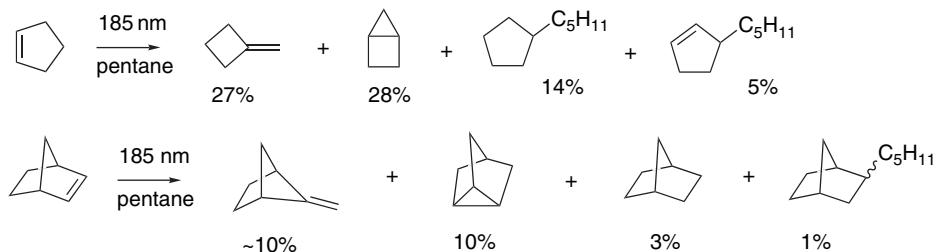


Fig. 12.16. Sequential events in the excitation and return to ground state for cyclohexene. Reproduced from *J. Am. Chem. Soc.*, **123**, 7101 (2001), by permission of the American Chemical Society.

The *trans* isomers of cyclopentene and norbornene are too strained to be formed. Rather, they give products in methanol that result from hydrogen abstraction and other radical-like processes.³⁹



Photolysis in hydrocarbon solvents leads to rearranged products similar to those from other cycloalkenes, as well as hydrogen abstraction and coupling products.⁴⁰



The nature of the excited states involved in formation of the carbene intermediates has been explored using CAS-SCF/6-31G* computations including the σ , σ^* , π , and

³⁹. P. J. Kropp, *J. Am. Chem. Soc.*, **91**, 5783 (1969).

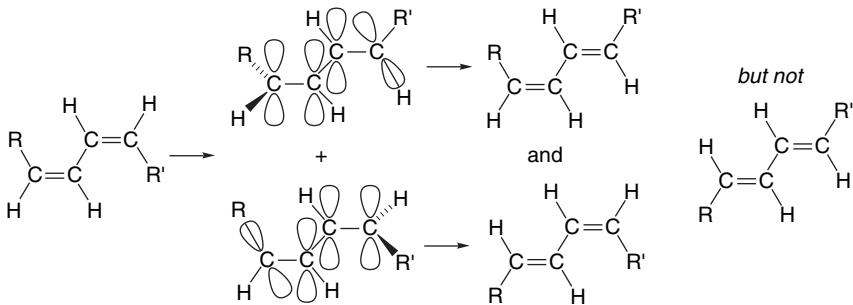
⁴⁰. R. Srinivasan and K. H. Brown, *J. Am. Chem. Soc.*, **100**, 4602 (1978); Y. Inoue, T. Mukai, and T. Hakushi, *Chem. Lett.*, 1045 (1982).

π^* orbitals of the double bond and directly attached atoms.⁴¹ Hydrogen and carbon migration leading to carbene intermediates occurs without any barrier from the excited states. These structures represent CIs corresponding to 1,2-migrations of hydrogen or carbon. The carbenoid structures can account for the rearranged products.

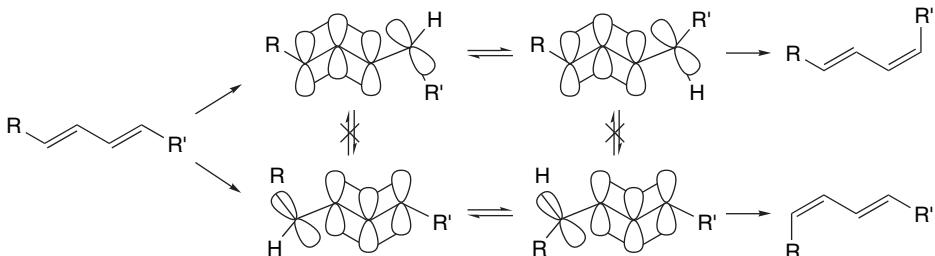


12.2.3. Photoisomerization of 1,3-Butadiene

The *cis-trans* isomerization reaction of 1,3-dienes can provide insight into the structure of the excited state. If the excited state is an allylmethylene diradical, only one of the two double bonds would be isomerized in any single excitation event.



On the other hand, if the excited state resembles a 1,4-but-2-enyl diradical, isomerization could take place at both double bonds. It is this latter situation that apparently exists in the triplet state. The triplet state has a high bond order between C(2) and C(3) and resists rotation about this bond, but the barrier to rotation at both of the terminal carbons is low.⁴² Both double bonds can isomerize through this excited state. In contrast, direct irradiation of 2,4-hexadiene at 257 nm isomerizes only one of the double bonds.⁴³ The singlet state apparently retains a substantial barrier to rotation about the bonds in the allyl system.



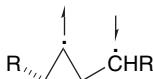
An alternative description of the singlet excited state is a cyclopropylmethyl singlet diradical. Only one of the terminal carbons would be free to rotate in such a structure.

⁴¹. S. Wilsey and K. N. Houk, *J. Am. Chem. Soc.*, **124**, 11182 (2002).

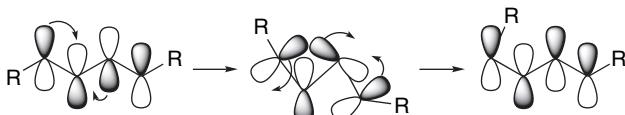
⁴². J. Saltiel, L. Metts, and M. Wrighton, *J. Am. Chem. Soc.*, **91**, 5684 (1969).

⁴³. J. Saltiel, L. Metts, and M. Wrighton, *J. Am. Chem. Soc.*, **92**, 3227 (1970).

(See p. 1138 for a discussion of the role of this structure in the S_2 excited state of 1,3-butadiene.)



Orbital symmetry control of subsequent ring opening could account for isomerization at only one of the double bonds. Taking ψ_3 as the controlling frontier orbital, it can be seen than a concerted return to ψ_2 leads to rotation at only one terminus of the diene.



The conclusion from these studies is that singlet *cis-trans* isomerization of substituted conjugated dienes such as 2,4-hexatriene must proceed through a structure that is free to rotate at only one terminus, whereas sensitized (triplet) isomerization involves a structure that can rotate at both termini.

The discussion of *cis-trans* photoisomerization of alkenes, styrene, stilbene, and dienes has served to introduce some important ideas about the interpretation of photochemical reactions. We see that thermal barriers are usually low, so that reactions are very fast. Because excited states are open-shell species, they present new kinds of structures, such as the twisted and pyramidalized CIs that are associated with both isomerization and rearrangement of alkenes. However, we will also see familiar structural units as we continue our discussion of photochemical reactions. Thus the triplet diradical involved in photosensitized isomerization of dienes is not an unanticipated species, given what we have learned about the stabilization of allylic radicals.

12.2.4. Orbital Symmetry Considerations for Photochemical Reactions of Alkenes and Dienes

The photochemistry of alkenes, dienes, and conjugated polyenes in relation to orbital symmetry relationships has been the subject of extensive experimental and theoretical study.⁴⁴ The analysis of concerted pericyclic reactions by the principles of orbital symmetry leads to a complementary relationship between photochemical and thermal reactions. A process that is forbidden thermally is allowed photochemically and vice versa. The complementary relationship between thermal and photochemical reactions can be illustrated by considering some of the reaction types discussed in Chapter 10 and applying orbital symmetry considerations to the photochemical mode of reaction. The case of $[2\pi+2\pi]$ cycloaddition of two alkenes, which was classified as a forbidden thermal reaction (see Section 10.1), can serve as an example. The correlation diagram (Figure 12.17) shows that the ground state molecules would lead to a doubly excited state of cyclobutane, and would therefore involve a prohibitive thermal activation energy.

How does the situation change when a photochemical reaction involving one ground state alkene and one excited state alkene is considered? If we assume a

⁴⁴. B. H. O. Cook and W. J. Leigh, in *Chemistry of Dienes and Polyenes*, Vol. 2, Z. Rappoport, ed. John Wiley, Chichester, 2000, pp. 197–255.

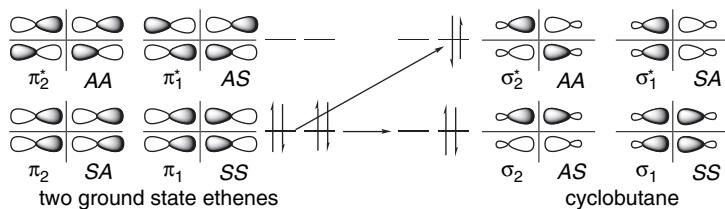


Fig. 12.17. Orbital correlation for two ground state ethenes and cyclobutane. The symmetry designations apply, respectively, to the horizontal and vertical planes for two ethene molecules approaching one another in parallel planes.

symmetrical approach as in the thermal reaction, then the same array of orbitals is involved, but the occupation of the orbitals is different: the π_1 (SS) orbital is doubly occupied, but π_2 (SA) and π_2^* (AA) are singly occupied. The reaction is therefore allowed in the sense that there is no high-energy barrier. Although the correlation diagram illustrated in Figure 12.18 might suggest that the product would initially be formed in an excited state, this is not necessarily the case. The concerted process can involve a transformation of the reactant excited state to the ground state of product. The nature of this transformation is discussed shortly.

Consideration of the HOMO-LUMO interactions also indicates that the $[2\pi+2\pi]$ addition is allowed photochemically. The HOMO in this case is the excited alkene π^* orbital. The LUMO is the π^* of the ground state alkene, and a bonding interaction is present between both pairs of carbons where new bonds must be formed. Similarly, the concept of aromatic transition states shows that the reaction has an antiaromatic 4π combination of basis set orbitals, which predicts an *allowed photochemical reaction*. Thus, orbital symmetry considerations indicate that photochemical $[2\pi+2\pi]$ cycloaddition of alkenes is feasible.

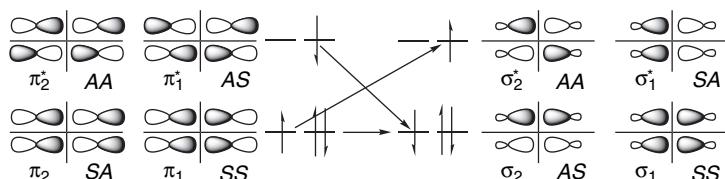
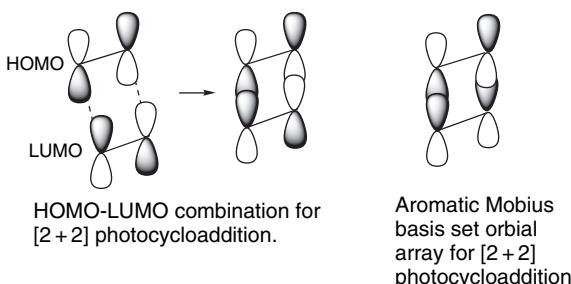


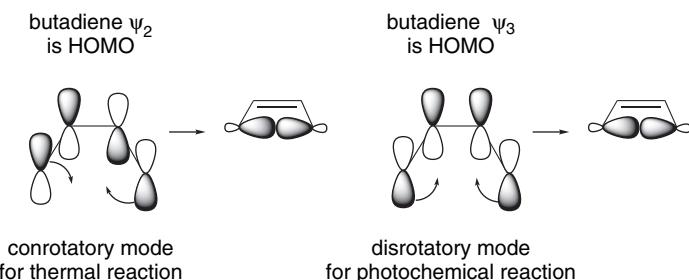
Fig. 12.18. Orbital correlation diagram for one ground state ethene and one ethene in an excited state. The symmetry designations apply, respectively, to the horizontal and vertical planes for two ethene molecules approaching one another in parallel planes.

SECTION 12.2

Photochemistry of
Alkenes, Dienes, and
Polyenes

It is a general result that the Woodward-Hoffmann rules predict that photochemical reactions will be complementary to thermal reactions. What is allowed photochemically is forbidden thermally, and vice versa. *The physical basis for this complementary relationship is that the high barrier associated with forbidden thermal reactions provides a point for strong interaction of the ground state and excited state species.* As the two states are close in energy and of the same symmetry, they “mix” and allow the excited molecule to reach the ground state. This interaction is necessary for efficient photochemical reactions.⁴⁵

Let us now consider photochemical electrocyclic reactions. In Chapter 10, we described the distinction between the conrotatory and disrotatory modes of reaction as a function of the number of electrons in the system. Striking illustrations of the relationship between orbital symmetry considerations and the outcome of photochemical reactions are found in the stereochemistry of electrocyclic reactions. Orbital symmetry predicts that photochemical electrocyclic reactions will show a reversal of stereochemistry relative to thermal reactions.⁴⁶ One way of making this prediction is to construct an electronic energy state diagram for the reactant and product molecule and observe the correlation between the states.⁴⁷ The reactions in which the reacting state correlates with a state of the product that is not appreciably higher in energy are permitted.⁴⁸ The orbitals involved in the photochemical butadiene-to-cyclobutene conversion are ψ_1 , ψ_2 , and ψ_3 of the first excited state of butadiene and σ , π , and π^* for cyclobutene. The appropriate elements of symmetry are the plane of symmetry for the conrotatory and the axis of symmetry for the disrotatory process. The correlation diagram for this reaction is shown in Figure 12.19. This analysis shows that disrotatory cyclization is allowed, whereas conrotation would lead to a highly excited σ^1 , π^2 , σ^{*1} configuration of cyclobutene. The same conclusion is reached if it is assumed that the frontier orbital will govern reaction stereochemistry.



Although orbital symmetry provides a starting point for analyses of photochemical reactions of conjugated dienes and polyenes, experimental studies have identified a number of additional facets of the problem, some of which have to do with the fundamental assumptions of the orbital symmetry analysis. One of the underlying

⁴⁵. H. E. Zimmerman, *J. Am. Chem. Soc.*, **88**, 1566 (1966); W. Th. A. M. van der Lugt and L. J. Oosterhoff, *Chem. Commun.*, 1235 (1968); W. Th. A. M. van der Lugt and L. J. Oosterhoff, *J. Am. Chem. Soc.*, **91**, 6042 (1969); R. C. Dougherty, *J. Am. Chem. Soc.*, **93**, 7187 (1971); J. Michl, *Top. Current Chem.*, **46**, 1 (1974); J. Michl, *Photochem. Photobiol.*, **25**, 141 (1977).

⁴⁶. R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395 (1965).

⁴⁷. H. C. Longuet-Higgins and E. W. Abrahamson, *J. Am. Chem. Soc.*, **87**, 2045 (1965).

⁴⁸. R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Academic Press, New York, 1970.

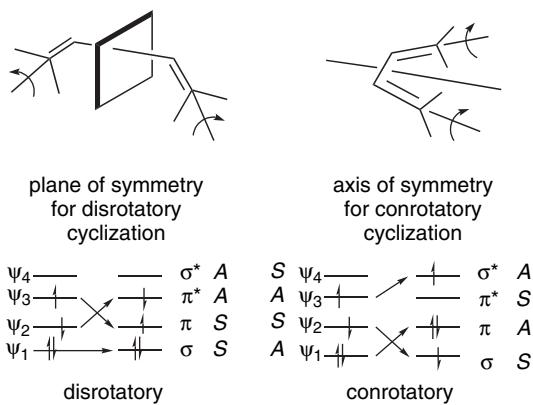


Fig. 12.19. Orbital correlation diagram for the states involved in the photochemical interconversion of butadiene and 1,3-butadiene.

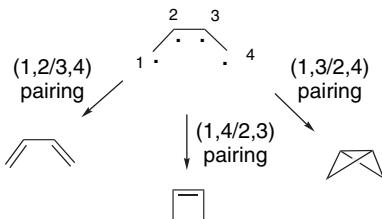
assumptions is that the processes are *concerted*. Although the criteria for concertedness are fairly clear in thermal reactions (the existence or nonexistence of an intermediate), the case for photochemical reactions is not so clear. Several excited state transformations and CIs can appear on the overall reaction path, but there may be no significant barrier. The orbital symmetry analysis also makes assumptions about the *geometry of the interacting molecules*, usually choosing the most symmetrical arrangement. We have to consider whether this assumption is justified. Another difference between the thermal and photochemical reactions is that the *principle of microscopic reversibility applies to the former, but not to the latter*. Concerted thermal pericyclic reactions traverse the same minimum energy pathway in the forward and reverse directions. In photochemical processes, the initial reactant geometries are different, and owing to the NEER principle (see p. 1078) these differences may persist in excited states and influence their reactivity. We first consider some of the experimental observations for dienes and then look at the mechanistic interpretations that have been developed. Computational studies have been applied to the structure of CIs, as was discussed for alkene *cis-trans* isomerization, and these have provided new insights into the photochemical reactions of conjugated dienes and polyenes.

12.2.5. Photochemical Electrocyclic Reactions

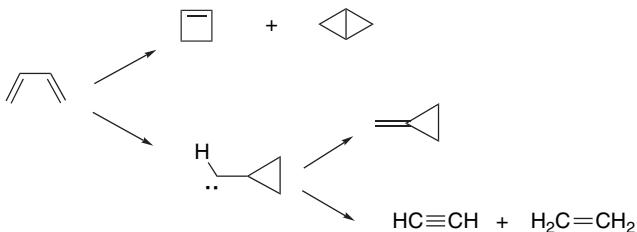
The case of butadiene-cyclobutene interconversion, which one might expect to provide a straightforward example illustrating the stereoselectivity of photochemical electrocyclization, is actually quite complex, especially when substituted systems are involved. We first consider experimental outcomes from the photolysis of butadiene and substituted derivatives, as well as the reverse reaction, the photochemical ring-opening reactions of cyclobutenes. We then examine the 1,3,5-hexatriene system in the same way.

In addition to cyclobutene, bicyclo[1.1.0]butane, methylenecyclopropane, and the fragmentation products ethene and ethyne are formed in the direct photolysis of butadiene. These results can be interpreted in terms of CIs related to those described for ethene and other alkenes. Formation of cyclobutene and bicyclobutane can be attributed to different re-pairing schemes that correlate with different motions into and

out of the area of a CI that can be described as a tetraradicaloid. (1,2/3,4)-pairing leads to 1,3-butadiene, (1-4/2-3)-pairing leads to cyclobutene, and (1,3/2,4)-pairing leads to bicyclo[1.1.0]butane.

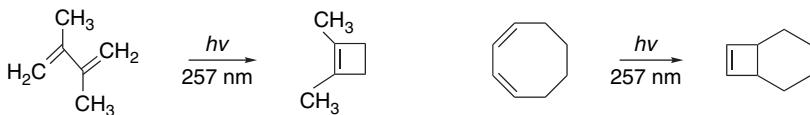


The rearrangement and fragmentation products are thought to arise from a carbene intermediate.

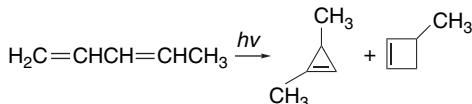


After excitation to the S_2 surface and transition to S_1 , the CI leads to partitioning to products and starting material. These processes occur on the femtosecond time scale. Lifetimes have been assigned to several of the transformations, as illustrated in Figure 12.20.⁴⁹

Electrocyclization of conjugated dienes occurs in competition with *cis-trans* isomerization. The cyclization occurs from the *s-cis* conformation of the diene.⁵⁰ Cyclization is favored in cyclic dienes and for other dienes where the *s-cis* diene conformation is dominant.⁵¹ For several dienes, the quantum yield in nonpolar solvents at 257 nm is about 0.1.⁵² As the cyclized alkenes do not absorb at this wavelength, the reaction can give substantial preparative yields, despite the competing *cis-trans* isomerization.



On direct irradiation of 1,3-pentadiene, *cis-trans* isomerization is accompanied by cyclization to 1,3-dimethylcyclopropene and 3-methylcyclobutene.⁵³



⁴⁹ W. Fuss, W. E. Schmid, and S. A. Trushin, *Chem. Phys. Lett.*, **342**, 91 (2001).

⁵⁰ M. E. Squillacote and T. C. Semple, *J. Am. Chem. Soc.*, **112**, 5546 (1990).

⁵¹ W. J. Leigh, K. Zheng, and K. B. Clark, *J. Org. Chem.*, **56**, 1574 (1991); W. H. Laarhoven, *Org. Photochem.*, **9**, 129 (1987).

⁵² R. Srinivasan, *J. Am. Chem. Soc.*, **84**, 4141 (1982).

⁵³ S. Boué and R. Srinivasan, *J. Am. Chem. Soc.*, **92**, 3226 (1970).

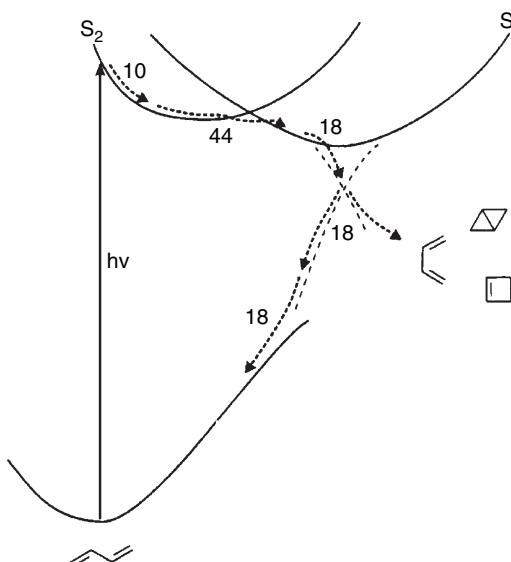
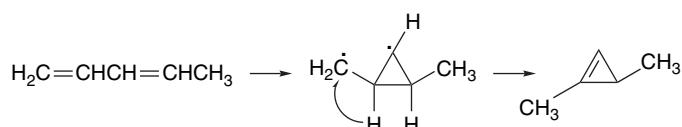
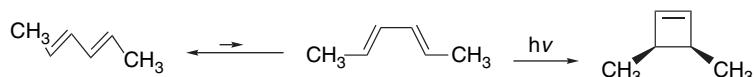


Fig. 12.20. Representation of the 1,3-butadiene potential energy surface based on experimental observations. The broken arrows show the path for return to the ground state reactant and other products. Lifetimes are given in femtoseconds. The dashed lines indicate a conical intersection for partitioning between products. Adapted from *Chem. Phys. Lett.*, **342**, 91 (2001).

The latter product is an example of a photochemically allowed electrocyclic reaction. The cyclopropene arises from (2,4)-pairing and hydrogen migration.



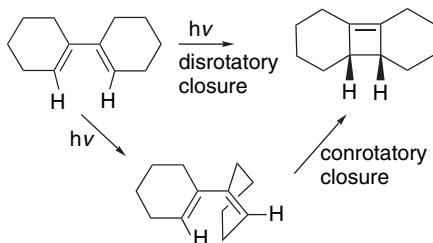
For *E,E*-2,4-hexadiene, the cycloaddition reaction is stereospecific and in accord with the Woodward-Hoffmann predictions.⁵⁴



Cyclic dienes can give cyclobutenes by either direct photochemical electrocyclization or by isomerization to the *E*-isomer in one ring, followed by [2 + 2] cycloaddition. The latter process can be intercepted by methanol (see p. 1094).⁵⁵

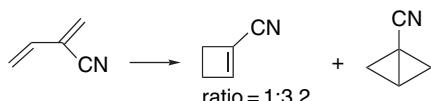
⁵⁴. R. Srinivasan, *J. Am. Chem. Soc.*, **90**, 4498 (1968).

⁵⁵. Y. Daino, S. Hagiwara, T. Hakushi, Y. Inoue, and A. Tai, *J. Chem. Soc., Perkin Trans. 2*, 275 (1989).

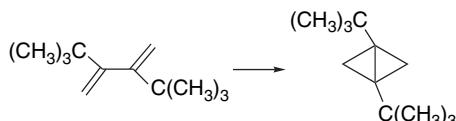


Ref. 56

Substituents can affect the partitioning among the competing reaction paths. The formation of the bicyclo[1.1.0]butane product is favored by radical-stabilizing substituents.⁵⁷

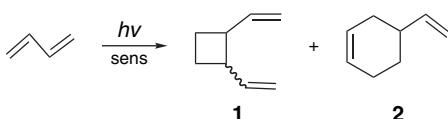


The steric effect of 2,3-di-*t*-butyl groups causes the cyclization to the bicyclo[1.1.0]butane to become the dominant reaction.⁵⁸



Ref. 59

Reactions of conjugated dienes can also occur through the triplet state generated by photosensitization. 1,3-Butadiene gives a mixture of *cis*- and *trans*-1,2-divinylcyclobutane (**1**) and 4-vinylcyclohexene (**2**).



The ratio of divinylcyclobutanes to cyclohexene product depends on the E_T of the sensitizer that is used. With sensitizer $E_T > 60$ kcal/mol, either the *s-trans* (dominant) or *s-cis* conformation can be excited. With $E_T \sim 55$ kcal/mol, the *s-cis* is preferentially excited (see Figure 12.15). The excited *s-trans* conformer can give only cyclobutanes, whereas the excited *s-cis* structure can also form the cyclohexene product.⁶⁰ Isoprene shows a similar effect with cyclohexene formation being at a maximum with E_T at 46–54 kcal/mol.

⁵⁶ J. Saltiel, G. R. Marchand, and R. Bonneau, *J. Photochem.*, **28**, 367 (1987).

⁵⁷ D. M. Gale, *J. Org. Chem.*, **35**, 970 (1970); M. Olivucci, F. Bernardi, S. Ottani, and M. A. Robb, *J. Am. Chem. Soc.*, **116**, 2034 (1994).

⁵⁸ M. Garavelli, B. Frabboni, M. Fato, P. Celani, F. Bernardi, M. A. Robb, and M. Olivucci, *J. Am. Chem. Soc.*, **121**, 1537 (1999).

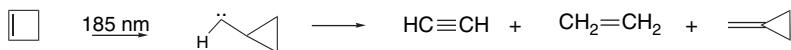
⁵⁹ H. Hopf, H. Lipka, and M. Traetteberg, *Angew. Chem. Int. Ed. Engl.*, **33**, 204 (1994).

⁶⁰ R. S. H. Liu, N. J. Turro, Jr., and G. S. Hammond, *J. Am. Chem. Soc.*, **87**, 3406 (1965).

Sensitizer	E_T	Product composition	
		1	2
Acetophenone	73.6	97	3
Benzophenone	68.5	92	2
Flavone	62.0	93	7
2-Acetyl naphthalene	59.6	92	8
1-Acetyl naphthalene	56.4	80	20
Benzil	53.7	55	45
Fluorenone	53.3	57	43
Benzanthrone	47	65	35
3-Acetyl pyrene	45	55	45
Anthracene	42.5	85	15

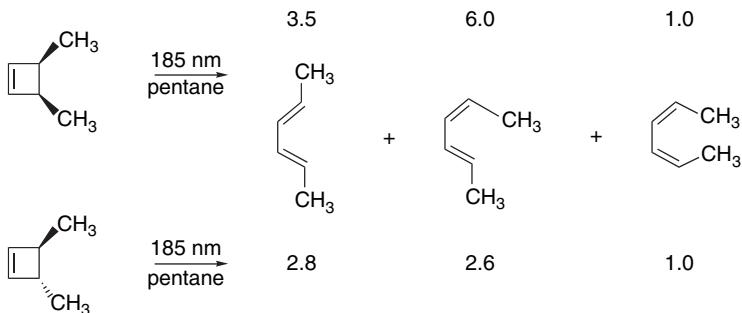
Summarizing these experimental results on conjugated dienes, we find that the singlet state electrocyclization to cyclobutenes generally follows the Woodward-Hoffmann expectation and are disrotatory. There are competing reactions, including formation of bicyclo[1.1.0]butanes and rearrangement products. With direct excitation, the *cis-trans* isomerization occurs by rotation at only one double bond. In contrast, for triplet-sensitized reactions, isomerization can occur at both double bonds (see Section 12.1.2.4). Considerable dimerization is observed in the triplet state reactions. The difference in outcomes of the singlet and triplet processes has been ascribed to differences in the structure of the two excited states. In the singlet state, there is a very close interaction among all of the carbons of the diene system. Transformations of the singlet species are also very fast. The T_1 state is more flexible and longer-lived, which allows the triplet to capture ground state butadiene, leading to dimerization.⁶¹

Let us now turn to the *photochemical ring opening of cyclobutenes to 1,3-dienes*. This reaction requires excitation with light of $\lambda < 200\text{ nm}$. Interpretation of the resonance Raman spectra of cyclobutene following photoexcitation provides insight into the dynamics of ring opening and is consistent with the predicted disrotatory stereochemistry.⁶² Cyclobutene gives ethene, ethyne, and methylenecyclopropane in addition to butadiene.⁶³ These competing reactions are believed to occur by ring contraction to a carbene, followed by rearrangement or fragmentation.⁶⁴ This species is also formed by excitation of butadiene.



Surprisingly, the ring opening of *cis*- and *trans*-3,4-dimethylcyclobutene is not stereospecific.⁶⁵ When irradiated with far-UV light, alkyl-substituted cyclobutenes,

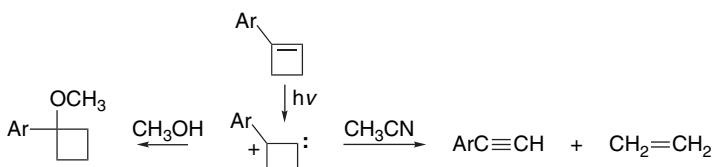
- ⁶¹. M. Klessinger and J. Michl, *Excited States and Photochemistry of Organic Molecules*, VCH Publishers, New York, 1995, pp. 339–341.
- ⁶². M. K. Lawless, S. D. Wickham, and R. A. Mathies, *J. Am. Chem. Soc.*, **116**, 1593 (1994).
- ⁶³. W. Adam, T. Oppenlander, and G. Zang, *J. Am. Chem. Soc.*, **107**, 3921 (1985).
- ⁶⁴. W. J. Leigh, K. Zheng, N. Nguyen, N. H. Werstiuk, and J. Ma, *J. Am. Chem. Soc.*, **113**, 4993 (1993).
- ⁶⁵. K. B. Clark and W. J. Leigh, *J. Am. Chem. Soc.*, **109**, 6086 (1987).



A number of other nonstereospecific photolytic ring openings of substituted cyclobutenes have been reported.⁶⁷

These results are not consistent with a concerted disrotatory mechanism for the ring opening and several descriptions of the mechanism have been provided.^{64,68} One possibility is that the ring opening proceeds stereospecifically to an *excited state* of the diene, which then decays to the ground state with a stereoselectivity that is independent of the stereochemistry of the original cyclobutene.⁶⁹ The transformations are believed to occur via a twisted CI in which all of the π electrons are unpaired, similar to that from singlet excited 1,3-butadiene. Passage through the CI can lead to mixture of stereoisomers.⁶⁸ The composition is governed by dynamic and steric factors.

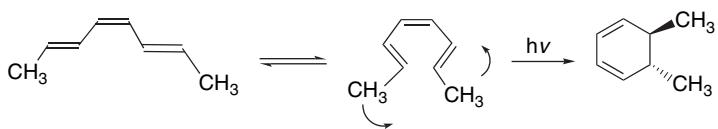
1-Aryl substituted cyclobutenes undergo cycloreversion to arylalkynes but can also give addition products in hydroxylic solvents.⁷⁰ These reactions are singlet state processes. The aryl derivatives of cyclobutene do not open to 1,3-butadienes, and based on substituent effects, the excited states appear to have zwitterionic character. These results suggest that the aryl substituent favors the formation of a zwitterionic excited state.



The cyclohexadiene-hexatriene photochemical interconversion is predicted by orbital symmetry considerations to involve conrotatory motion. Cyclohexadiene derivatives undergo photochemical electrocyclic ring opening. The photostationary state

- ⁶⁶ W. J. Leigh, *Can. J. Chem.*, **71**, 147 (1993); W. J. Leigh, *Chem. Rev.*, **93**, 487 (1993); W. J. Leigh, K. Zheng, and K. B. Clark, *Can. J. Chem.*, **68**, 1988 (1990).
- ⁶⁷ W. G. Dauben and J. E. Haubrich, *J. Org. Chem.*, **53**, 600 (1988); W. J. Leigh and K. Zhang, *J. Am. Chem. Soc.*, **113**, 2163 (1985); G. Maier and A. Bothur, *Eur. J. Org. Chem.*, 2063 (1998).
- ⁶⁸ F. Bernardi, M. Olivucci, and M. A. Robb, *Acc. Chem. Res.*, **23**, 405 (1990); F. Bernardi, M. Olivucci, I. N. Ragazos, and M. A. Robb, *J. Am. Chem. Soc.*, **114**, 2752 (1992).
- ⁶⁹ W. J. Leigh, J. A. Postigo, and K. C. Zheng, *Can. J. Chem.*, **74**, 951 (1996).
- ⁷⁰ W. J. Leigh and J. A. Postigo, *Can. J. Chem.*, **73**, 191 (1995).

favors the triene, and the reaction is highly stereospecific.⁷¹ *E,Z,E*–Octa-2,4,6-triene gives *trans*-5,6-dimethylcyclohexene.⁷²



Ring opening of more highly substituted cyclohexadienes also follows the Woodward-Hoffmann rules.

The conrotatory electrocyclic ring opening of 1,3-cyclohexadiene can be observed by several ultrafast techniques.⁷³ It is believed that the first step after excitation is attainment of a planar geometry, which occurs within 10^{-11} s.⁷⁴ The observations are consistent with an excitation followed by return to the ground state via a CI that permits formation of either reactant or *Z*-1,3,5-hexatriene. The lifetimes of the two excited states are both shorter than 100 fs, and the product is formed within 200 fs.⁷⁵ These results are summarized in Figure 12.21.

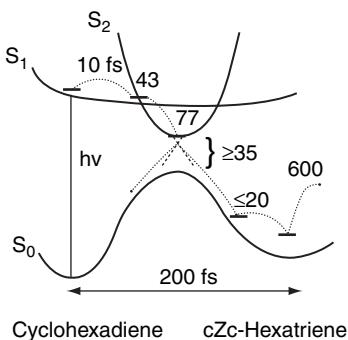
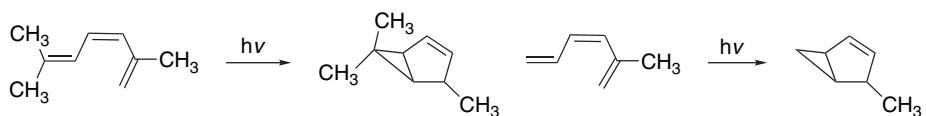


Fig. 12.21. Lifetime in femtoseconds for regions on the potential energy surface for isomerization of 1,3-cyclohexadiene to 1,3,5-hexatriene. Reproduced from *Chem. Phys.*, **232**, 161 (1998) by permission of Elsevier.

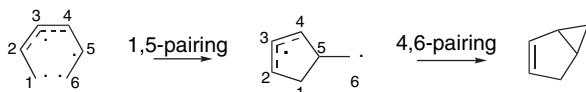
- ⁷¹. H. J. C. Jacobs and E. Havinga, *Adv. Photochem.*, **11**, 305 (1979); H. J. C. Jacobs and W. H. Laarhoven, in *CRC Press Handbook of Organic Photochemistry and Biology*, W. H. Horspool, ed., CRC Press, Boca Raton, FL, 1995, pp. 155–164.
- ⁷². G. J. Fonken, *Tetrahedron Lett.*, 549 (1962).
- ⁷³. H. Ihee, V. A. Lebastov, U. M. Gomez, B. M. Goodson, R. Srinivasan, C.-Y. Ruan, and A. H. Zewail, *Science*, **291**, 458 (2001); W. Fuss, W. E. Schmid, and S. A. Trushin, *J. Chem. Phys.*, **112**, 8347 (2000); S. A. Trushin, W. Fuss, T. Schikavski, W. E. Schmid, and K. L. Kompa, *J. Chem. Phys.*, **106**, 9386 (1997); S. H. Pullen, N. A. Anderson, L. A. Walker, II, and R. J. Sension, *J. Chem. Phys.*, **108**, 556 (1998).
- ⁷⁴. P. J. Reid, M. K. Lawless, S. D. Wickham, and R. A. Mathies, *J. Phys. Chem.*, **98**, 5597 (1994); W. Fuss, T. Hoefer, P. Hering, K. L. Kompa, S. Lochbrunner, T. Schikarski, and W. E. Schmid, *J. Phys. Chem.*, **100**, 921 (1996).
- ⁷⁵. W. Fuss, S. Lochbrunner, A. M. Mueller, T. Schikarski, W. E. Schmid, and S. A. Trushin, *Chem. Phys.*, **232**, 161 (1998).

Particularly interesting photoproducts from hexatrienes are the bicyclo[3.1.0]hex-2-enes.

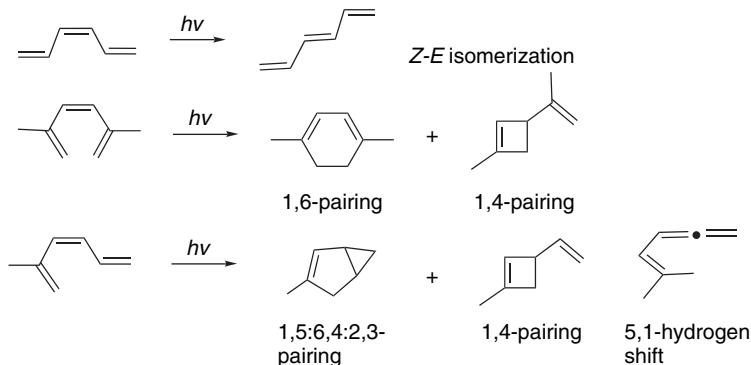


Ref. 76

These products can be formulated as occurring from a tetra-radicaloid CI via a diradical intermediate by (1,5/4,6)-pairing.⁷⁷



The partitioning among *cis-trans* isomerization, closure to cyclohexadiene, and formation of bicyclo[3.1.0]hexenes-2-enes is believed to depend on the conformation of the ground state triene.⁷⁸ An extended conformation, as in 1,3,5-hexatriene, is not favorable to cyclization. A conformation that is *s-cis* at both C(2)–C(3) and C(4)–C(5) as well as *Z* at C(3)–C(4) is favorable to electrocyclization. An *s-cis* conformation at C(2)–C(3) and *Z*-configuration at C(3)–C(4) favors formation of the bicyclo[3.1.0]hexene structure.



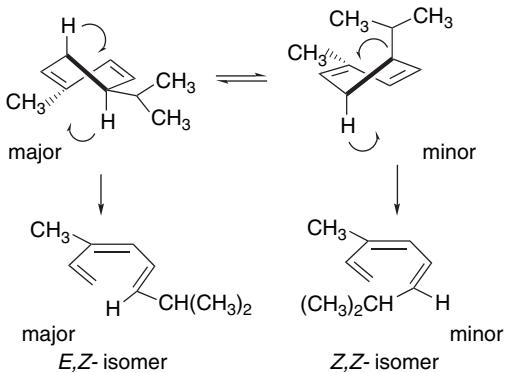
The stereochemistry of the product from ring opening is also dependent on the ground state conformation of the cyclohexadiene. For example, the composition of

⁷⁶ P. Courtot, R. Rumin, and J.-Y. Salaun, *Pure Appl. Chem.*, **49**, 317 (1977); P. Courtot and R. Rumin, *Tetrahedron*, **32**, 441 (1976).

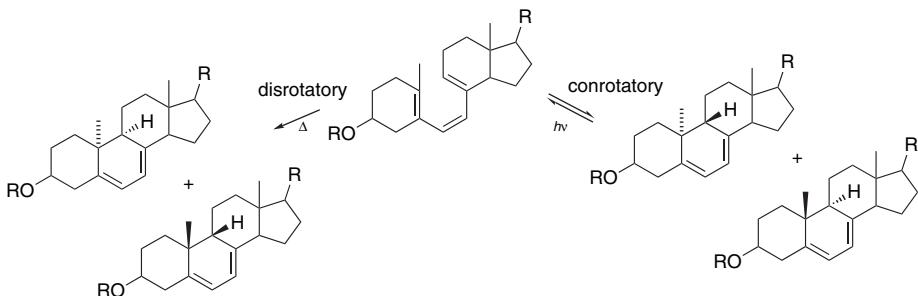
⁷⁷ M. Garavelli, R. Celani, M. Fato, M. J. Bearpark, B. R. Smith, M. Olivucci, and M. A. Robb, *J. Phys. Chem. A*, **101**, 2023 (1997).

⁷⁸ P. J. Vroegop, J. Lugtenburg, and E. Havinga, *Tetrahedron*, **29**, 1393 (1973); E. Havinga, *Experientia*, **29**, 1181 (1973).

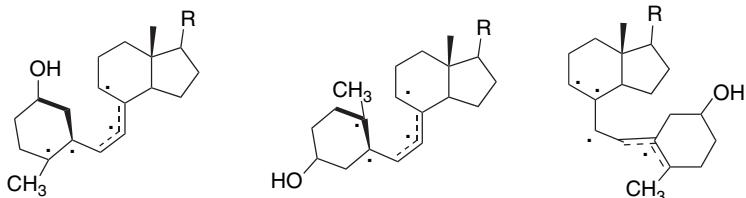
the conrotatory ring-opening products from photolysis of α -phellandrene mirrors the ground state conformational equilibrium.⁷⁹



These results are in accord with orbital symmetry principles. Indeed, examples found in the study of vitamin D provided the initial examples of the dichotomy between thermal and photochemical processes that led to development of the concepts underlying the Woodward-Hoffmann rules for photochemical reaction.⁸⁰ It was found that the triene precalciferol gave ergosterol on photocyclization, but the stereoisomer lumisterol on heating.



The vitamin D photochemical system can also be interpreted in terms of CIs with tetradral radicaloid character. Three such structures have been identified by computation, and they account for the observed products.⁸¹



Thus, looking broadly over these results on electrocyclic reactions of conjugated systems, we find that the picture is in general accord with orbital symmetry considerations, *except for the nonstereospecific ring opening of cyclobutenes*. The results also

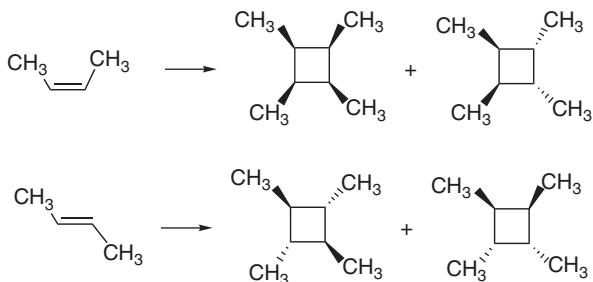
⁷⁹ J. E. Baldwin and S. M. Krueger, *J. Am. Chem. Soc.*, **91**, 6444 (1969).

⁸⁰ R. B. Woodward, in *Aromaticity*, Chemical Society Special Publication No. 21, 217 (1967); E. Havinga and J. L. M. A. Schlatmann, *Tetrahedron*, **16**, 146 (1961); J. A. Berson, *Tetrahedron*, **48**, 3 (1992).

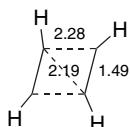
⁸¹ F. Bernardi, M. Olivucci, I. N. Ragazos, and M. A. Robb, *J. Am. Chem. Soc.*, **114**, 8211 (1992).

12.2.6. Photochemical Cycloaddition Reactions

As described on p. 1098, the original orbital symmetry interpretation of alkene $[2\pi+2\pi]$ cycloaddition was in terms of a suprafacial transition structure with a rectangular geometry. This arrangement leads to a photochemical process that is allowed by orbital symmetry criteria. Early experimental work also provided examples of stereospecific $[2\pi+2\pi]$ cycloadditions, lending support to a concerted reaction path. For example, dimerization of Z-2-butene gives two products that retain *cis*-methyl groups. The adducts from *E*-2-butene have *trans*-methyl groups.⁸² This establishes that the configuration is retained at both alkene double bonds during the formation of the dimers.



The prototypical ethene + ethene cycloaddition has been explored computationally and a somewhat different picture has emerged.⁸³ The CI for ethene dimerization is calculated to be rhomboid.⁸⁴



These computations lead to an energy surface featuring the rhomboid CI, which can lead to formation of cyclobutane or separation into two ethene molecules, as shown in Figure 12.22. Point *E* is the rhomboid CI that permits rapid return to the ground state surface. The process is expected to be very fast and this is consistent with the observed retention of alkene stereochemistry in substituted cases. In contrast to the pathway through the rhomboid CI, a completely symmetrical rectangular approach does not lead to minima.

⁸². H. Yamazaki and R. J. Cvetanovic, *J. Am. Chem. Soc., Chem. Commun.*, **91**, 520 (1969).

⁸³. F. Bernardi, S. De, M. Olivucci, and M. A. Robb, *J. Am. Chem. Soc.*, **112**, 1737 (1990); F. Bernardi, A. Bottini, M. Olivucci, A. Venturini, and M. A. Robb, *J. Chem. Soc., Faraday Trans.*, **90**, 1617 (1994).

⁸⁴. F. Bernardi, M. Olivucci, and M. A. Robb, *Pure Appl. Chem.*, **67**, 17 (1995).

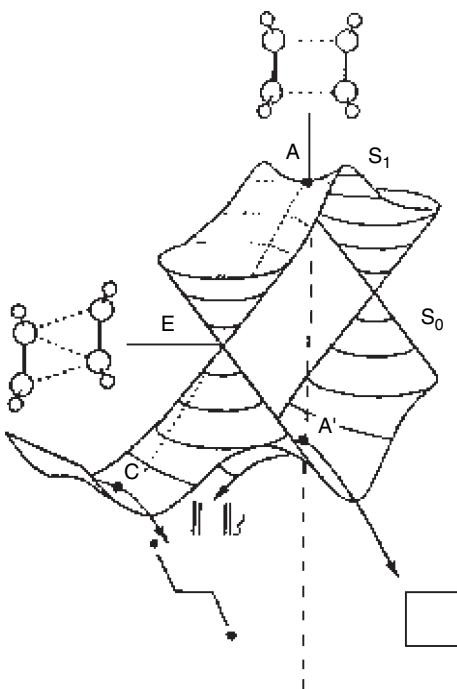
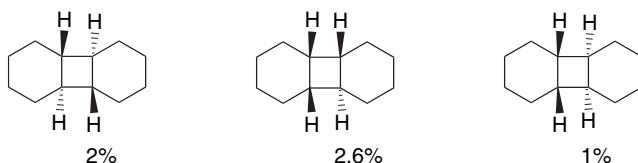
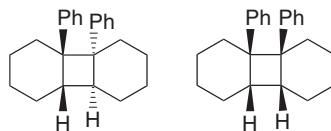


Fig. 12.22. Energy surface depicting the S_1 and S_0 potential energy surfaces for singlet state photodimerization of ethene. Adapted from *J. Photochem. Photobiol.*, **105**, 365 (1997), by permission of Elsevier.

Photodimerization of cyclohexene sensitized by xylene gives a low yield of a mixture of stereoisomers. The reaction was interpreted as a $Z \rightarrow E$ isomerization followed by a nonstereospecific ground state $[2\pi + 2\pi]$ addition.⁸⁵



1-Phenylcyclohexene can be photodimerized by irradiation at $\lambda > 280\text{ nm}$.⁸⁶ E -2-Phenylcyclohexene is generated under these conditions and can be trapped in methanol. The fact that the tail-to-tail products are formed from both singlet and triplet excited states indicates an intermediate with diradical character.

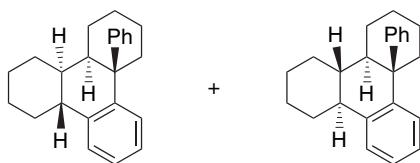


With high-intensity (laser) irradiation, the reaction also gives stereoisomeric $[2+4]$ dimers. These products are believed to be formed by dimerization of the E -isomer.

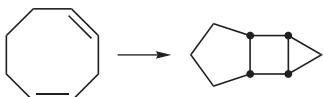
⁸⁵ P. J. Kropp, J. J. Snyder, P. C. Rawlings, and H. G. Fravel, Jr., *J. Org. Chem.*, **45**, 4471 (1980).

⁸⁶ D. J. Unett, R. A. Caldwell, and D. C. Hrcic, *J. Am. Chem. Soc.*, **118**, 1682 (1996).

Under low intensity, the concentration of the *E*-isomer is too low to permit this reaction.

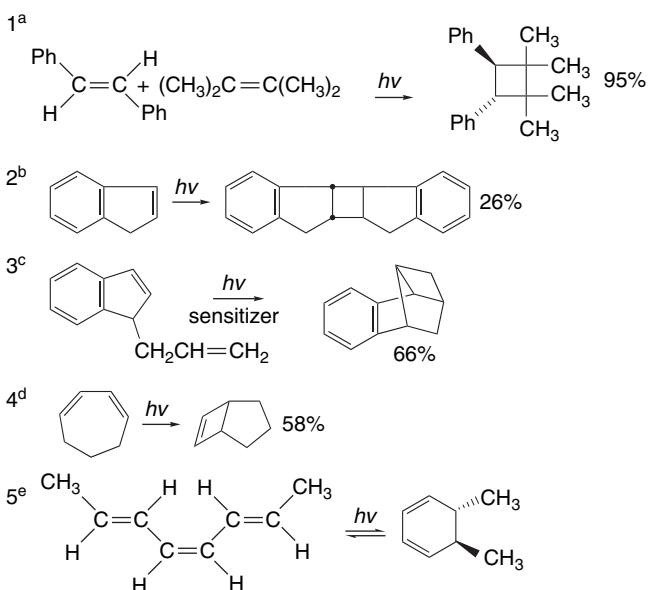


Intramolecular cycloaddition is observed for 1,4-cyclooctadiene.⁸⁷



The most useful intermolecular [2 π +2 π] cycloadditions from a synthetic point of view involve alkenes and cyclic α,β -unsaturated carbonyl compounds. These reactions are discussed in more detail in Section 6.3.2 of Part B. Scheme 12.1 lists some examples of photochemical cycloaddition and electrocyclic reactions of the type that are consistent with the predictions of orbital symmetry considerations.

Scheme 12.1. Examples of Electrocyclic Reactions and Cycloadditions



a. O. L. Chapman and W. R. Adams, *J. Am. Chem. Soc.*, **99**, 2333 (1968).

b. A. G. Anastassiou, F. L. Setliff, and G. W. Griffin, *J. Org. Chem.*, **31**, 2705 (1966).

c. A. Padwa, S. Goldstein, and M. Pulwer, *J. Org. Chem.*, **47**, 3893 (1982).

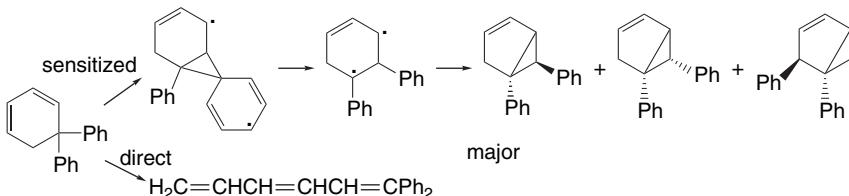
d. O. L. Chapman, D. J. Pasto, G. W. Borden, and A. A. Griswold, *J. Am. Chem. Soc.*, **84**, 1220 (1962).

e. G. J. Fonken, *Tetrahedron Lett.*, 549 (1962).

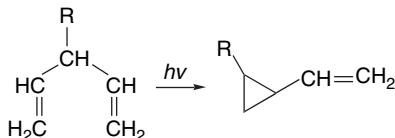
⁸⁷. S. Moon and C. R. Ganz, *Tetrahedron Lett.*, 6275 (1968).

12.2.7. Photochemical Rearrangements Reactions of 1,4-Dienes

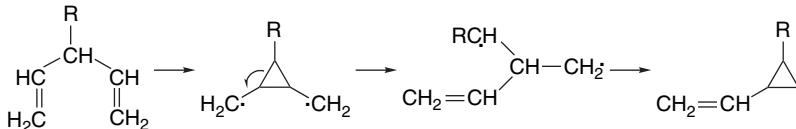
In addition to the electrocyclic and cycloaddition reactions described earlier, certain dienes undergo interesting rearrangements. For example, 5,5-diphenylcyclohexa-1,3-diene shows divergent photochemical behavior, depending on whether the reaction is induced by direct irradiation or by photosensitization. On direct irradiation, the electrocyclic ring opening to 1,1-diphenylhexatriene is dominant, whereas a rearrangement involving migration one of the aromatic rings is the major reaction of the triplet excited state formed by photosensitization.⁸⁸



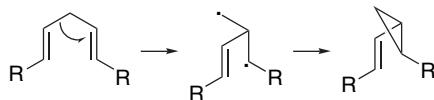
The latter reaction is an example of the *di- π -methane rearrangement*,⁸⁹ which is a quite general reaction for 1,4-dienes and other systems that have two π systems separated by an sp^3 -carbon atom. The π systems can be a double bond, an aromatic ring, or, as we will see in Section 12.3, a carbonyl group.



The transformation can be formulated in terms of bonding between C(2) and C(4) involving formation of a cyclopropyl diradical intermediate. This diradical can fragment to form a new 1,3-diradical that gives the cyclic product.



An alternative mechanism involves a direct migration of one of the vinyl groups, followed by formation of the ring.⁹⁰

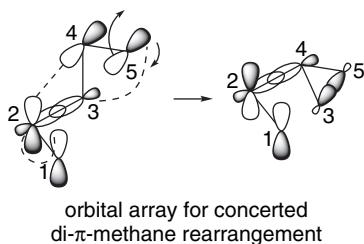


⁸⁸ H. E. Zimmerman and G. A. Epling, *J. Am. Chem. Soc.*, **94**, 8749 (1972); J. S. Swenton, J. A. Hyatt, T. J. Walker, and A. L. Crumrine, *J. Am. Chem. Soc.*, **93**, 4808 (1971); M.-D. Su, *J. Org. Chem.*, **60**, 6621 (1995).

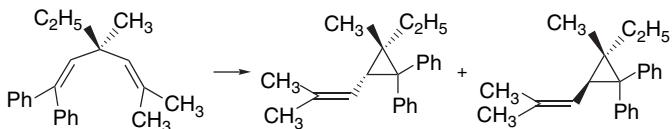
⁸⁹ For reviews of the di- π -methane rearrangement, see S. S. Hixson, P. S. Mariano, and H.E. Zimmerman, *Chem. Rev.*, **73**, 531 (1973); H. E. Zimmerman, in *Rearrangements in Ground and Excited States*, Vol. 3, P. de Mayo, ed., Academic Press, New York, 1980, Chap. 16; H. E. Zimmerman, in *Organic Photochemistry and Photobiology*, W. H. Horspool and P.-S. Song, eds., CRC Press, Boca Raton, FL, 1995, pp. 184–193; H. E. Zimmerman and D. Armesto, *Chem. Rev.*, **96**, 3065 (1996).

⁹⁰ L. A. Paquette and E. Bay, *J. Org. Chem.*, **47**, 4597 (1982).

In some cases, the di- π -methane rearrangement can proceed through either a singlet or a triplet excited state.⁹¹ The singlet reaction can be formulated as a concerted process, and this mechanism is followed in the case of some acyclic dienes and for cyclic systems in which a concerted process is sterically feasible. Note that the orbital array is of the Möbius topology with a phase change depicted between the C(1) and C(2) positions. This corresponds to an allowed photochemical process since there are six electrons involved in bonding changes and this is an antiaromatic system.



The di- π -methane rearrangement is a stereospecific reaction. There are several elements of stereochemistry to be considered. It is known that the double bond that remains uncyclized retains the *E*- or *Z*-configuration present in the starting material. This result excludes any intermediate with a freely rotating terminal radical. The concerted mechanism implies that C(3) would undergo inversion of configuration since the new C(3)–C(5) bond is formed using the back lobe of the C(2)–C(3) σ -bond. This inversion of configuration has been confirmed.⁹²



Thus the TS depicted above for the concerted reaction correctly predicts the stereochemical course of the di- π -methane rearrangement, as does the computational analysis discussed below.

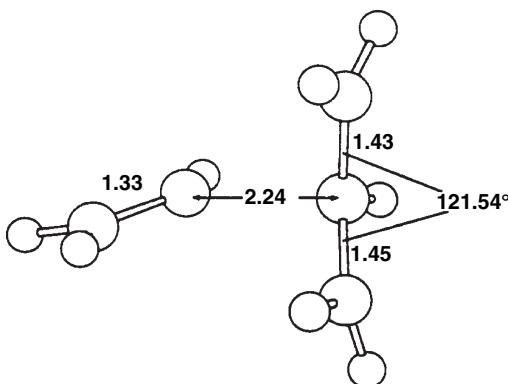
The di- π -methane rearrangement of 1,4-pentadiene has been modeled using CAS-SCF/4-31G calculations. The results indicate that a singlet 1,3-diradical is the key intermediate.⁹³ This species can be reached from the excited state via a CI that involves vinyl migration. It consists of a vinyl group associated with the central carbon of an allylic system and is similar in structure to the CI involved in alkene sigmatropic rearrangements (see p. 1093). The structure of the CI is also consistent with the

⁹¹ H. E. Zimmerman and P. S. Mariano, *J. Am. Chem. Soc.*, **91**, 1718 (1969); P. S. Mariano, R. B. Steitle, D. G. Watson, M. J. Peters, and E. Bay, *J. Am. Chem. Soc.*, **98**, 5899 (1976).

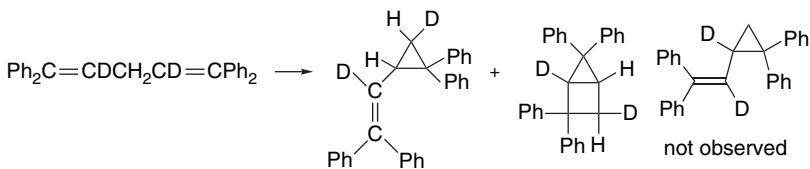
⁹² H. E. Zimmerman, J. D. Robbins, R. D. McKelvey, C. J. Samuel, and L. R. Sousa, *J. Am. Chem. Soc.*, **96**, 1974, 4630 (1974).

⁹³ M. Reguero, F. Bernardi, H. Jones, M. Olivucci, I. N. Ragazos, and M. A. Robb, *J. Am. Chem. Soc.*, **115**, 2073 (1993).

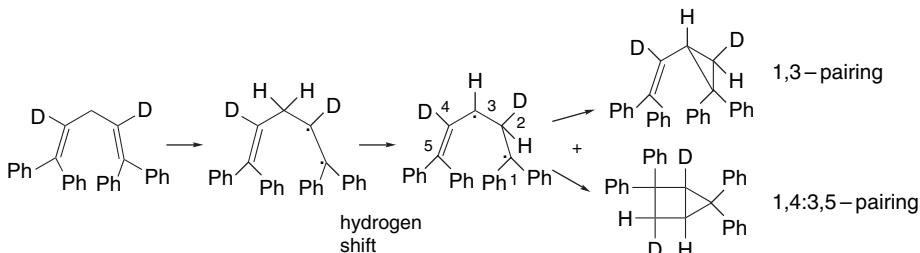
observed stereochemistry of the reaction. It remains to be seen if this mechanism applies to the more highly substituted systems that have been studied experimentally.



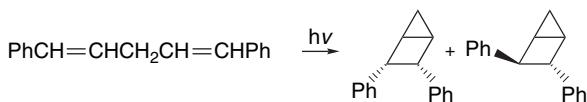
The di- π -methane rearrangement has been studied in a sufficient number of cases to recognize some of the substituent effects. When the central sp^3 -carbon is unsubstituted, the di- π -methane path becomes less favorable. The case of 1,1,5,5-tetraphenyl-1,4-pentadiene is illustrative. Although one of the products has the expected structure for di- π -methane rearrangement, labeling with deuterium proves that an alternative mechanism operates.



The cyclopropane ring is formed only after hydrogen atom migration. The driving force for this migration may be the fact that it produces a more stable allylic radical. The resulting 1,3-diradical can re-pair to give the observed products.



Photolysis of 1,5-diphenyl-1,4-pentadiene is another example where a compound undergoes cycloaddition in preference to di- π -methane rearrangement.⁹⁴



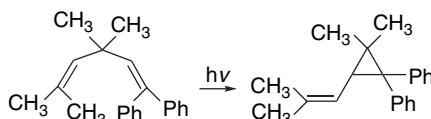
⁹⁴. E. Block and H. W. Orf, *J. Am. Chem. Soc.*, **94**, 8438 (1972).

The resistance of the 3-unsubstituted system to the di- π -methane rearrangement probably occurs at the stage of the vinyl rearrangement.⁹⁵ If the central carbon is unsubstituted this step results in the formation of a primary radical and would be energetically unfavorable.

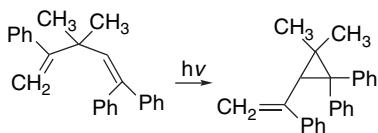
Kinetic studies of **3a**, **3b**, and **3c** have provided experimental evidence that a cyclopropyl diradical is an intermediate.⁹⁶ The product composition reveals a temperature dependence that implicates an intermediate. These compounds undergo both *cis-trans* isomerization and di- π -methane rearrangement on direct irradiation and mainly *cis-trans* isomerization when photosensitized (triplet) by benzophenone. The quantum yield of the di- π -methane rearrangement increases dramatically with substitution at the allylic position.

3		
$R^1, R^{1'}$	$E-Z$	di- π -methane
a H,H	.30	.005
b H,CH ₃	.11	.21
c CH ₃ ,CH ₃	.074	.42

The groups at the termini of the 1,4-pentadiene system also affect the efficiency and direction of the di- π -methane reaction. The general trend is that cyclization occurs at the diene terminus that best stabilizes radical character. Thus, a terminus substituted with aryl groups will cyclize in preference to an unsubstituted or alkyl-substituted terminus.



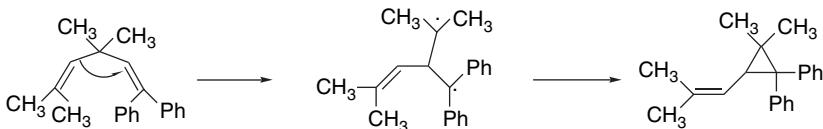
Ref. 97



Ref. 98

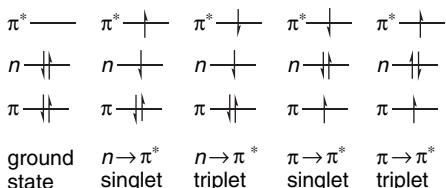
- ⁹⁵ H. E. Zimmerman and J. A. Pincock, *J. Am. Chem. Soc.*, **95**, 2957 (1973).
⁹⁶ F. D. Lewis, X. Zuo, R. S. Kalgutkar, M. A. Miranda, E. Font-Sanchis, and J. Perez-Prieto, *J. Am. Chem. Soc.*, **122**, 8571 (2000); F. D. Lewis, X. Zuo, R. S. Kalgutkar, J. M. Wagner-Brennan, M. A. Miranda, E. Font-Sanchis, and J. Perez-Prieto, *J. Am. Chem. Soc.*, **123**, 11883 (2001).
⁹⁷ H. E. Zimmerman and A. C. Pratt, *J. Am. Chem. Soc.*, **92**, 1409 (1970).
⁹⁸ H. E. Zimmerman and A. A. Baum, *J. Am. Chem. Soc.*, **93**, 3646 (1971).

This result can be rationalized in terms of the vinyl migration mechanism by noting that rearrangement will occur to give the more stable of the two possible 1,3-diradicals.⁹⁹ The cyclopropane ring in the final product will then incorporate this terminus.



12.3. Photochemistry of Carbonyl Compounds

The photochemistry of carbonyl compounds has been extensively studied, both in solution and in the gas phase. There are major differences between the two phases. In the gas phase, the energy transferred by excitation is not lost rapidly by collision, whereas in the liquid phase the excess vibrational energy is rapidly transferred to the solution. We emphasize solution photochemistry here because both mechanistic study and preparative applications of organic reactions usually involve solution processes. The reactive excited state of alkyl ketones is usually the $n-\pi^*$ state. On excitation, an electron from an oxygen nonbonding orbital is transferred to the π -antibonding orbital of the carbonyl group. The singlet excited state is formed initially, but intersystem crossing to the triplet can occur. For saturated ketones, the singlet and the triplet lie, respectively, about 80–85 and 75–80 kcal/mol above the ground state. The first excited singlet (S_1) and triplet (T_1) can be described structurally from spectroscopic data available for formaldehyde, which is the simplest analog. In both excited states, the molecule is pyramidal, the C–O bond is lengthened, and the dipole moment is reduced.¹⁰⁰ The reduction of the dipole moment results from the transfer of electron density from an orbital localized on oxygen to one that also encompasses the carbon atom. An alternative excited state involves promotion of a bonding π electron to the antibonding π^* orbital. This is called the $\pi-\pi^*$ excited state and is most likely to be involved when the carbonyl group is conjugated with an extended π -bonding system, as is the case for aryl ketones. The excited carbonyl groups have radical character at both carbon and oxygen, and the oxygen is rather similar in its reactivity to alkoxy radicals. The MO diagrams for the $n-\pi^*$ and $\pi-\pi^*$ states are depicted below.



MP2/6-311G calculations have described the geometric and charge distribution of the excited state of formaldehyde as summarized below.¹⁰¹ Three valence shell

⁹⁹ H. E. Zimmerman and A. C. Pratt, *J. Am. Chem. Soc.*, **92**, 6259, 6267 (1970).

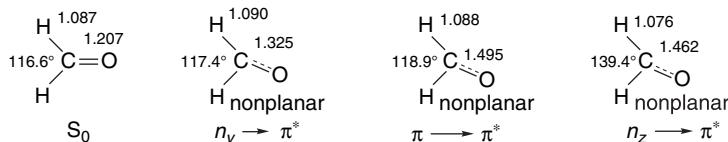
¹⁰⁰ J. C. D. Brand and D. G. Williamson, *Adv. Phys. Org. Chem.*, **1**, 365 (1963); D. E. Freeman and W. Klemperer, *J. Chem. Phys.*, **45**, 52 (1966).

¹⁰¹ C. M. Hadad, J. B. Foresman, and K. B. Wiberg, *J. Phys. Chem.*, **97**, 4293 (1993).

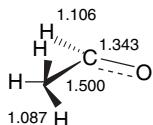
excited states corresponding to $n_y \rightarrow \pi^*$, $\pi \rightarrow \pi^*$, and $n_z \rightarrow \pi^*$ have been described, and there are several Rydberg states as well. The atomic populations and bond orders were calculated using the AIM method.

State	E (eV)	Atomic population						Bond order			
		C		O		H		C—O		C—H	
		π	Total	π	Total	π	Total	π	Total	π	Total
S_0	0.00	0.431	4.833	1.541	9.207	0.014	0.980	0.664	1.43	0.006	0.958
$n_y \rightarrow \pi^*$	4.58	1.025	5.438	1.890	8.821	0.043	0.871	0.094	0.871	0.000	0.886
$\pi \rightarrow \pi^*$	9.19	0.521	5.170	1.425	9.063	0.028	0.883	0.171	0.957	0.011	0.867
$n_z \rightarrow \pi^*$	9.97	1.069	5.467	1.844	8.674	0.043	0.930	0.263	0.797	0.041	0.943

According to these results the $n_y \rightarrow \pi^*$ shows 0.39e and 0.11e lost from O and H, respectively, whereas C gains 0.61e compared to the ground state. The $\pi \rightarrow \pi^*$ state shows a smaller loss from both O (0.140 e) and from H (0.10). The π bond order in all the excited states is decreased by the population of an antibonding π^* orbital. The charge shifts in the σ and π systems are in opposite senses, but the overall effect is that the O becomes less electron rich and takes on the character of an electrophilic radical. The excited states are nonplanar. Some of the computed bond distances and angles are shown below.¹⁰²



The excited states of other saturated carbonyl compounds are similar. Alkyl groups somewhat stabilize the excited state and reduce the excitation energy. In acetaldehyde, the conformation of the $n \rightarrow \pi^*$ state changes from the H—O eclipsed structure in the ground state (see p. 148) to an H—O staggered conformation.¹⁰³



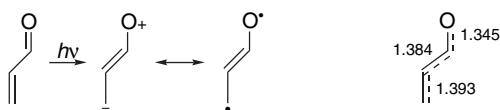
For conjugated carbonyl compounds, such as α,β -enones, the orbital diagram is similar, except that the HOMO of the ground state is ψ_2 of the enone system, rather than an oxygen unshared pair orbital. In the $\pi-\pi^*$ state, the C=O and C=C bonds lengthen and the C(1)—C(2) bond shortens.¹⁰⁴ Population of the π^* orbital shifts

¹⁰². M. Dallos, T. Muller, H. Lischka, and R. Shepard, *J. Chem. Phys.*, **114**, 746 (2001).

¹⁰³. J. M. Price, J. A. Mack, G. v. Helden, X. Yang, and A. M. Wodtke, *J. Phys. Chem.*, **98**, 1791 (1994).

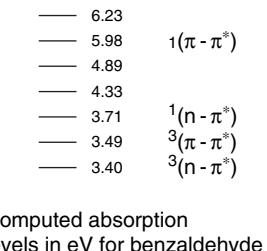
¹⁰⁴. C. S. Page and M. Olivucci, *J. Comput. Chem.*, **24**, 298 (2003).

electron density from oxygen to carbon. The excited state can be represented as a hybrid with dipolar and diradical structures.



Although Lewis structures of this type are not entirely adequate descriptions of the excited states, they do correspond to the MO picture by indicating polarization of charge and the presence of polar radical-like centers. In addition to the increased energy content, the high reactivity of the excited states is associated with the presence of half-filled orbitals. The two SOMO orbitals in the excited states have enhanced radical, cationic, or anionic character.

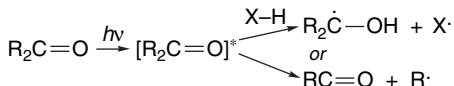
For aromatic carbonyl compounds, as for styrene (see p. 1084), there are excited states associated with the aromatic ring. The absorption spectrum of benzaldehyde, for example, is believed to include two triplet levels and at least five singlet bands.¹⁰⁵



For acetophenone, the S_1 state, like acetaldehyde adopts a H–C–C–O staggered conformation, whereas T_1 retains the eclipsed conformation found in the ground state.¹⁰⁶

12.3.1. Hydrogen Abstraction and Fragmentation Reactions

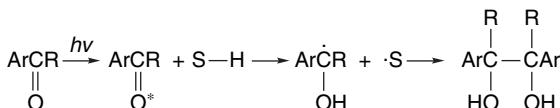
One of the most common reactions of photoexcited carbonyl groups is hydrogen atom abstraction from solvent or some other hydrogen donor. A second common reaction is cleavage of the carbon–carbon bond adjacent to the carbonyl group, which is called α -cleavage.



The hydrogen atom abstraction can be either intramolecular or intermolecular. The intermediates that are generated are free radicals. If these radicals come to thermal equilibrium, they have the same structure and reactivity as radicals generated by

¹⁰⁵ V. Molina and M. Merchan, *J. Phys. Chem. A*, **105**, 3745 (2001).

¹⁰⁶ J. L. Tomer, L. H. Spanier, and D. W. Pratt, *J. Am. Chem. Soc.*, **110**, 1615 (1988).



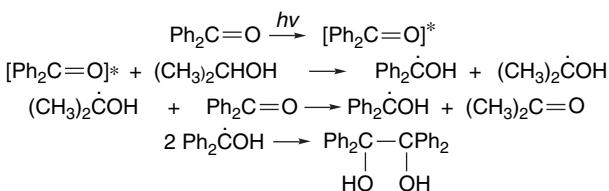
These reactions usually occur via the triplet excited state T_1 . The intersystem crossing of the initially formed singlet excited state is so fast ($k \sim 10^{10} \text{ s}^{-1}$) that reactions of the S_1 state are usually not observed. The reaction of the benzophenone T_1 state has been particularly closely studied. Some of the facts that have been established in support of the general mechanism outlined above are as follows:

1. For a given hydrogen donor S–H, replacement by S–D leads to a decreased rate of reduction, relative to nonproductive decay to the ground state.¹⁰⁷ This decreased rate is consistent with a primary isotope effect in the hydrogen abstraction step.
2. The photoreduction can be quenched by known triplet quenchers. The effective quenchers are those that have T_1 states less than 69 kcal/mol above S_0 . Quenchers with higher triplet energies are ineffective because the benzophenone $\pi-\pi^*$ triplet is not sufficiently energetic to effect energy transfer.
3. The intermediate diphenylhydroxymethyl radical has been detected after generation by flash photolysis.¹⁰⁸ Photolysis of benzophenone in benzene solution containing potential hydrogen donors results in the formation of two intermediates that are detectable, and their rates of decay have been measured. One intermediate is the $\text{Ph}_2\dot{\text{C}}\text{OH}$ radical, which disappears by dimerization in a second-order process. A much shorter-lived species disappears with first-order kinetics in the presence of excess amounts of various hydrogen donors. The pseudo-first-order rate constants vary with the structure of the donor; with 2,2-diphenylethanol, for example, $k = 2 \times 10^6 \text{ s}^{-1}$. The rate is much less with poorer hydrogen atom donors. The rapidly reacting intermediate is the triplet excited state of benzophenone.
4. In 2-propanol, the quantum yield for dimeric conversion of benzophenone to the dimeric reduction product is 2.0.¹⁰⁹ The reason is that the radical remaining after abstraction of a hydrogen atom from 2-propanol transfers a hydrogen atom to ground state benzophenone in a nonphotochemical reaction. Because of this process, two molecules of benzophenone are reduced for each one that is photoexcited. These results suggest the following mechanism:

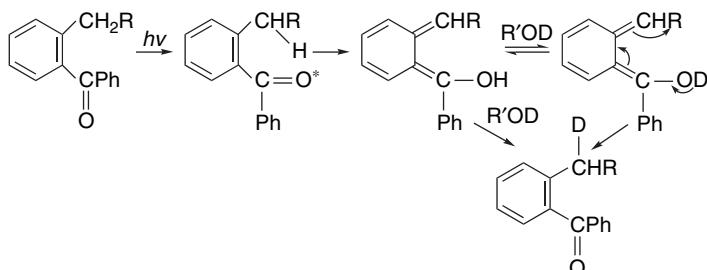
¹⁰⁷ W. M. Moore, G. S. Hammond, and R. P. Foss, *J. Am. Chem. Soc.*, **83**, 2789 (1961); G. S. Hammond, W. P. Baker, and W. M. Moore, *J. Am. Chem. Soc.*, **83**, 2795 (1961).

¹⁰⁸ J. A. Bell and H. Linschitz, *J. Am. Chem. Soc.*, **85**, 528 (1963).

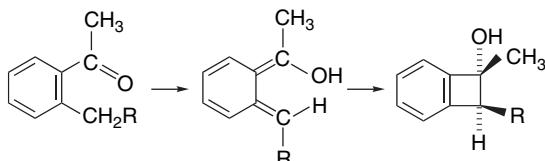
¹⁰⁹ N. J. Turro, *Molecular Photochemistry*, W. A. Benjamin, New York, 1965, pp. 143, 144.



The efficiency of photoreduction of benzophenone derivatives is greatly diminished when an *ortho* alkyl substituent is present because a new photoreaction, intramolecular hydrogen atom transfer, becomes the dominant process. Hydrogen abstraction takes place from the benzylic position on the adjacent alkyl chain, giving an unstable enol that can revert to the original benzophenone without photoreduction. This process, known as *photoenolization*,¹¹⁰ can be detected by photolysis in deuterated hydroxylic solvents even though there is no net transformation of the reactant. The proton of the enolic hydroxyl is rapidly exchanged with solvent, so deuterium is introduced at the benzylic position. Deuterium is also introduced if the enol is protonated at the benzylic carbon by solvent.



The reactive dienols can also undergo thermal electrocyclization to cyclobutenols.¹¹¹



The dominant photochemical reaction of ketones in the gas phase is cleavage of one of the carbonyl substituents, which is followed by decarbonylation and subsequent reactions of the free radicals that are formed. The initial cleavage occurs within 100 fs of excitation. There is an activation barrier for decarbonylation (see Table 11.2), so decarbonylation can be relatively slow with excitation at 270 nm.¹¹² At shorter wavelengths, there may be sufficient excess energy for rapid decarbonylation. This reaction is referred to as the *Type-I or α-cleavage* reaction of carbonyl compounds.



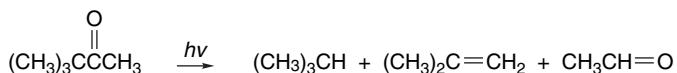
¹¹⁰. P. G. Sammes, *Tetrahedron*, **32**, 405 (1976).

¹¹¹. P. J. Wagner, D. Subrahmanyam, and B.-S. Park, *J. Am. Chem. Soc.*, **113**, 709 (1991).

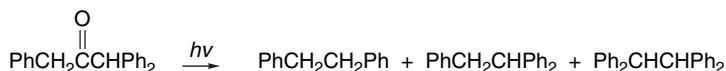
¹¹². S. K. Kim and A. H. Zewail, *Chem. Phys. Lett.*, **250**, 279 (1996); E. W. G. Diau, C. Kotting, T. I. Solling, and A. H. Zewail, *Chem. Phys. Chem.*, **3**, 57 (2000); A. P. Baronavski and J. C. Owrusky, *Chem. Phys. Lett.*, **33**, 36 (2001).

The energetics of α -cleavage and decarbonylation depend on the structure of the ketone. For acetone, the S_1 and T_1 states are 88 and 80 kcal/mol above the ground state, respectively. For acetone, both α -cleavage and decarbonylation are slightly endothermic, owing to the low stability of the methyl radical.¹¹³ However, the reaction is exothermic with radical-stabilizing substituents, as illustrated in Figure 12.23.

Dibenzyl ketone, for example, is readily cleaved photolytically.¹¹⁴ Similarly, *t*-butyl ketones undergo α -cleavage quite readily on photolysis in solution.¹¹⁵ The radicals generated undergo coupling, disproportionation, and hydrogen abstraction reactions.



Ref. 115



Ref. 114

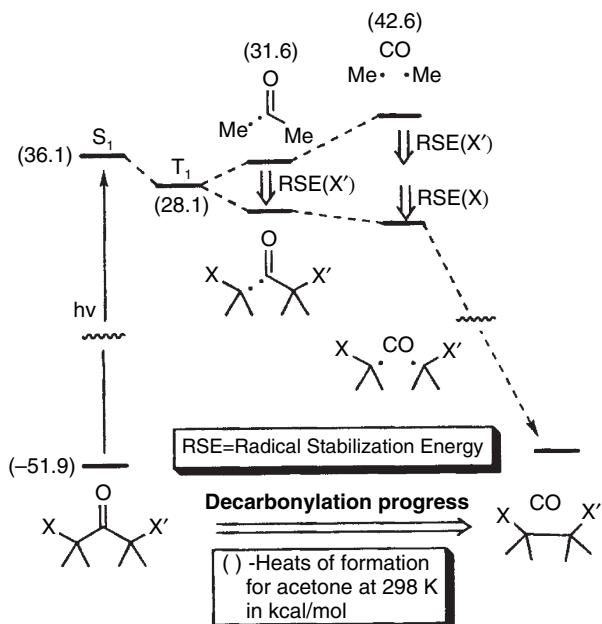


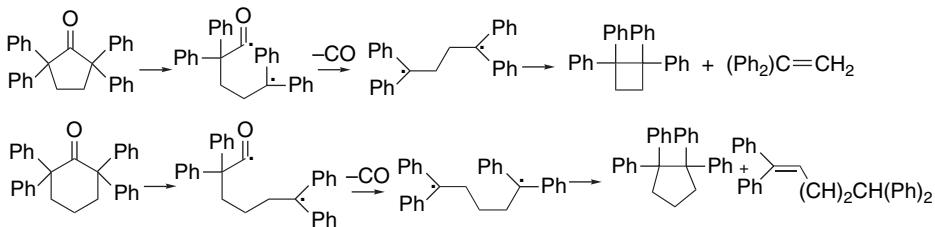
Fig. 12.23. Energetics for α -cleavage and decarbonylation of acetone showing the effect of radical stabilization. Reproduced from *J. Org. Chem.*, **67**, 3749 (2002), by permission of the American Chemical Society.

¹¹³ L. M. Campos, H. Dang, D. Ng, Z. Yang, H. L. Martinez, and M. A. Garcia-Garibay, *J. Org. Chem.*, **67**, 3749 (2002).

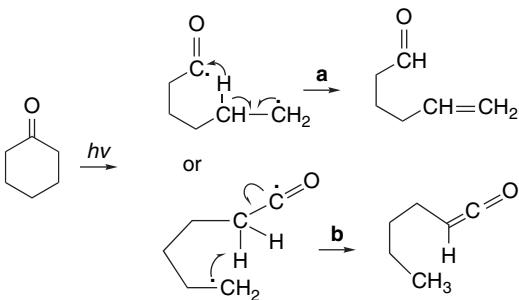
¹¹⁴ G. Quinkert, K. Opitz, W. W. Wiersdorff, and J. Weinlich, *Tetrahedron Lett.*, 1863 (1963).

¹¹⁵ N. C. Yang and E. D. Feit, *J. Am. Chem. Soc.*, **90**, 504 (1968).

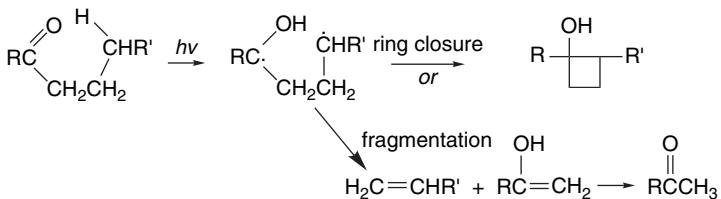
Ketones such as 2,2,5,5-tetraphenylcyclopentanone and 2,2,6,6-tetraphenylcyclohexanone decarbonylate readily because of the stabilization afforded by the phenyl groups. The products result from recombination, disproportionation, or fragmentation of the diradical intermediate.¹¹⁶



With some cyclic ketones, the α -cleavage can also be followed by intramolecular hydrogen abstraction that eventually leads to an unsaturated ring-opened aldehyde.¹¹⁷ An alternative reaction path involves formation of a ketene. The competition between these two reactions is determined by the effect of substituents on the conformation and reactivity of the diradical intermediate.¹¹⁸



For ketones having propyl or longer alkyl groups as a carbonyl substituent, intramolecular hydrogen abstraction can be followed by either cleavage of the bond between the α - and β -carbon atoms or by formation of a cyclobutanol.



Cleavage between C_α and C_β is referred to as *Type-II photoelimination* to distinguish it from α -cleavage. Type-II photoeliminations are observed for both aryl and allyl ketones.¹¹⁹ Studies aimed at establishing the identity of the reactive excited state

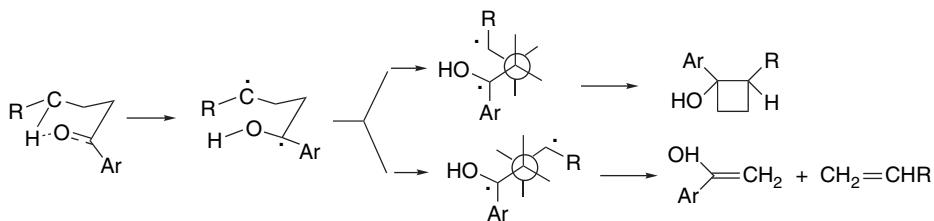
¹¹⁶ D. H. R. Barton, B. Charpiot, K. U. Ingold, L. J. Johnston, W. B. Motherwell, J. C. Scaiano, and S. Stanforth, *J. Am. Chem. Soc.*, **107**, 3607 (1985).

¹¹⁷ W. C. Agosta and W. L. Schreiber, *J. Am. Chem. Soc.*, **93**, 3947 (1971); P. J. Wagner and R. W. Spoerke, *J. Am. Chem. Soc.*, **91**, 4437 (1969).

¹¹⁸ P. J. Wagner, *Top. Curr. Chem.*, **61**, 1 (1976).

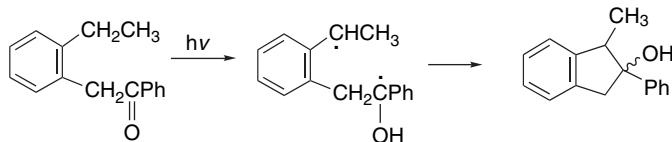
¹¹⁹ P. J. Wagner and P. Klan, in *CRC Handbook of Photochemistry and Photobiology*, W. Horspool and F. Lenci, eds., CRC Press, Boca Raton, FL, 2004, Chap 52.

indicate that both S_1 and T_1 are involved for allyl ketones, but when one of the carbonyl substituents is aryl, intersystem crossing is very fast and T_1 is the reactive state. Theoretical analysis indicates that the hydrogen abstraction involves an in-plane (n) orbital on oxygen, rather than a π orbital. Usually, cleavage is the dominant reaction, with cyclobutanol yields being rather low, but there are exceptions. Activation energies for the hydrogen abstraction process from a methylene group are about 4 kcal, whereas the activation energy for carbon-carbon bond cleavage is 8–12 kcal. The competition between these two processes can be understood in terms of the structure and conformation of the diradical intermediates.¹²⁰ The hydrogen abstraction reaction is believed to occur through a chairlike conformation. The diradical can give cyclobutanol from the *gauche* conformation or fragment through the *anti* conformation.

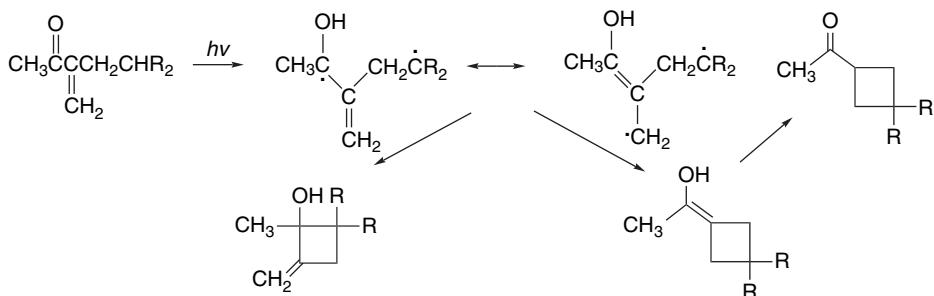


The nature of substituents on the aryl ring can affect the balance between the competing reactions.¹²¹

With aryl benzyl ketones, indanols can be formed.¹²² This is a particularly favorable case because of the benzylic stabilization of both radical sites.



Intramolecular hydrogen atom abstraction is also an important process for acyclic α,β -unsaturated ketones.¹²³ The intermediate diradical then cyclizes to give the enol of a cyclobutyl ketone. Among the by-products of such photolyses are methylenecyclobutanols resulting from alternative modes of cyclization of the diradical intermediate.



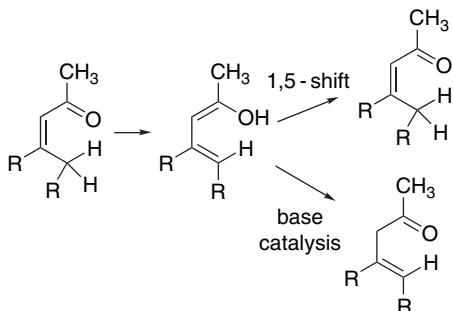
¹²⁰ P. J. Wagner, *Acc. Chem. Res.*, **4**, 168 (1971).

¹²¹ M. V. Encina, E. A. Lissi, E. Lemp, A. Zanocco, and J. C. Scaiano, *J. Am. Chem. Soc.*, **105**, 1856 (1983).

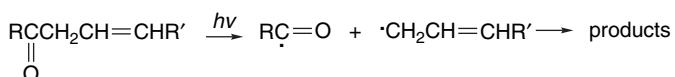
¹²² P. J. Wagner, A. Zand, and B.-S. Park, *J. Am. Chem. Soc.*, **118**, 12856 (1996).

¹²³ R. A. Cormier, W. L. Schreiber, and W. C. Agosta, *J. Am. Chem. Soc.*, **95**, 4873 (1973); R. A. Cormier and W. C. Agosta, *J. Am. Chem. Soc.*, **96**, 618 (1974).

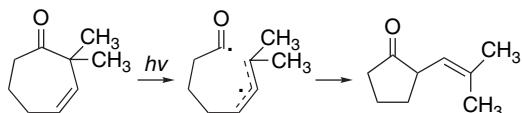
α,β -Unsaturated ketones with γ -hydrogens can undergo hydrogen atom transfer resulting in formation of a dienol. Because the hydrogen atom transfer occurs through a cyclic TS, the originally formed dienol has Z-stereochemistry. The dienol is unstable and two separate processes have been identified for ketonization: a [1,5]-sigmatropic shift of hydrogen leading back to the conjugated enone and a base-catalyzed proton transfer that leads to the β,γ -enone.¹²⁴ The deconjugated enone is formed because of a kinetic preference for reprotonation of the dienolate at the α -carbon. Photochemical deconjugation is a synthetically useful way of effecting isomerization of α,β -unsaturated ketones and esters to the β,γ -isomers.



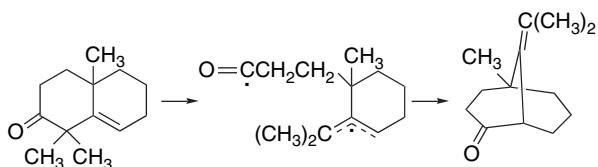
Ketones in which the double bond is located in the β,γ -position are likely candidates for α -cleavage because of the stability of the allyl radical that is formed. This is an important process in direct irradiation. Products then arise by recombination of the radicals before or after decarbonylation.



For cyclic ketones, the diradical intermediates can recombine, leading to isomerized ketones.



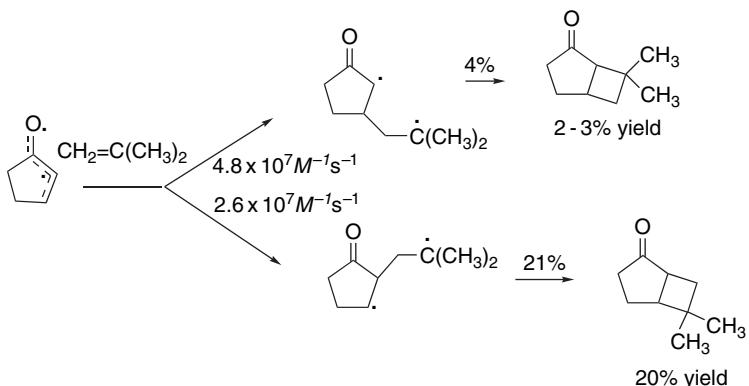
Ref. 125



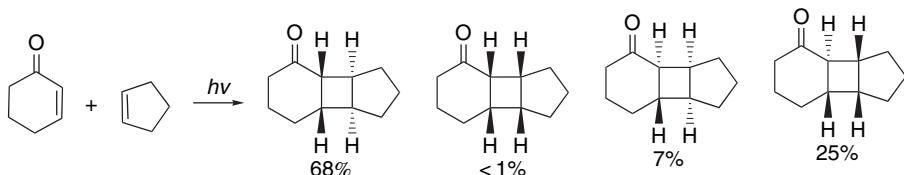
Ref. 126

- ¹²⁴. R. Ricard, P. Sauvage, C. S. K. Wan, A. C. Weedon, and D. F. Wong, *J. Org. Chem.*, **51**, 62 (1986).
¹²⁵. H. Sato, N. Furutachi, and K. Nakanishi, *J. Am. Chem. Soc.*, **94**, 2150 (1972); L. A. Paquette, R. F. Eizember, and O. Cox, *J. Am. Chem. Soc.*, **90**, 5153 (1968).
¹²⁶. P. S. Engel and M. A. Schnexnayder, *J. Am. Chem. Soc.*, **97**, 145 (1975).

Cyclic α,β -unsaturated ketones present a rich array of photochemical reactions, some of which are of considerable synthetic value (see Part B, Section 6.3.2.2). Generally, noncyclic enones relax rapidly by *cis-trans* interconversion and do not undergo intermolecular photochemical reactions. One useful reaction of cyclic enones is photochemical addition of alkenes.¹²⁷ The reaction involves the $\pi-\pi^*$ triplet excited state and 1,4-diradical intermediates.¹²⁸ Both the regiochemistry and stereochemistry of the reaction are determined by the properties of the diradical intermediate. It appears that initial bonding can occur at either C(2) or C(3) of the excited enone system. The alkene reacts at its less-substituted terminus, generating the more stable radical. The regiochemistry is determined by the relative efficiency of cyclization to product versus fragmentation back to reactants. In the case of cyclopentenone and isobutene, both the relative rates of addition and the fraction proceeding on to product have been determined. The preferred regioisomer results from a larger fraction of cyclization for the intermediate with radical character at the β -carbon.¹²⁹



Significantly, both *cis* and *trans* ring junctures are formed.¹³⁰ Cyclohexenone and cyclopentene, for example, give four adducts with about a 2:1 *cis:trans* ratio.¹³¹



¹²⁷ P. de Mayo, *Acc. Chem. Res.*, **4**, 41 (1971); D. I. Schuster, G. Lem, and N. A. Kaprinidis, *Chem. Rev.*, **93**, 3 (1993).

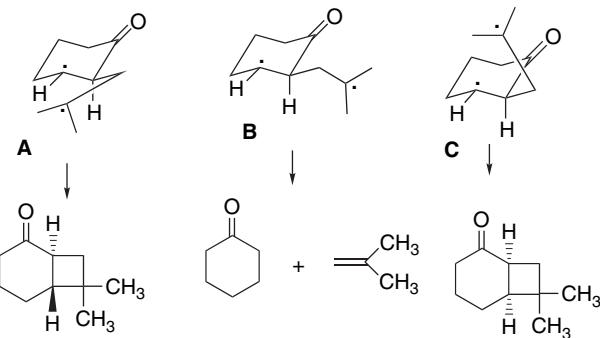
¹²⁸ D. I. Schuster, D. A. Dunn, G. E. Heibel, P. B. Brown, J. M. Rao, J. Woning, and R. Bonneau, *J. Am. Chem. Soc.*, **113**, 6245 (1991).

¹²⁹ D. Andrew, D. J. Hastings, D. L. Oldroyd, A. Rudolph, A. C. Weedon, D. F. Wong, and B. Zhang, *Pure Appl. Chem.*, **64**, 1327 (1992); D. Andrew, D. J. Hastings, and A. C. Weedon, *J. Am. Chem. Soc.*, **116**, 10870 (1994); D. Andrew and A. C. Weedon, *J. Am. Chem. Soc.*, **117**, 5647 (1995).

¹³⁰ E. J. Corey, J. D. Bass, R. Le Mahieu, and R. B. Mitra, *J. Am. Chem. Soc.*, **86**, 5570 (1964).

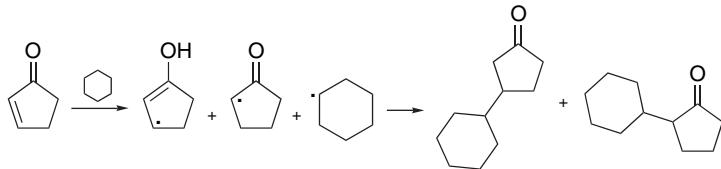
¹³¹ D. I. Schuster, N. Kaprinidis, D. J. Wink, and J. C. Dewan, *J. Org. Chem.*, **56**, 561 (1991).

The *trans* products obviously are more strained. The stereochemistry can be traced to conformational factors in the diradical. For example, the diradical from cyclohexenone and isobutene can be formed in several conformations.

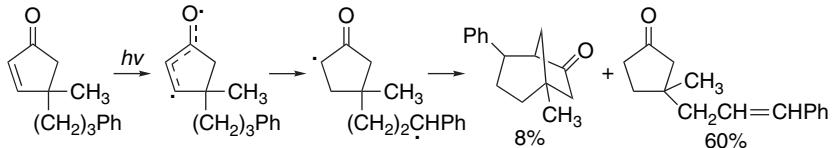


The extended radical **B** is likely to fragment. The *gauche* radicals **A** and **C** lead to *trans* and *cis* ring junctions, respectively. In this particular case, it has been proposed that there is less steric repulsion to cyclization of radical **A**, resulting in a preference for formation of the *trans* ring closure.¹³² In general, the competing modes of attack of alkene and the ease of cyclization of the diradical govern the stereochemistry of the ring juncture.

In hydrocarbon solvents, the principal products from cyclopentenones result from hydrogen abstraction processes. Irradiation of cyclopentenone in cyclohexane gives a mixture of 2- and 3-cyclohexylcyclopentanone.¹³³ These products can be formed by intermolecular hydrogen abstraction, followed by recombination of the resulting radicals. It is interesting that as in the alkene cycloaddition reaction, reactivity is observed at both C(2) and C(3) of the excited enone system.



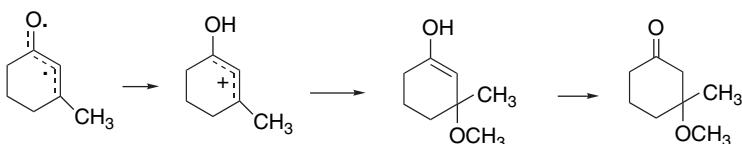
If a substituent chain is present on the cyclopentenone ring, an intramolecular hydrogen abstraction can take place.



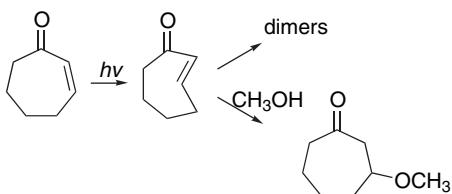
The bicyclic product is formed by coupling of the two radical sites, whereas the unsaturated side chain results from an intramolecular hydrogen atom transfer. These reactions can be sensitized by aromatic ketones and quenched by typical triplet quenchers, and are therefore believed to proceed via triplet excited states.

¹³² P. G. Bauslaugh, *Synthesis*, 287 (1970).

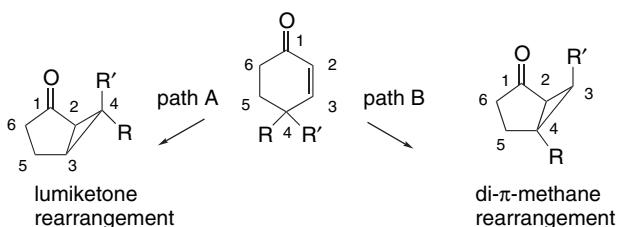
¹³³ S. Wolff, W. L. Schreiber, A. B. Smith, III, and W. C. Agosta, *J. Am. Chem. Soc.*, **94**, 7797 (1972).



In the case of cycloheptenone and larger rings, the main initial photoproducts are the *trans*-cycloalkenones produced by photoisomerization. In the case of the seven- and eight-membered rings, the *trans*-double bonds are sufficiently strained that rapid reactions follow. In nonnucleophilic solvents dimerization takes place, whereas in nucleophilic solvents addition reactions occur.¹³⁵



There are also important rearrangement reactions for cyclic enones. For cyclohexenones two prominent reactions are the *lumiketone rearrangement* (Path A) and the *di- π -methane rearrangement* (Path B). The di- π -methane rearrangement pathway is restricted to 4-aryl or 4-vinyl cyclohexenones. 4,4-Dialkylcyclohexenones undergo the lumiketone rearrangement, which involves the shift of the C(4)–C(5) bond to C(3) and formation of a new C(2)–C(4) bond.¹³⁶

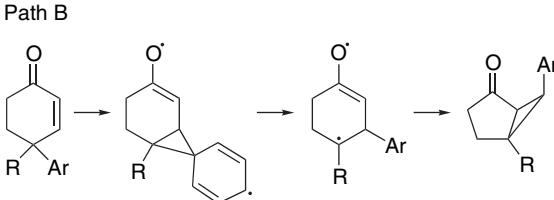
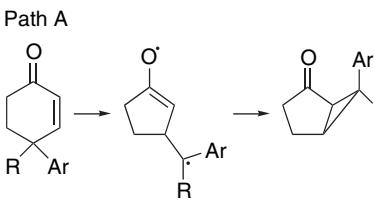


Both reactions proceed via triplet excited species and to some extent depend on whether the $\pi-\pi^*$ or $n-\pi^*$ states are involved. At the most basic level of mechanism, the reactions can be depicted as involving the following steps.

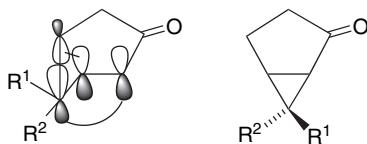
¹³⁴ D. I. Schuster, J.-M. Yang, J. Woning, T. A. Rhodes, and A. W. Jensen, *Can. J. Chem.*, **73**, 2004 (1995).

¹³⁵ H. Hart, B. Chen, and M. Jeffares, *J. Org. Chem.*, **44**, 2722 (1979).

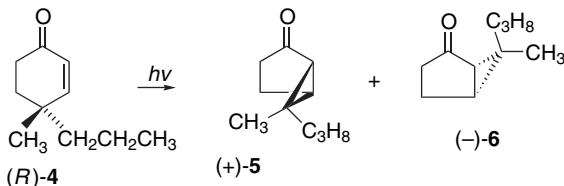
¹³⁶ For a review of this reaction, see D. I. Schuster, in *Rearrangements in Ground and Excited States*, Vol. 3, P. de Mayo, ed., Academic Press, New York, 1980, Chap. 17.



The lumiketone rearrangement is stereospecific and can be described as a $[\pi 2_a + \sigma 2_a]$ cycloaddition. This mechanism requires that inversion of configuration occur at C(4) as the new σ bond is formed at the back lobe of the reacting C(4)–C(5) σ bond.

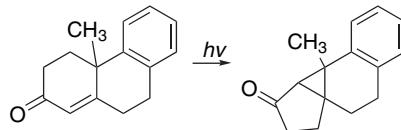


It has been demonstrated in several systems that the reaction is in fact stereospecific with the expected inversion occurring at C(4). The ketone **4** provides a specific example. The stereoisomeric products **5** and **6** are both formed, but in each product inversion has occurred at C(4).



Ref. 137

The lumiketone rearrangement also proceeds in the case of some 4-alkyl-4-arylcylohexenones.

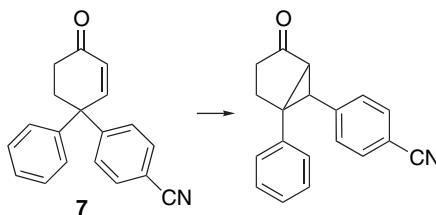


Ref. 138

With 4,4-diarylcylohexenones, the di- π -methane rearrangement is the preferred reaction. For compounds in which the two aryl groups are substituted differently, it

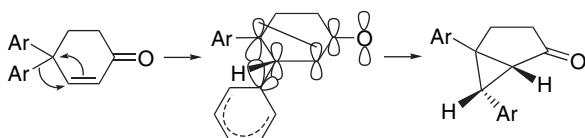
¹³⁷. D. I. Schuster and J. M. Rao, *J. Org. Chem.*, **46**, 1515 (1981); D. I. Schuster, R. H. Brown, and B. M. Resnick, *J. Am. Chem. Soc.*, **100**, 4504 (1978).

¹³⁸. O. L. Chapman, J. B. Sieja, and W. J. Welstead, Jr., *J. Am. Chem. Soc.*, **88**, 161 (1966).

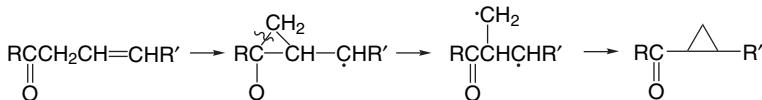


Ref. 139

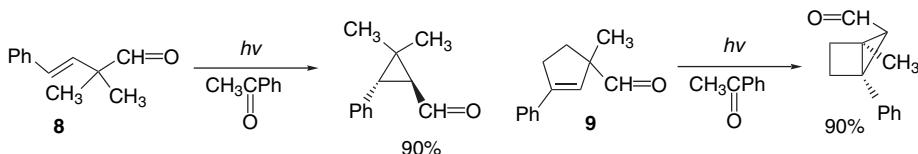
As described on p. 1113, di- π -methane rearrangement can be considered to occur via a TS in which C(2)–C(4) bridging is accompanied by a $4 \rightarrow 3$ aryl migration.¹⁴⁰ Note that the *endo* product is predicted by the concerted mechanism. It is the major product, even though it is sterically more congested than the *exo* isomer. This stereospecificity is characteristic of the reaction.



Excitation of acyclic β,γ -unsaturated ketones by triplet photosensitization can give cyclopropyl ketones.¹⁴¹ This reaction is known as the *oxadi- π -methane rearrangement*.



Oxadi- π -methane rearrangements have been observed by both direct and triplet-sensitized excitation. The reaction is generally associated with the $\pi-\pi^*$ excited state, but there are also examples that involve other levels. The most favorable cases for the rearrangement involve conjugation at the γ -carbon (e.g., aryl) and disubstitution or a bulky substituent at the α -carbon. The reaction is also favored by more or less rigid cyclic systems. These features are present in reactants such as **8** and **9**, which give particularly high yields.¹⁴²



As with other reactions involving triplet excited states, the efficiency of inter-system crossing appears to be a major factor in the outcome of the reaction.¹⁴³ The

^{139.} H. E. Zimmerman, R. D. Rieke, and J. R. Scheffer, *J. Am. Chem. Soc.*, **89**, 2033 (1967).

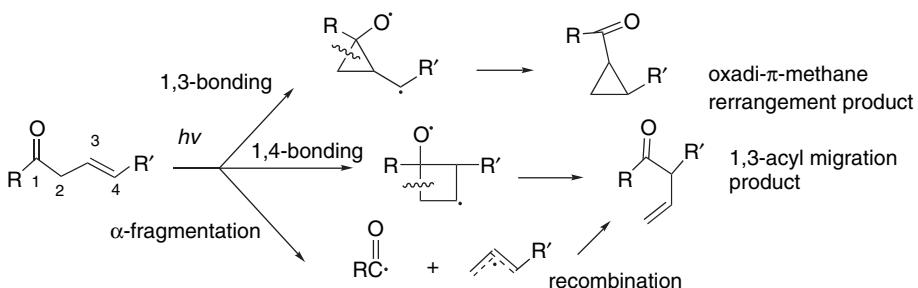
^{140.} H. E. Zimmerman, *Tetrahedron*, **30**, 1617 (1974).

^{141.} W. G. Dauben, M. S. Kellogg, J. I. Seeman, and W. A. Spitzer, *J. Am. Chem. Soc.*, **92**, 1786 (1970).

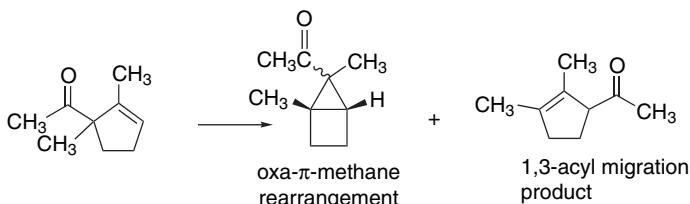
^{142.} D. Armesto, M. J. Ortiz, and S. Romano, *Tetrahedron Lett.*, **36**, 965 (1995).

^{143.} B. Reimann, D. E. Sadler, and K. Schaffner, *J. Am. Chem. Soc.*, **108**, 5527 (1986); M.-D. Su, *J. Org. Chem.*, **61**, 3080 (1996).

reaction pathway has been modeled computationally (MC-SCF/6-31G*) using the simplest β,γ -unconjugated carbonyl compound, but-3-en-1-one.¹⁴⁴ The results suggest that two short-lived diradical intermediates are involved, one leading to oxadi- π -methane rearrangement and the other to 1,3-acyl migration. These structures are closely related to CIs that provide efficient crossing to the ground state. The computations suggest that both the singlet and triplet states are energetically comparable. A dissociation-recombination mechanism is also available for the 1,3-shift. It appears that individual structural differences can favor any of the competing reaction paths.



This conclusion is in general agreement with experimental studies that indicate that several excited states can lead to oxadi- π -methane rearrangement and the related reactions.¹⁴⁵ For example, 1,2-dimethylcyclopent-2-enyl methyl ketone reacts by all three pathways. In the gas phase about 25% of the 1,3-acyl migration occurs by a dissociation mechanism, as indicated by the ability of NO and O₂ to divert a part but not all of the intermediate.¹⁴³



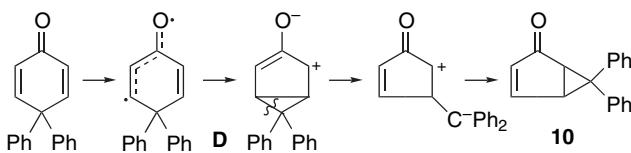
Other conjugated carbonyl compounds that have received a great deal of attention are the cyclohexadienones.¹⁴⁶ The main photolysis product of 4,4-diphenylcyclohexadienone, for example, is **10**.¹⁴⁷ Quenching and photosensitization

¹⁴⁴ S. Wilsey, M. J. Bearpark, F. Bernardi, M. Olivucci, and M. A. Robb, *J. Am. Chem. Soc.*, **118**, 176 (1996).

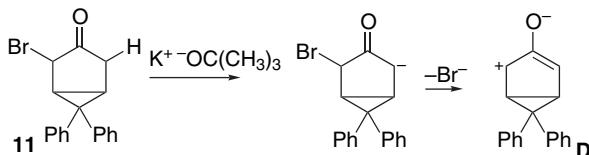
¹⁴⁵ T. J. Eckersley, S. D. Parker, and N. A. J. Rogers, *Tetrahedron*, **40**, 3749 (1984); T. J. Eckersley and N. A. J. Rogers, *Tetrahedron*, **40**, 3759 (1984); M. J. C. M. Koppes and H. Cerfontain, *Rec. Trav. Chim. Pays-Bas*, **107**, 549 (1988).

¹⁴⁶ H. E. Zimmerman, *Angew. Chem. Int. Ed. Engl.*, **8**, 1 (1969); K. Schaffner and M. Demuth, in *Rearrangements in Ground and Excited States*, Vol. 3, P. de Mayo, ed., Academic Press, New York, 1980, Chap. 18; D. I. Schuster, *Acc. Chem. Res.*, **11**, 65 (1978).

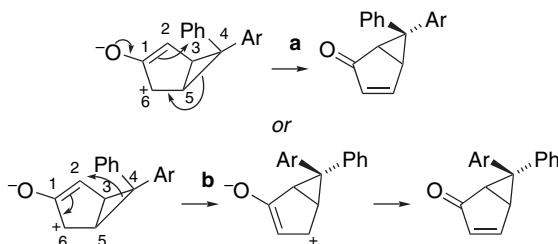
¹⁴⁷ H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.*, **83**, 4486 (1961).



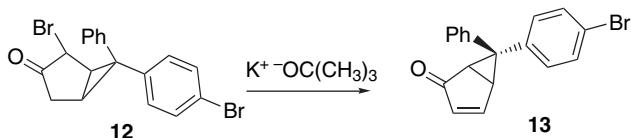
It is believed that a reactive ground state species, the zwitterion **D**, is an intermediate and that it rearranges to the observed product.¹⁴⁸ To test this mechanism, generation of species **D** by nonphotochemical means was undertaken.¹⁴⁹ α -Haloketones, when treated with strong base, ionize to such dipolar intermediates. Thus, the bromoketone **11** is a potential precursor of intermediate **D**.



The zwitterion prepared by this route did indeed lead to **10**, as required if it is an intermediate in the photochemical reaction. Further study of this process established another aspect of the reaction mechanism. The product could be formed by a process involving inversion at C(4) (Path **a**) or by one involving a pivot about the bond C(3)–C(4) (Path **b**).



The two mechanisms predict the formation of stereochemically different products when the aryl groups at C(4) are different. When the experiment was carried out on **12** only **13** the product corresponding to inversion of configuration at C(4) was observed.¹⁵⁰

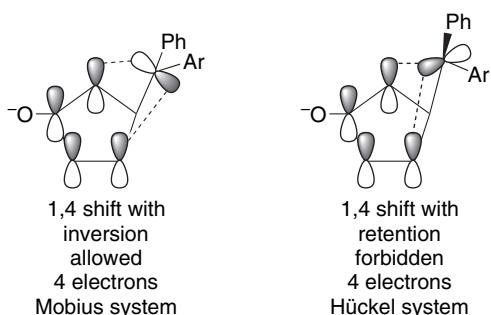


The rearrangement step is a ground state thermal process and may be classified as a [1,4]-sigmatropic shift of carbon across the face of a 2-oxybutenyl cation. The Woodward-Hoffmann rules require a sigmatropic shift of this type to proceed with inversion of configuration. The orbitals involved in a [1,4]-sigmatropic shift are shown below.

¹⁴⁸ H. E. Zimmerman and J. S. Swenton, *J. Am. Chem. Soc.*, **89**, 906 (1967).

¹⁴⁹ H. E. Zimmerman, D. Döpp, and P. S. Huyffer, *J. Am. Chem. Soc.*, **88**, 5352 (1966).

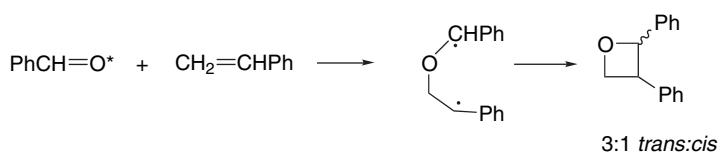
¹⁵⁰ H. E. Zimmerman and D. S. Crumrine, *J. Am. Chem. Soc.*, **90**, 5612 (1968).



As is clear from the preceding examples, there are a variety of overall reactions that can be initiated by photolysis of ketones. The course of photochemical reactions of ketones is very dependent on the structure of the reactant. Despite the variety of overall processes that can be observed, the number of individual steps involved is limited. For ketones, the most important are inter- and intramolecular hydrogen abstraction, α -cleavage at the carbonyl group, and substituent migration to the β -carbon atom of α,β -unsaturated ketones. Reexamination of the mechanisms illustrated in this section will reveal that most of the reactions of carbonyl compounds that have been described involve combinations of these fundamental processes. The final products usually result from re-bonding of reactive intermediates generated by these steps.

12.3.3. Cycloaddition of Carbonyl Compounds and Alkenes

Ketones and aldehydes can undergo photochemical [2+2] cycloaddition reactions with alkenes to give oxetanes. This is called the *Paterno-Buchi reaction*. For alkyl carbonyl compounds both singlet and triplet excited states seem to be involved, but for aromatic compounds the reaction occurs through the triplet state.¹⁵¹ The regiochemistry can usually be accounted for on the basis of formation of the most stable 2-oxa-1,4-diradical. For example, styrene and benzaldehyde give 2,3- not 2,4-diphenyloxetane.¹⁵²

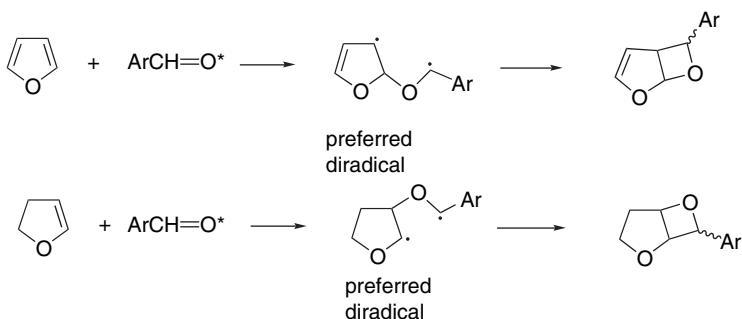


The same generalization can also account for the reversal of orientation between furan and dihydrofuran.¹⁵³

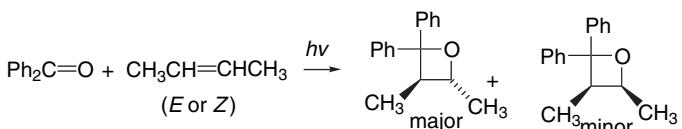
¹⁵¹. R. A. Caldwell, G. W. Sovocool, and R. P. Gajewski, *J. Am. Chem. Soc.*, **95**, 2549 (1973).

¹⁵². S. A. Fleming and J. J. Gao, *Tetrahedron Lett.*, **38**, 5407 (1997).

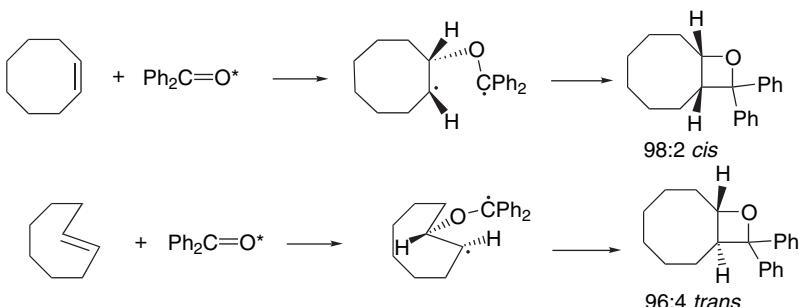
¹⁵³. A. G. Griesbeck and S. Stadtmuller, *Chem. Ber.*, **123**, 357 (1990).



The Paterno-Buchi reaction is ordinarily not stereospecific, but instead favors the more stable adduct for either alkene isomer, indicating the involvement of a relatively a long-lived diradical intermediate.¹⁵⁴



An exception to this generalization has been noted for *E*- and *Z*-cyclooctene.¹⁵⁵ This reaction is nearly stereospecific at low temperature. This result is attributed to conformationally distinct 1,4-diradical intermediates that undergo intersystem crossing and cyclization faster than stereochemical interconversion.



At higher temperature, some stereorandomization occurs as the result of competition between rotational processes and fragmentation of the 1,4-diradical intermediate.

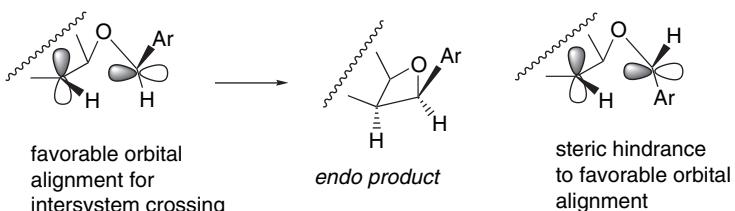
Many of the details of both regio- and stereoselectivity of the Paterno-Buchi reaction can be understood in terms of the conformation and lifetime of the 1,4-diradical intermediates. Griesbeck and co-workers have proposed that the relative lifetime of the radicals, and whether they cyclize or revert to reactants, is governed by the rate of intersystem crossing, which in turn depends on the efficiency of spin-orbit coupling.¹⁵⁶ With cyclic alkenes, for example, the *endo* stereoisomer is often preferred. This can be explained by noting that the conformation leading to *exo* product is not well oriented for the perpendicular orbital interaction that favors intersystem crossing (see p. 1075).

¹⁵⁴ D. R. Arnold, R. L. Hinman, and A. H. Glick, *Tetrahedron Lett.*, 1425 (1964).

¹⁵⁵ W. Adam, V. R. Stegmann, and S. Weinkotz, *J. Am. Chem. Soc.*, **123**, 2452 (2001); W. Adam and V. R. Stegmann, *J. Am. Chem. Soc.*, **124**, 3600 (2002).

¹⁵⁶ A. G. Griesbeck and S. Stadtmüller, *J. Am. Chem. Soc.*, **112**, 1281 (1990); A. G. Griesbeck, H. Mauder, and S. Stadtmüller, *Acc. Chem. Res.*, **27**, 70 (1994).

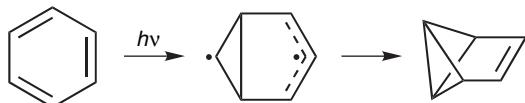
Computational modeling of orbital interactions supports this proposal.¹⁵⁷



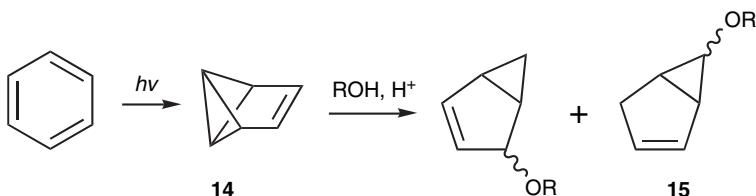
The Paterno-Buchi reaction, particularly its synthetic application,¹⁵⁸ is considered in more detail in Section 6.3.2.3 of Part B.

12.4. Photochemistry of Aromatic Compounds

Irradiation of benzene and certain of its derivatives results in bond reorganization and formation of nonaromatic products.¹⁵⁹ Irradiation of liquid benzene with light $\lambda = 254\text{ nm}$ wavelength results in the accumulation of fulvene and a very small amount of tricyclo[3.1.0.0^{2,6}]hex-3-ene, also known as benzvalene.¹⁶⁰ The maximum conversion to this product in liquid benzene is about 0.05%. The key intermediate is believed to be a diradical formed by 1,3-bonding.



Because of the low photostationary concentration of benzvalene, photolysis is not an efficient way of accumulating this compound. However, the highly reactive molecule can be trapped if it is generated in the presence of other molecules with which it reacts. Irradiation of benzene in acidic hydroxylic solvents gives products resulting from 1,3-bonding in the benzene ring and addition of a molecule of solvent. The compounds of structure **15** arise by solvolysis of, the initial photoproduct benzvalene.¹⁶¹



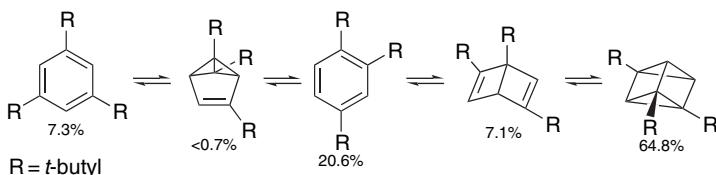
¹⁵⁷ A. G. Kutateladze, *J. Am. Chem. Soc.*, **123**, 9279 (2001).

¹⁵⁸ T. Bach, *Synthesis*, 683 (1998).

¹⁵⁹ D. Bryce-Smith and A. Gilbert, *Tetrahedron*, **32**, 1309 (1976); A. Gilbert, in *Organic Photochemistry and Photobiology*, W. M. Horspool and P.-S. Song, eds., CRC Press, Boca Raton, FL, 1995, pp. 229–236.

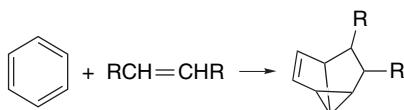
¹⁶⁰ K. E. Wilzbach, J. S. Ritscher, and L. Kaplan, *J. Am. Chem. Soc.*, **89**, 1031 (1967).

¹⁶¹ L. Kaplan, D. J. Rausch, and K. E. Wilzbach, *J. Am. Chem. Soc.*, **94**, 8638 (1972).

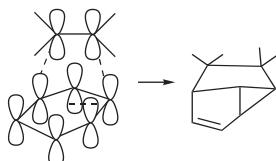


These various photoproducts are all valence isomers of the normal benzenoid structure. The alternative bonding patterns are reached from the excited state, but it is difficult to specify a precise mechanism. The presence of the *t*-butyl groups introduces a steric factor that works in favor of the photochemical cyclization. Although the *t*-butyl groups are coplanar in the aromatic ring, the geometry of the bicyclic products reduces steric interactions between adjacent *t*-butyl groups.

Irradiation of solutions of alkenes in benzene or substituted benzenes gives primarily 1:1 adducts in which the alkene bridges *meta* positions of the aromatic ring.¹⁶³



These reactions are believed to proceed through a complex of the alkene with a singlet excited state of the aromatic compound (an exciplex). The alkene and aromatic ring are presumed to be oriented in such a manner that the alkene π system reacts with *p* orbitals on the 1,3-carbons of the ring. This addition to the aromatic ring is evidently concerted because the relative geometry of the substituents on the alkene is retained in the product. Note that the re-bonding scheme is related to that observed in benzvalene formation. Lesser amounts of products involving addition to 1,2- or 1,4- positions of the aromatic ring are also formed in some cases.¹⁶⁴

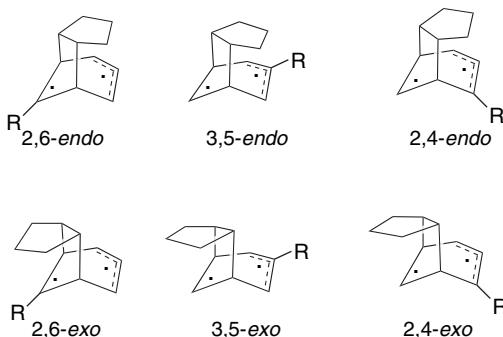


The product distribution of addition of cyclopentene to substituted benzenes has been studied in detail. Three regiosomeric and two stereoisomeric orientations are possible. *Endo* addition is generally preferred.^{163f}

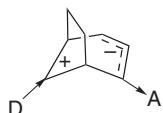
¹⁶². K. E. Wilzbach and L. Kaplan, *J. Am. Chem. Soc.*, **87**, 4004 (1965).

¹⁶³. (a) K. E. Wilzbach and L. Kaplan, *J. Am. Chem. Soc.*, **88**, 2066 (1966); (b) J. Cornelisse, V. Y. Merritt, and R. Srinivasan, *J. Am. Chem. Soc.*, **95**, 6197 (1973); (c) A. Gilbert and P. Yianni, *Tetrahedron*, **37**, 3275 (1981); (d) D. Bryce-Smith and A. Gilbert, *Tetrahedron*, **33**, 2459 (1977); (e) T. Wagner-Jauregg, *Synthesis*, 165, 769 (1980); (f) J. Cornelisse, *Chem. Rev.*, **93**, 615 (1993).

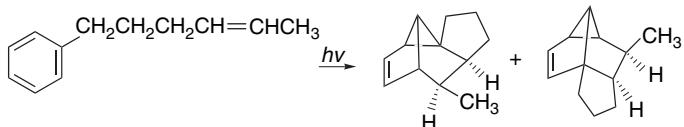
¹⁶⁴. K. E. Wilzbach and L. Kaplan, *J. Am. Chem. Soc.*, **93**, 2073 (1971).



Donor substituents favor the 2,6-regioisomer, whereas EWGs favor the 2,4-orientation.¹⁶⁵ These results suggest that there is considerable polar character to the reaction between the excited aromatic and the alkene. Acceptor substituents at C(3) can stabilize the negative charge at C(3) and C(5), whereas donor substituents can stabilize the positive charge at C(1).¹⁶⁶



Addition of alkenes and aromatic rings has also been realized intramolecularly when the distance between the alkene and phenyl substituent is sufficient to permit bonding.



The photocycloaddition of ethene and benzene has been studied by CAS-SCF computation using the 6-31G* basis set for energies and 4-31G orbitals for structural minimization.¹⁶⁷ The structure of the CI is shown in Figure 12.24. The *ortho* and *meta* cycloaddition processes proceed through alternate electron-pairing schemes from a single CI without barriers. For unsubstituted alkenes, the *meta* CI is lower in energy than the *ortho*, whereas the *ortho* CI is stabilized by alkenes with ERG and EWG substituents. Product compositions tend to reflect these differences.¹⁶⁸

¹⁶⁵. P. de Vaal, E. M. Osselton, E. S. Krijnen, G. Lodder, and J. Cornelisse, *Rec. Trav. Chim. Pays-Bas*, **107**, 407 (1988).

¹⁶⁶. D. Bryce-Smith, B. Foulger, J. Forrester, A. Gilbert, B. H. Orger, and H. M. Tyrrell, *J. Chem. Soc., Perkin Trans. 1*, 55 (1980); G. Weber, J. Runsink, and J. Mattay, *J. Chem. Soc., Perkin Trans.*, **1**, 2333 (1987); V. Y. Merritt, J. Cornelisse, and R. Srinivasan, *J. Am. Chem. Soc.*, **95**, 8250 (1973).

¹⁶⁷. S. Clifford, M. J. Bearpark, F. Bernardi, M. Olivucci, M. A. Robb, and B. R. Smith, *J. Am. Chem. Soc.*, **118**, 7353 (1996).

¹⁶⁸. A. Gilbert and P. Yianni, *Tetrahedron*, **37**, 3275 (1981); J. Mattay, *Tetrahedron*, **41**, 2405 (1985).

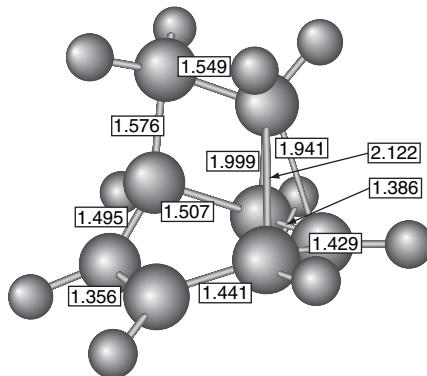
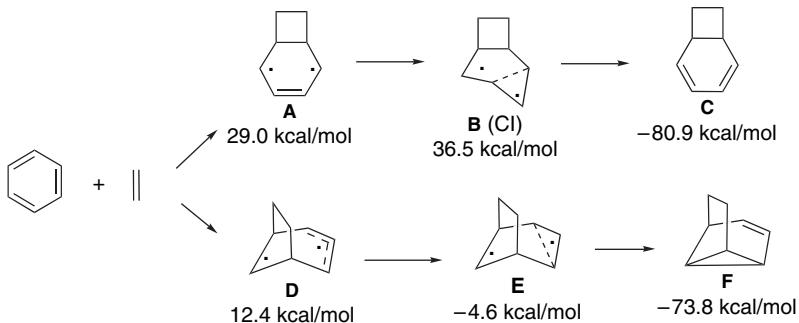


Fig. 12.24. Structure of conical intersection for benzene + ethene addition from *J. Am. Chem. Soc.*, **118**, 7353 (1996), by permission of the American Chemical Society.



Topic 12.1. Computational Interpretation of Diene and Polyene Photochemistry

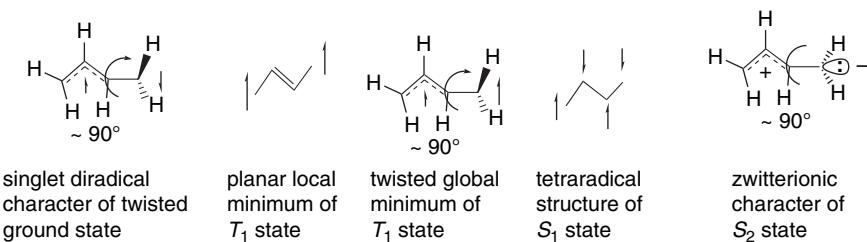
As a starting point for the mechanistic discussion, it is useful to review the structural features of the excited states. The first singlet excited state of butadiene, S_1 , can be approximated as the $\psi_2 \rightarrow \psi_3$ /HOMO \rightarrow LUMO $\pi\text{-}\pi^*$ transition.¹⁶⁹ The lack of fluorescence from this excited state indicates that a very facile path exists for nonradiative energy transfer. The S_2 state has doubly excited character and relaxes to a structure with ionic character that can rotate at the pyramidal carbon but not at the allyl fragment. The minimum energy of the T_1 state corresponds to the allyl-methylene diradical with a nearly 90° twist and slight pyramidalization at the methylene carbon. In substituted systems, one or the other of the zwitterion structures (e.g., allyl cation versus allyl anion) may be favored.¹⁷⁰

¹⁶⁹. K. B. Wiberg, C. M. Hadad, G. B. Ellison, and J. B. Foresman, *J. Phys. Chem.*, **97**, 13586 (1993).

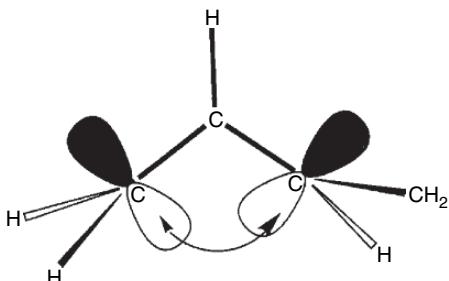
¹⁷⁰. M. E. Squillacote and T. C. Semple, *J. Am. Chem. Soc.*, **109**, 892 (1987).

As computational methods for describing excited states have been refined, additional understanding of the structures has developed. Relatively early computational studies provided some indication of the geometries associated with the butadiene excited states.¹⁷¹ The ground state has a maximum at a twist of 90° about the C(1)–C(2) bond. This structure, which can be approximately described as a singlet methylene-allyl diradical, is found at about 2.3 eV and is more stable than a structure with 90° twist at both terminal groups (3.1 eV). There is no major pyramidalization of the methylene groups in this second structure. The spectroscopic (Franck-Condon) T_1 state is about 3.5 eV above S_0 . A *local planar minimum* is found to have a shortened C(2)–C(3) bond and lengthened C(1)–C(2) and C(3)–C(4) bonds. The energy of this structure is about 2.7 eV. The C(2)–C(3) bond distance is 1.36 Å, so the bond has considerable double-bond character. This local minimum can be represented as a 1,4-but-2-enyl diradical. The *global minimum* on the T_1 surface is a twisted triplet allyl-methylene diradical that is at about 2.3 eV. This structure is very similar in geometry to the singlet diradical on the ground state surface.

The *initial* S_1 state has all bonds lengthened and both ends are able to rotate. The most stable geometry for this state is twisted and pyramidalized at both ends. The energy is about 5.5 eV, but is slightly higher (5.7 eV) when only one end is twisted 90°. All the C–C bonds are around 1.48 Å, and the structure can be described as a completely unpaired singlet tetraradical. The S_2 state also has a *local planar minimum* and has considerable 3p (Rydberg) character in this geometry. The S_2 *global minimum* energy structure has one end twisted 90°; this end is strongly pyramidalized and the structure has considerable zwitterionic character. Approximate representations of these are given below, and this representation of the excited states in terms of energy is given in Figure 12.25.



As we shall see shortly, the singlet state often gives rise to products with 1,3-bridging, which suggests that there is a pronounced C(1)–C(3) interaction.¹⁷²



¹⁷¹. M. Aoyagi, Y. Osamura, and S. Iwata, *J. Chem. Phys.*, **83**, 1140 (1985); P. G. Szalay, A. Karpfen, and H. Lischka, *Chem. Phys.*, **130**, 219 (1989).

¹⁷². M. Ito and I. Ohmine, *J. Phys. Chem.*, **106**, 3159 (1997).

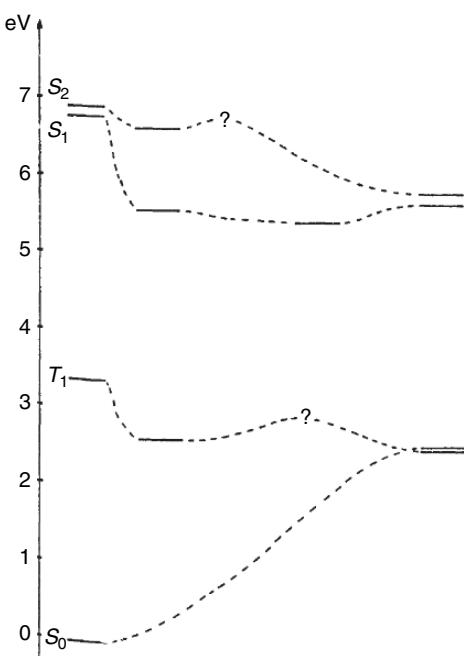


Fig. 12.25. Energy level diagram for the low-lying states of *trans*-1,3-butadiene. The left-hand levels correspond to the vertical excitation energies; the intermediate levels correspond to planar structures resulting from relaxation of bond lengths; and the right-hand levels are the 90° twist structures. Reproduced from *J. Phys. Chem.* **83**, 1140 (1985), by permission of the American Chemical Society.

More recent studies have refined these structural representations. The excited states can be attained by excitation of either the *s-trans* or *s-cis* conformers of 1,3-butadiene, and the excited state structure depends on the original conformation. The structures of the *initial* excited states have been calculated at the MC-SCF/4-31G level.¹⁷³ Two slightly different structures were found for each of the conformations. The lower-energy structures are shown in Figure 12.26. Both structures show stretching and twisting about the C=C, indicating loss of electron pairing. These excited state structures can continue to twist at the C(2)-C(3) bond to reach the global minima.¹⁷⁴

The singlet photochemistry of 1,3-butadiene is believed to be dominated by the S_2 state, which is rapidly reached from the S_1 state by rotation. S_1 and S_2 are, respectively, singly and doubly excited $\pi \rightarrow \pi^*$ states. The return to ground state is believed to involve an S_2 - S_0 CI. The S_2 energy surface of butadiene has been modeled by a computation that combines molecular mechanics and a valence bond structural

¹⁷³. (a) M. Olivucci, I. N. Ragazos, F. Bernardi, and M. A. Robb, *J. Am. Chem. Soc.*, **115**, 3710 (1993); (b) M. Olivucci, F. Bernardi, S. Ottani, and M. A. Robb, *J. Am. Chem. Soc.*, **116**, 2034 (1994); (c) F. Bernardi, M. Olivucci, and M. A. Robb, *J. Photochem. Photobiol.*, **105**, 365 (1997); (d) M. Garavelli, F. Bernardi, P. Celani, M. A. Robb, and M. Olivucci, *J. Photochem. Photobiol.*, **114**, 109 (1998).

¹⁷⁴. V. Bonacic-Koutecky, M. Persico, D. Dohnert, and A. Sevin, *J. Am. Chem. Soc.*, **104**, 6900 (1982); M. Aoyagi, Y. Osamura, and S. Iwata, *J. Chem. Phys.*, **83**, 1140 (1985).

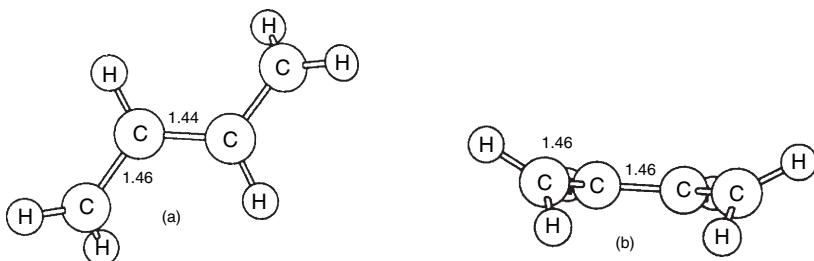


Fig. 12.26. Computed initial excited state structures of butadiene. (a) *s-trans* S_1 ; (b) *s-cis* S_1 . Reproduced from *J. Am. Chem. Soc.*, **115**, 3710 (1993), by permission of the American Chemical Society.

representation.^{173a} The structural parameters that were followed were the rotations of the C(1)–C(2) (α), C(2)–C(3) (β), and C(3)–C(4) (α') bonds. The structures that were located were then refined using MC-SCF/4-31G calculations. The excited state near the CI involves rotation at all three bonds and can be represented as having all four π electrons unpaired.

Comparison of the disrotatory and conrotatory paths for electrocyclization indicates that the disrotatory path can proceed without a barrier. Figure 12.27 is a cross section of the S_2 and S_0 surfaces and depicts the formation of the observed products via transition from S_2 to the ground state surface. Figure 12.28 is a “reaction cube” in which each of the edges represents rotation about one of the bonds. The shaded central area is near 90-90-90 and is the region in which the CIs are located. Figure 12.29 shows the structures of three CIs found in this area.

There are also higher-energy CIs, which resemble the H migration carbenoid structures found for ethene.¹⁷⁵ (See Figure 12.29) These structures have also been located

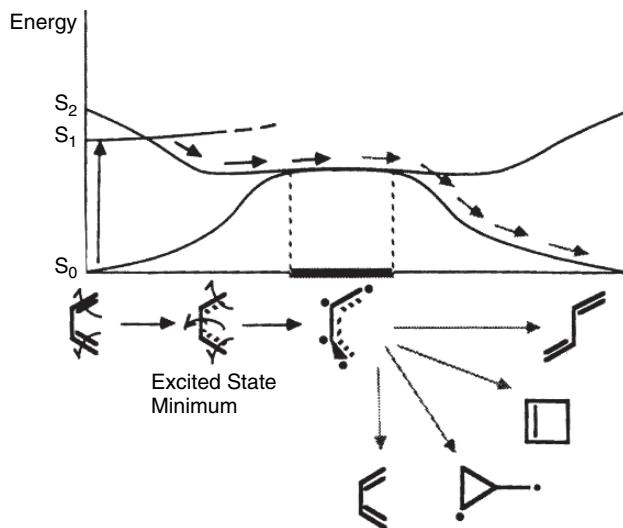


Fig. 12.27. Cross section of energy surface indicating re-pairing of S_2 to reactant and other products. Reproduced from *J. Am. Chem. Soc.*, **115**, 3710 (1993), by permission of the American Chemical Society.

¹⁷⁵ S. Wilsey and K. N. Houk, *Photochem. Photobiol.*, **76**, 616 (2002).

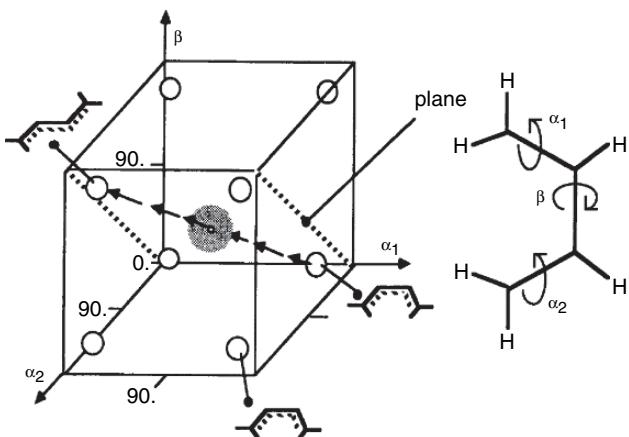


Fig. 12.28. Reaction cube locating the butadiene conical intersection in relation to rotation at each of the bonds. The shaded area in the center represents the location of the conical intersection with all bond rotations near 90°. The open circles represent initial excited states. The energy surface in Figure 12.27 represents the diagonal plane bisecting the cube. Reproduced from *J. Am. Chem. Soc.*, **115**, 3710 (1993), by permission of the American Chemical Society.

at the MC-SCF/4-31G level of computation.^{173a} CASPT2 theory, which is appropriate for excited states with large ionic character,¹⁷⁶ gives a similar description of the CI.¹⁷⁷ Other descriptions of the butadiene excited surface have also been developed,^{178,179} including explicit consideration of the formation of bicyclo[1.1.0]butane by 1,3-bonding.¹⁸⁰

The energy profile in Figure 12.30 compares the disrotatory and conrotatory paths for cyclization. There is no barrier on the disrotatory path but the conrotatory path

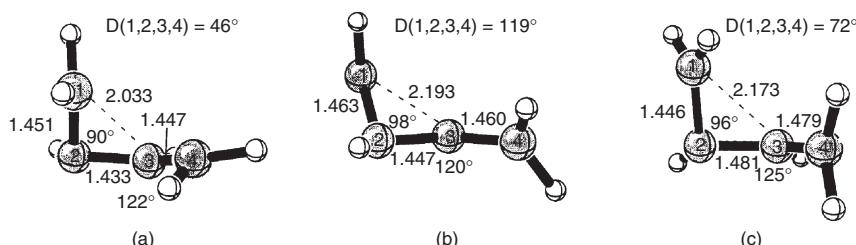


Fig. 12.29. Structure of the 1,3-butadiene conical intersections from CAS(6,6)/6-31G* computations: (a) cisoid, (b) transoid, (c) central. Reproduced from *Photochem. Photobiol.*, **76**, 616 (2002), by permission of Elsevier.

- ¹⁷⁶ C. S. Page and M. Olivucci, *J. Comput. Chem.*, **24**, 298 (2003).
- ¹⁷⁷ B. Ostojic and W. Domcke, *Chem. Phys.*, **269**, 1 (2001); R. P. Krawczyk, K. Malsch, G. Hohlneicher, R. C. Gillen, and W. Domcke, *Chem. Phys. Lett.*, **320**, 535 (2000).
- ¹⁷⁸ S. Saki, *Chem. Phys. Lett.*, **287**, 263 (1998); R. P. Krawczyk, K. Malsch, G. Hohlneicher, R. C. Gillen, and W. Domcke, *Chem. Phys. Lett.*, **320**, 535 (2000).
- ¹⁷⁹ M. Olivucci, I. N. Ragazos, F. Bernardi, and M. A. Robb, *J. Am. Chem. Soc.*, **115**, 3710 (1993); M. Olivucci, F. Bernardi, S. Ottani, and M. A. Robb, *J. Am. Chem. Soc.*, **116**, 2034 (1994).
- ¹⁸⁰ S. Sakai, *Chem. Phys. Lett.*, **319**, 687 (2000).

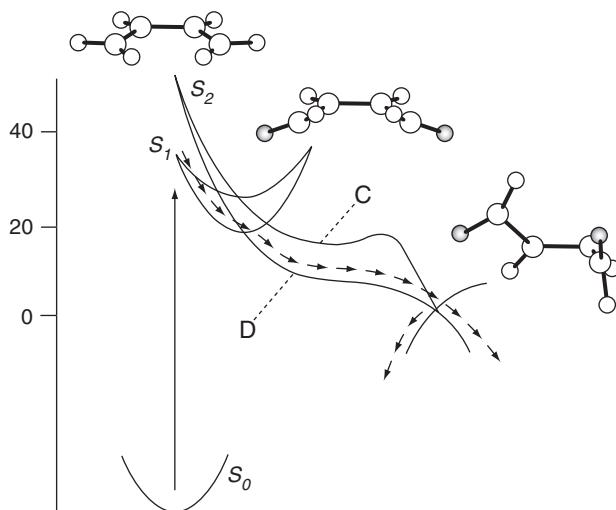
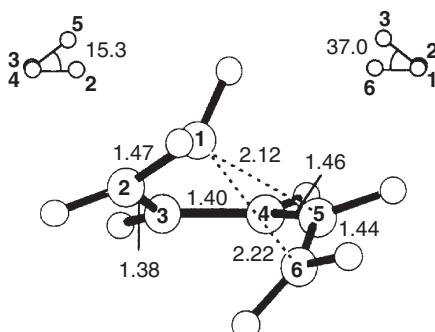


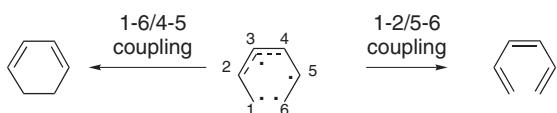
Fig. 12.30. Comparison of disrotatory (D) and conrotatory (C) minimum energy paths for photocyclization of 1,3-butadiene. The disfavored conrotatory motion encounters a barrier. Reproduced from *J. Photochem. Photobiol.*, **105**, 365 (1997), by permission of Elsevier.

encounters a small barrier. The reverse reaction, opening of cyclobutene to butadiene, has also been explored computationally, using CAS-SCF/double ζ calculations. The disrotatory pathway is found to be favored, although the interpretation is somewhat more complex than the simplest Woodward-Hoffmann formulation. Computational quantum dynamics calculations have been used to model the very early stages of the photoreaction of cyclobutene (<50 fs).¹⁸¹ The C=C bond stretches and the CH₂–CH₂ bond weakens as the CH₂ groups move toward sp^2 hybridization. The motion is in agreement with the predicted (Woodward-Hoffmann) disrotatory motion.¹⁸² It can be shown that a CI exists for the disrotatory but not the conrotatory mode.¹⁸³

The 1,3,5-hexatriene-1,3-cyclohexadiene system has also been studied by computation. A CI connecting the excited state to the ground state has been located. The CI can be described as a tetraradical.¹⁸² The structure is shown below.



- ¹⁸¹. M. Ben-Nun and T. J. Martinez, *J. Am. Chem. Soc.*, **122**, 6299 (2000).
¹⁸². M. Garavelli, F. Bernardi, M. Olivucci, T. Vreven, S. Klein, P. Celani, and M. A. Robb, *Faraday Discussions*, **110**, 51 (1998); P. Celani, S. Offani, M. Olivucci, F. Bernardi, and M. A. Robb, *J. Am. Chem. Soc.*, **116**, 10141 (1994).
¹⁸³. Y. Haas and S. Zilberg, *J. Photochem. Photobiol.*, **144**, 221 (2001).



The minimum energy reaction path after transit through the CI has also been investigated.¹⁸⁴ Two major reaction channels were identified that lead to the two products. These channels are sufficiently comparable in terms of their topological features that product formation can occur along both routes in approximately equal amounts. It would be expected that substituents that favored one or the other pathway would alter the relative yields of the two types of products. There is also a minor channel that can lead to formation of the bicyclo[3.1.0]hex-2-ene ring system. This situation is represented schematically in Figure 12.31.

Another kind of tetraradicaloid CI has been invoked and computationally characterized for photoisomerization of cyclooctatetraene.¹⁸⁵ Photoexcitation leads to return to reactant, double-bond shift, and formation of semibullvalene. The tetraradicaloid

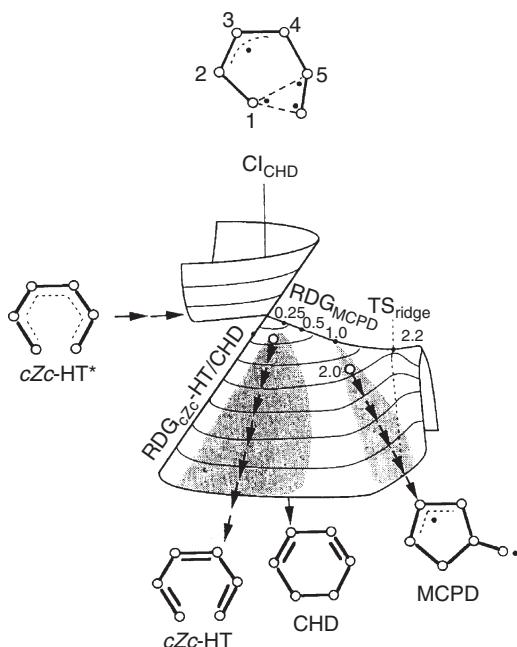
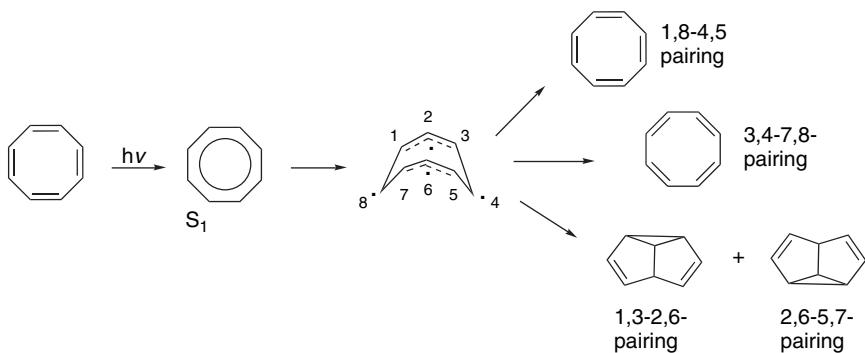


Fig. 12.31. Schematic representation of conical intersection showing partitioning between 1,3,5-hexatriene, 1,3-cyclohexadiene, and bicyclo[3.1.0]hex-2-ene products. Reproduced from *J. Phys. Chem. A*, **101**, 2023 (1997), by permission of the American Chemical Society.

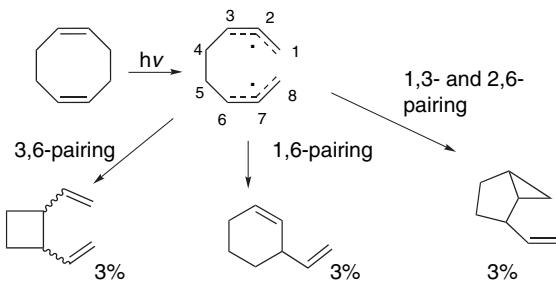
¹⁸⁴ M. Garavelli, P. Celani, M. Fato, M. J. Bearpark, B. R. Smith, M. Olivucci, and M. A. Robb, *J. Phys. Chem. A*, **101**, 2023 (1997).

¹⁸⁵ M. Garavelli, F. Bernardi, V. Molino, and M. Olivucci, *Angew. Chem. Int. Ed. Engl.*, **40**, 1466 (2001).

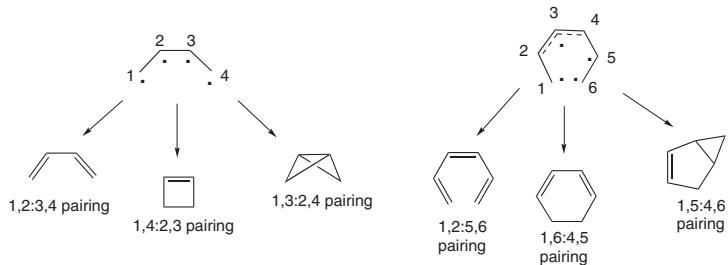
CI consist of two allyl fragments and two localized unpaired electrons. Alternate re-pairing schemes lead to the observed products.



Photolysis of both acyclic and cyclic 1,5-dienes leads to both 1,3-sigmatropic shifts and formation of allylcyclopropanes by 1,2-shift followed by cyclization.¹⁸⁶ The product mixture from 1,5-cyclooctadiene illustrates these reaction patterns.



The pattern that emerges from the experimental and computational studies of the conjugated dienes and trienes is the involvement of CIs having certain features in common. The singlet CI for the dienes appears to be a tetraradicaloid with the potential for several re-bonding schemes. In the absence of steric problems, it is structurally compact. The hexatriene-cyclohexadiene system also appears to involve a tetraradicaloid structure, one component of which is an allylic system. These structures can account for the major product types in both systems.



These results, as well as those from cyclooctatetraene and 1,5-cyclooctadiene, indicate that structures with isolated and allylic unpaired electrons play a key role in diene

¹⁸⁶ T. D. R. Manning and P. J. Kropf, *J. Am. Chem. Soc.*, **103**, 889 (1981).

and polyene photochemistry. For triplet excited states of dienes, the minimum energy corresponds to a twisted diradical that consists of an allylic radical and a localized radical. The pattern continues for higher polyenes with the excited states consisting of components similar to those recognized for simple alkenes and dienes.

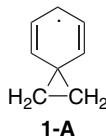
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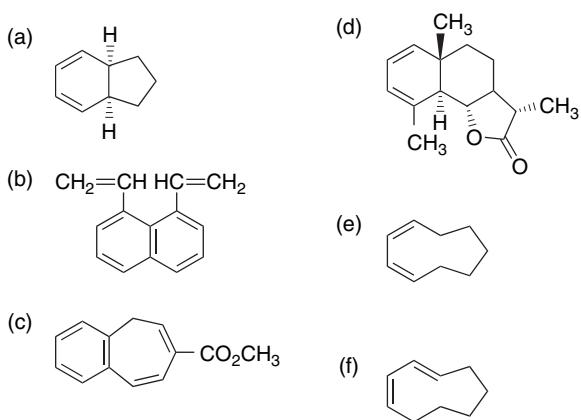
Problems

(References for these problems will be found on page 1168.)

- 12.1. The bridged radical **1-A** has been suggested as a possible intermediate in the photochemical decarbonylation of 3-phenylpropanal. Suggest an experiment to test this hypothesis.

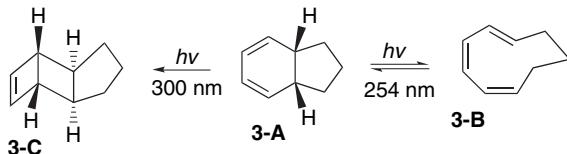


- 12.2. Predict the structure, including all aspects of the stereochemistry, based on orbital symmetry principles for the following photochemical electrocyclic and cycloaddition reactions.

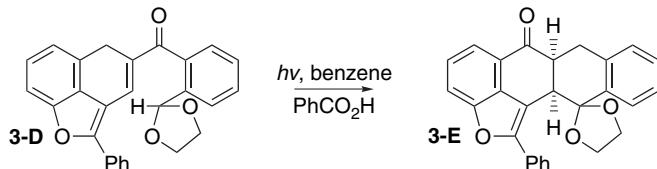


12.3. Suggest reasonable mechanisms for the following observations:

- The optically active allene, 2,3-pentadiene, is racemized under toluene-sensitized photolysis.
- Direct photolysis of diene **3-A** at 254 nm produces a photostationary state containing about 30% **3-A** and 70% **3-B**. When photolysis is carried out at 300 nm, photocyclization to **3-C** occurs and little **3-B** is present in the mixture.

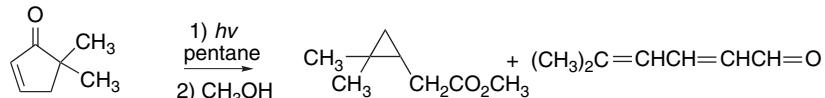


- Photocyclization of the acetal **3-D** to **3-E** is catalyzed by benzoic acid.

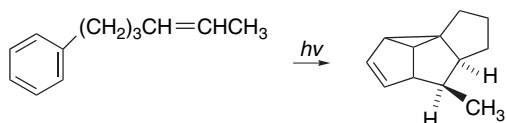


12.4. Provide a mechanistic rationalization for each of the following reactions:

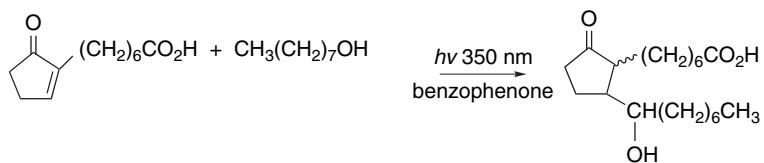
a.



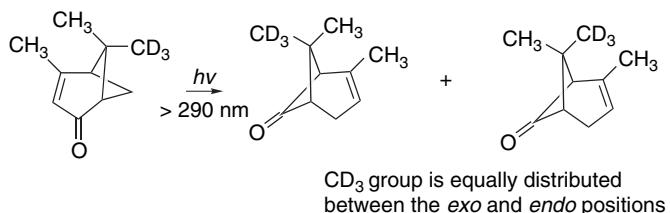
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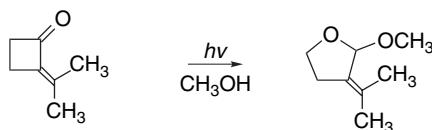
c.



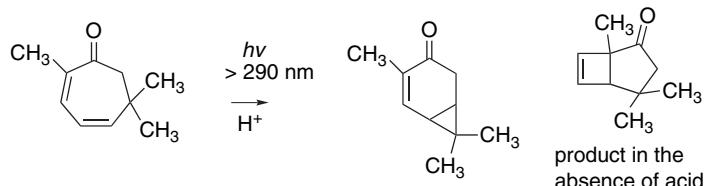
d.



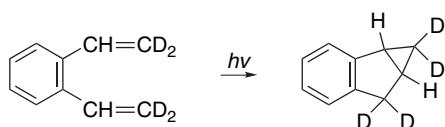
e.



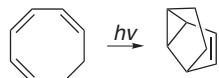
f.



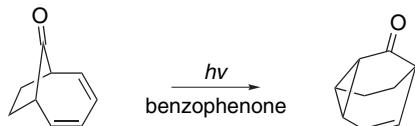
g.

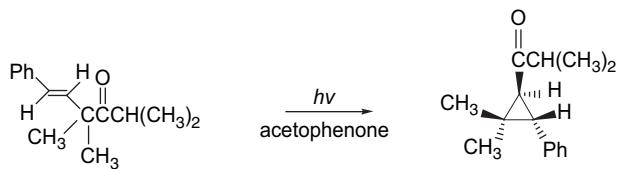


h.

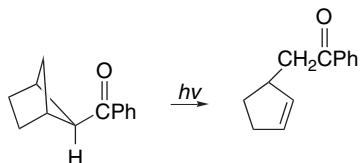


i.

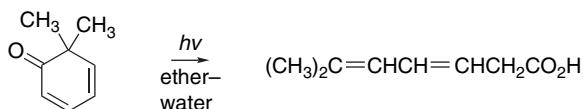




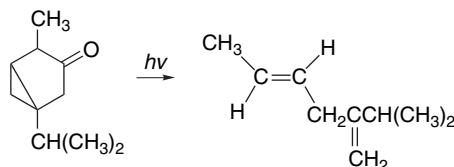
k.



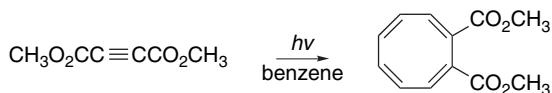
l.



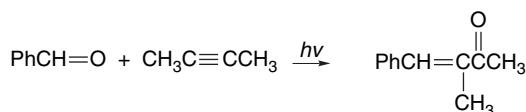
m.



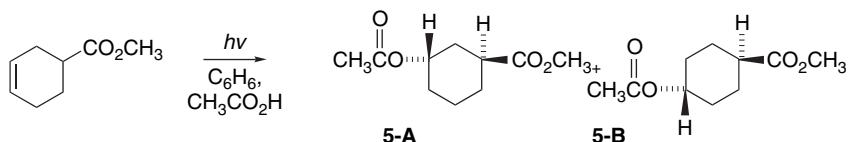
n.



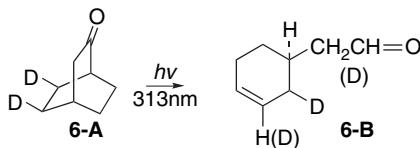
o.



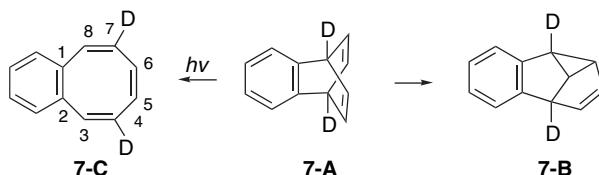
- 12.5. Benzene-sensitized photolysis of methyl 3-cyclohexene-1-carboxylate in acetic acid leads to addition of acetic to the double bond. Only the *trans* adducts are formed. What factor(s) might be responsible for this stereo-selectivity? Which of the two regioisomers do you expect to be the major product?



- 12.6. Photolysis of bicyclo[2.2.2]octan-2-one (**6-A**) gives **6-B** in good yield. When **6-A** is labeled as shown, the aldehyde group carries 48.3% of the deuterium. Write a mechanism to account for the overall transformation. Calculate the isotope effect for the hydrogen abstraction step. What mechanistic conclusion do you draw from the magnitude of the isotope effect?

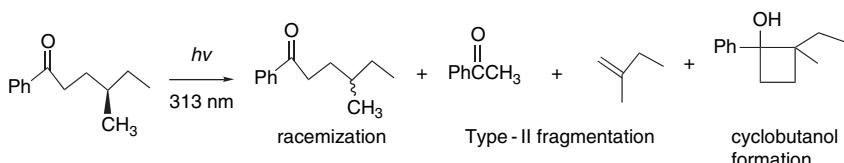


- 12.7. The photolysis of benzobarrelene **7-A** has been studied in considerable detail. Direct photolysis gives **7-C** (benzocyclooctatetraene), but when acetone is used as a photosensitizer, the di- π -methane rearrangement product **7-B** (benzosemibullvalene) is formed. A deuterium-labeling study gave the results shown. What mechanistic conclusions do you draw from these results? Is there a feasible mechanism that would have resulted in a different isotopic label distribution in **7-B**?



(A small amount of D is at C-3,8.)

- 12.8. Quantum yield data for three competing processes that occur on photolysis of *S*-methyl-1-phenyl-1-hexanone at 313 nm in benzene have been determined and are tabulated below. When the reaction is run in *t*-butanol, the racemization is entirely suppressed and the Type-II fragmentation is the major reaction. What information do these data provide about the mechanism operating under these conditions?

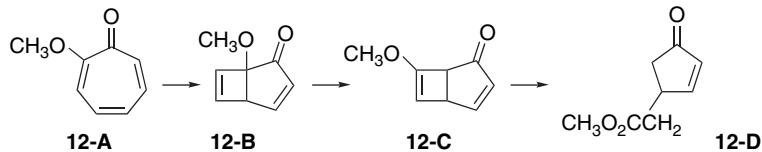


Process	Quantum yield	
	Benzene	<i>t</i> -Butanol
Type-II fragmentation	0.23	0.94
Cyclobutanol formation	0.03	0.05
Racemization	0.78	0.0

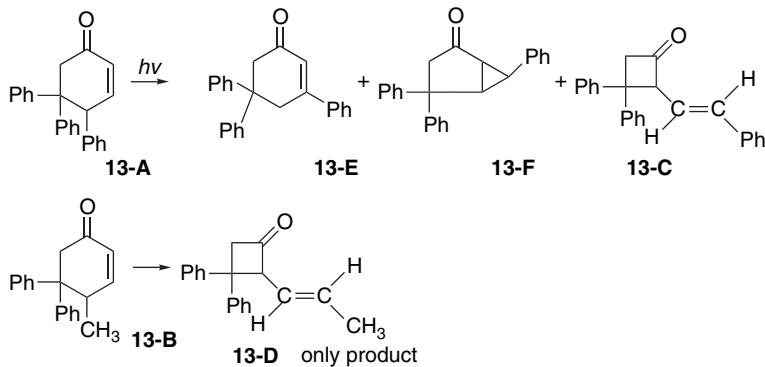
- 12.9. Show by means of an energy diagram the reason that the energy of light emitted from an excited electronic state by fluorescence or phosphorescence

is of lower energy than the exciting radiation. Would you expect the shift in energy to be more pronounced for fluorescence or phosphorescence? Explain?

- 12.10. *cis*-2-Propyl-4-*t*-butylcyclohexanone undergoes cleavage to 4-*t*-butylcyclohexanone on photolysis. The *trans* isomer does not undergo fragmentation directly, but is converted to the *cis* isomer, which then fragments. The *trans* \rightarrow *cis* isomerization is quenched by 1,3-pentadiene, but the photofragmentation is not. Offer an explanation of this pronounced stereochemical effect.
- 12.11. The quantum yield for formation of 3-methylcyclobutene from *E*-1,3-pentadiene by 254 nm radiation is ten times greater than for cyclization of the *Z*-isomer. 1,3-Dimethylcyclopropene is also formed but the difference in Φ for this reactions is only a factor of two. Offer an explanation for these differences in terms of energy surfaces that are involved.
- 12.12. The irradiation of 2-methoxytropone (**12-A**) leads to methyl 4-oxo-2-cyclopentenylacetate (**12-D**). The course of the reaction can be followed by gas chromatography and two intermediates are observed, which have structures **12-B** and **12-C**. Indicate a mechanism for the three successive reactions. The first two are photochemical, whereas the third is probably an acid-catalyzed reaction that does not require light.

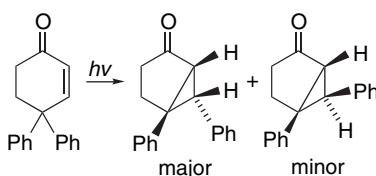


- 12.13. When an aryl substituent is placed at C(5) of a 4-substituted cyclohexenone, a new product type involving formation of a cyclobutanone ring is formed.

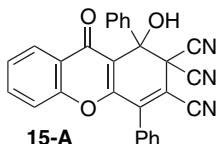


The reaction products are the same for both direct irradiation and acetophenone sensitization. When reactant **13-B** is used in enantiomerically pure form, the product **13-D** is nearly racemic (6% e.e.). Relate the formation of the cyclobutanone to the more normal products of 4-substituted cyclohexenones.

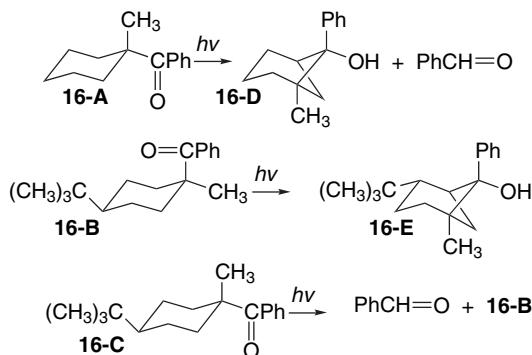
- 12.14. In the rearrangement of 4,4-diphenylcyclohex-2-enone to 5,6-diphenylbicyclo[3.1.0]hexan-2-one, there is a strong preference for formation of the *endo* phenyl stereoisomer. Offer an explanation for this stereoselectivity.



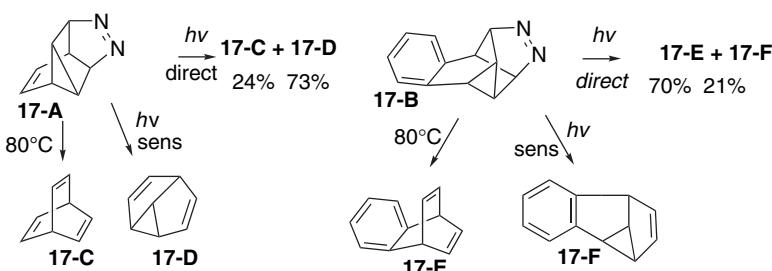
- 12.15. Compound **15-A** is photochromic; that is, it becomes colored on exposure to light. The process is reversible, giving back the starting material in the dark. Suggest a structure for the colored photoisomer.



- 12.16. The photolysis of **16-A**, **16-B**, and **16-C** has been studied. **16-A** gives both **16-D** and the cleavage product benzaldehyde. **16-B** gives only **16-E**. **16-C** gives **16-B** and benzaldehyde. Discuss how the presence of the *t*-butyl group and its stereochemistry can influence the reaction outcome.

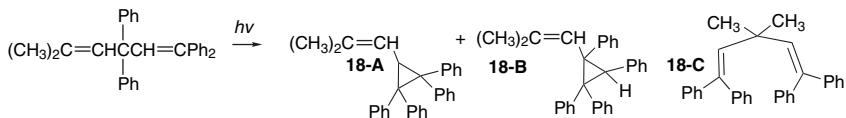


- 12.17. The azo compounds **17-A** and **17-B** were prepared and the thermal and photochemical behavior of these materials was investigated. The results are summarized in the Formulas below. It is also known that triplet photosensitization converts **17-C** to **17-D** and **17-E** to **17-F**, respectively. Discuss how these results relate to the mechanism of the di- π -methane rearrangement.

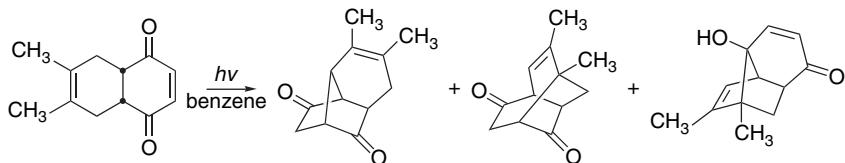


- 12.18. Direct irradiation of 1,1,3,3-tetraphenyl-5-methyl-1,4-hexadiene gives the products **18-A** and **18-B** shown below. When the reaction is carried out by

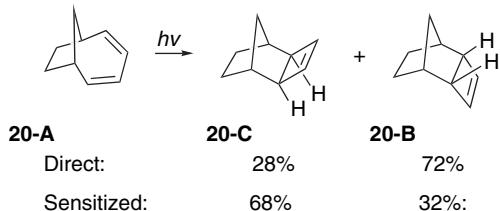
photosensitization, only **18-A** is formed. Suggest mechanisms for formation of **18-A** and **18-B**. A minor product **18-C** is formed only in the photosensitized reaction. What other products might have been expected? Can you explain the preference for the observed products?



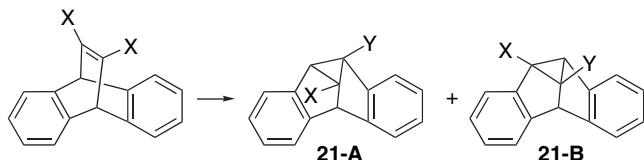
12.19. Suggest a mechanistic pathway for formation of each of the products formed on irradiation of the Diels-Alder adduct of 2,3-dimethylbutadiene and quinone.



12.20. The direct irradiation of **20-A** gives predominantly **20-B**, but the photosensitized reaction gives more **20-C**. Explain these observations.



12.21. 9,10-Ethanoanthracenes undergo the di- π -methane rearrangement. Analyze the substituent effects that are observed in this reaction.

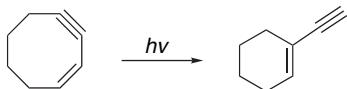


Substituent X	Substituent Y	% 21-A	% 21-B
H	CO ₂ CH ₃	0	100
H	CON(CH ₃) ₂	0	100
CON(CH ₃) ₂	CO ₂ CH ₃	3	97
CO ₂ CH ₃	CSOCH ₃	0	100
CH ₃	CO ₂ CH ₃	0	100
Ph	CO ₂ CH ₃	100	0

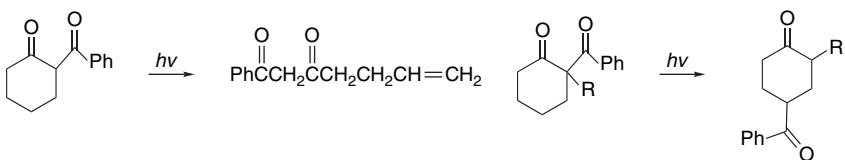
12.22. Formulate a mechanism for the following reaction.

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PROBLEMS



12.23. The photochemistry of 2-benzoylcyclohexanone and its 2-alkyl derivatives diverges. The unsubstituted compound undergoes ring cleavage, whereas the substituted compounds result in migration of the benzoyl substituent to the 4-position of the ring. Suggest mechanisms for both reactions and account for the effect of the alkyl substituent.



References for Problems

Chapter 1

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