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# STEREOCHEMISTRY OF CARBON COMPOUNDS

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## **STEREOCHEMISTRY OF CARBON COMPOUNDS**

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*To the Memory of*  
**LOUIS PASTEUR**



## PREFACE

The subject of stereochemistry is as old as organic chemistry itself. The discovery of optical rotation by Biot antedates Wöhler's famous urea synthesis, and the classical stereochemical research of Pasteur was contemporary with Kekulé's equally classical work on molecular structure. Despite the venerability of the subject, there has been a marked resurgence of interest in it since the end of World War II. The ascertainment of absolute configuration, the elucidation of the configuration of numerous important natural products, the stereoselective synthesis of many of these compounds, and the shaping of stereoregular polymers of distinctively useful physical properties are among the many examples of recent progress in the field. Conformational analysis has led to the systematic interpretation of much chemical knowledge as well as to the prediction of new facts. Last but not least, the years since 1940 have seen remarkable advances in the development and availability of physical instrumentation, with the result that such tools as ultraviolet, infrared, and nuclear magnetic resonance spectroscopy and, most recently, optical rotatory dispersion measurements are now making all-important contributions to the solution of stereochemical problems.

In view of this almost explosive development, it is dismaying that there has been no text in the field of stereochemistry for at least 10 years and that students seeking up-to-date knowledge are forced to proceed directly from the somewhat sketchy treatment of stereochemistry in advanced textbooks to the excellent, but necessarily specialized and unavoidably not comprehensive, information available in monographs and reviews. Although stereochemistry is used extensively in textbooks on reaction mechanism, its basic principles are generally taken for granted in such books.

Under the circumstances, the task of writing a new textbook in stereochemistry seemed timely. This book is designed to present the essentials of the subject to the beginning graduate student as well as to the advanced undergraduate who has had some prior acquaintance with both organic and physical chemistry. Perhaps the book may serve as a text in some of the more theoretically oriented courses in advanced organic chemistry, possibly in conjunction with a companion volume on reaction mechanism. In any case, this book should help the student to acquire the basic knowledge in the field of stereochemistry essential for his later progress. In addition, it may be of in-

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terest to those workers in the field who received their graduate training prior to 1950 and who wish to find a comprehensive treatment of modern stereochemistry under one cover. In order to make it possible for the student to follow this book regardless of his previous acquaintance with stereochemistry, the material has been developed from quite elementary concepts, especially in the early chapters. The reader who is already grounded in the subject will pass over these sections rapidly soon to encounter (it is hoped) more challenging topics.

This book is a text, not a treatise, and no pretense is made of complete coverage of the field (which would require a work of encyclopedic proportions). The choice of topics and the extent to which they are dealt with have necessarily been arbitrary and are in part a reflection of the author's personal interests. Advance apologies are tendered to any of my colleagues who find their own work slighted or their favored subjects discussed inadequately. In general, the highly selected literature documentation extends through late 1960. However, it has been possible to include a number of salient articles appearing in 1961. Pertinent monographs and reviews are listed at the end of each chapter.

Since the subjects of stereochemistry and reaction mechanisms are so intimately entwined, it needs to be stressed that this is not a text on organic reaction mechanisms—a field in which other up-to-date textbooks are available. However, since the dividing line between mechanisms and stereochemistry is not well marked, it had to be drawn arbitrarily. Thus, the stereochemical aspects of the fundamental organic processes (such as substitution, addition, and elimination) and of the principal organic intermediates (carbonium ions, radicals, carbanions, and carbenes) have been covered, but no effort has been made to deal with the stereochemistry of organic reactions at large. The area of steric effects in organic chemistry—in which there exists an excellent recent treatise—is also not covered as such in any detail.

A book of this magnitude cannot be produced without the help of many people and the availability of numerous review articles and monographs. Among the latter, I want to mention especially the series "Progress in Stereochemistry," one of whose editors, Professor W. Klyne, kindly made available to me the list of chapters of Volume 3 in advance of publication. These chapters have been included among the general references, even though, with one exception, *I had not seen them at the time of writing*.

I wish to take this opportunity to express my gratitude to numerous colleagues who provided helpful comments on smaller or larger portions of the manuscript. Professors Carl Niemann, San-ichiro Mizushima, J. Sicher, and Carl Djerassi made a number of detailed suggestions concerning Chapters 4, 6, 9, and 14, respectively. Professor Albert W. Burgstahler read and commented on Chapters 1 to 8, and Professors Jerome Berson and Kurt Mislow reviewed and critically commented on the entire work. I want to express my special appreciation to Professor Mislow, whose detailed and constructive criticism extended far beyond the call of duty of a reviewer, and who also helped with a number of references and supplied several manuscripts in advance of publication. My wife, Eva, and my niece, Kay Eliel, helped with

the compilation of the subject index. My wife and a number of my coworkers assisted me with the verification of references and the reading of galley proof. Mr. Thomas J. Brett, Jr. helped with the checking of the entire page proof.

Despite all this generous cooperation, I am solely and exclusively responsible for the contents of this book and for any and all of its errors and shortcomings.

The first part of this book was written while I was a National Science Foundation Senior Research Fellow, and thanks are due to the Foundation for its financial support and to the members of the Division of Chemistry and Chemical Engineering of the California Institute of Technology for their inspiration and hospitality during the fall semester of 1958.

*Ernest L. Eliel*



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## **STEREOCHEMISTRY OF CARBON COMPOUNDS**



# Chapter 1

## INTRODUCTION

### 1-1. Scope

Until a few years ago, stereochemistry was concerned almost exclusively with the subject of stereoisomerism. "Stereoisomers" are isomeric compounds of identical structure† but differing in the arrangement of the atoms in three-dimensional space. (The concept of spatial arrangement, or "configuration," will be dealt with in more detail in Chap. 5.) Today, the scope of stereochemistry extends considerably beyond the static description of molecular geometry and of the physical properties related to such geometry; stereochemistry is concerned also with the relationships in space between the different atoms and groups in a molecule during chemical reactions and the way in which chemical equilibria and rates of reaction are affected by those spatial relationships. While this aspect of stereochemistry borders on the study of reaction mechanism, we shall not deal here with reaction mechanisms as such. For a consideration of these, the reader is referred to other advanced texts.<sup>11-13</sup>

Despite the increasing importance of the dynamic aspects of stereochemistry, it is well to start the discussion by a consideration of static molecules. Since our knowledge of molecular geometry is closely linked to the development of structural organic theory, on the one hand, and to an understanding of the rotation of the plane of polarized light by organic molecules on the other, it is appropriate to consider briefly the history of these ideas.

### 1-2. History

Ordinary light may be considered as an electromagnetic vibration of a range of different wavelengths vibrating in many different planes at right angles to the direction of propagation of the light ray.‡ Monochromatic light, such as that emitted by a sodium lamp, is of discrete wavelength but

*Note:* All references above 9 are listed in General References at the end of the chapter.

† The structure of a molecule is completely defined by a statement of the number and kind of atoms in the molecule and of the linkages between them. The subject of structural isomerism is dealt with elegantly and thoroughly by Wheland<sup>10</sup> (chap. 2).

‡ The wave nature of light was recognized by Hooke in 1665 and by Huygens in 1678. The electromagnetic nature of the vibration was established much later (by Maxwell in 1873) but is not essential to the present argument.

still vibrates in an infinite number of planes. In 1808, the French physicist Malus discovered<sup>1</sup> that light reflected from opaque or transparent bodies at a certain angle is endowed with special properties which may be ascribed to the fact that the vibrations are all in one plane, called the "plane of polarization." Light of this kind is said to be "polarized." Malus also found that the two rays produced by the phenomenon of double refraction in Iceland spar (crystalline calcium carbonate) are polarized at planes perpendicular to each other. In fact, one of the most convenient ways of producing polarized light is to pass ordinary light through a prism constructed by cementing together, by means of Canada balsam, two pieces of Iceland spar cut at specified angles. Such a device, called a "Nicol prism" after its discoverer (Nicol, 1828), allows only one of the polarized rays to pass through (the other is reflected). The polarization of the ray of monochromatic light transmitted through a Nicol prism is readily detected by viewing it through a second Nicol prism: If the plane of polarization of the second prism is parallel to that of the first, it transmits the polarized ray with undiminished intensity, but if the plane of polarization of the second Nicol is perpendicular to that of the first (i.e., the Nicol prisms are "crossed"), the ray polarized by the first prism fails to pass through the second.

In 1813 the French physicist Biot, following an earlier observation<sup>2</sup> by his colleague Arago, discovered that a quartz plate cut at right angles to its crystal axis rotates the plane of a ray of polarized light through an angle proportional to the thickness of the plate. Some quartz crystals turn the plane of polarization to the right, others to the left. Two years later,<sup>3</sup> Biot laid the foundation of organic stereochemistry when he found that a similar rotation of the plane of polarized light is produced by certain organic liquids, such as turpentine, as well as solutions of certain organic compounds, such as sugar, camphor, tartaric acid. Biot recognized a difference between the rotation produced by quartz and that produced by organic materials: The former is a property of the crystal and depends on the direction in which the crystal is viewed, whereas the latter is a property of the individual molecules and may be observed even in solution or in the liquid or gaseous state where the molecules are arranged in random fashion.

In 1801, the French mineralogist Hauy had noticed that certain quartz crystals exhibit the phenomenon of hemihedrism. For the present purpose, hemihedrism may be defined as the absence of a plane, center, or alternating axis of symmetry (see Chap. 2) in the crystal. In crystals presenting hemihedrism, there are faces that make such crystals non-superimposable with their mirror images (Fig. 1-1). In 1821, Sir John Herschel, British astronomer, observed<sup>4</sup> that all quartz crystals having the odd faces inclined in one direction rotate the plane of polarized light in one and the same direction, whereas the mirror-image crystals, whose odd faces are inclined in the opposite direction, also rotate the plane of polarized light but in the opposite direction.

It was, however, left to the genius of Louis Pasteur to extend this correla-

<sup>1</sup> E. L. Malus, *Mém. soc. d'Arcueil*, **2**, 143 (1809).

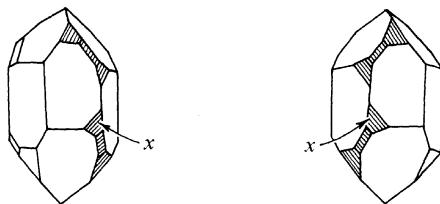
<sup>2</sup> D. F. Arago, *Mém. classe sciences math. phys. de l'Institut Imp. France*, **12**, 115 (1811).

<sup>3</sup> J. B. Biot, *Bull. soc. philomath. Paris*, 190 (1815); 125 (1816); *Mém. acad. roy. sci. inst. France*, **2**, 41, 114 (1817).

<sup>4</sup> J. F. W. Herschel, *Trans. Cambridge Phil. Soc.*, **1**, 43 (1821).

tion from the realm of crystals to the realm of molecules. In 1860, following some extensive observations (1848–1853) on optically active compounds which will be presented elsewhere in this book, Pasteur realized that optical activity is caused by an asymmetric grouping of the atoms in the optically active molecule and that molecules of the same substance rotating the plane of polarized light to the right and to the left are related to each other as is an object to its mirror image.<sup>5</sup>

About the same time, in 1858, the German chemist Kekulé had laid the foundation of modern structural organic chemistry when he recognized that carbon has a valence of 4 in all organic compounds and that complex structures can be built up by linking together carbon (and other polyvalent atoms) in chains.<sup>6</sup> It was not long until the concept of the quadrivalence of carbon and the suggestion that optical activity is caused by molecular asymmetry were combined and a new idea emerged, namely, that the four valences of carbon are directed in three-dimensional space toward the corners of a tetrahedron. As happens so often with scientific ideas for which the time is



**Fig. 1-1.** Hemihedral quartz crystals. X: asymmetric face. (From L. F. Fieser and M. Fieser, "Organic Chemistry," 3d ed., Reinhold Publishing Corporation, New York, 1956. By permission of the publishers.)

ripe, the concept of the tetrahedral carbon originated simultaneously (in 1874) in the minds of two chemists, van't Hoff,<sup>7</sup> who was then working for his Ph.D. degree† in Utrecht (Holland), and Le Bel,<sup>8</sup> working in Paris.‡ A com-

† However, for his Ph.D. thesis van't Hoff presented a rather routine investigation on cyanoacetic and malonic acids. No doubt he feared that his revolutionary work on the relation of optical activity to chemical constitution might not be received well by the examiners. That this fear may have been justified is evidenced by the acrid reception which van't Hoff's theory received at the hands of at least one of the older German chemists, Hermann Kolbe. (For a translation of Kolbe's rather devastating critique, see Ref. 10, p. 197.) Strange as it may seem, Kolbe's criticism may actually have furthered van't Hoff's ideas in that it brought the work of the young investigator to the attention of his older colleagues!

‡ Le Bel and van't Hoff had been working side by side in Wurtz's laboratory in Paris during the academic year preceding publication of their pioneering work. Nevertheless, it appears that they developed the concept of tetrahedral carbon independently and did not even discuss it with each other; see the van't Hoff Memorial Lecture by J. Walker, *J. Chem. Soc.*, 103, 1127 (1913).

<sup>5</sup> L. Pasteur, two lectures delivered before the Société Chimique de Paris, Jan. 20 and Feb. 3, 1860; cf. Ref. 14.

<sup>6</sup> A. Kekulé, *Ann.*, 106, 154 (1858).

<sup>7</sup> J. H. van't Hoff, *Bull. soc. chim. France*, [2]23, 295 (1875); cf. Ref. 14. (The original version appeared in Dutch in 1874.)

<sup>8</sup> J. A. Le Bel, *Bull. soc. chim. France*, [2]22, 337 (1874); cf. Ref. 14.

mon (although, as will be seen later, not a necessary) cause for the existence of optical activity is non-identity of the four atoms or groups around a single carbon atom in the active molecule. In such a case, two different arrangements may exist, as shown in Fig. 1-2, which are non-superimposable but

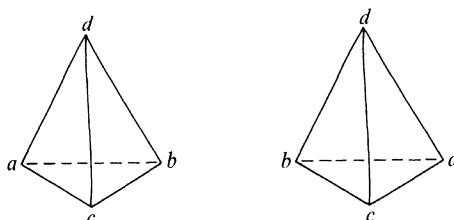


Fig. 1-2. Representation of isomeric arrangements of Cabcd.

which are mirror images of each other. According to van't Hoff and Le Bel, one of these arrangements corresponds to the isomer that rotates the plane of polarized light in one direction, whereas the isomer of opposite rotation corresponds to the other arrangement. When two or more of the atoms or groups attached to the tetrahedra in Fig. 1-2 become identical, the two forms become superimposable and are no longer distinct. Molecules of this type do not rotate the plane of polarized light.

The idea that the valencies of carbon are directed toward the corners of a tetrahedron, originally suggested to explain optical activity, is now firmly supported both by more direct physical measurements (e.g., electron diffraction) and by theoretical quantum-mechanical considerations.

### 1-3. Optical and Geometrical Isomerism

We thus recognize the existence and cause of one type of stereoisomerism (i.e., isomerism in space) which manifests itself by the rotation that the isomers impart to the plane of polarized light and is caused in many (though not all) instances by the attachment of four different atoms or groups to at least one of the carbon atoms in the molecules, as shown in Fig. 1-2. This type of isomerism, because of its manner of manifestation, is called "optical isomerism." There is another type of spatial isomerism, also recognized by van't Hoff and Le Bel but put on a firm experimental basis mainly through later work by the German chemist Wislicenus,<sup>9</sup> namely, the isomerism caused by different arrangements of groups around ethylenic double bonds (Fig. 1-3).

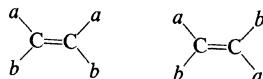


Fig. 1-3. Geometrical isomerism in substituted ethylenes.

<sup>9</sup> J. Wislicenus, *Abhandl. sächs. Ges. Wiss.*, **14**, I (1887); cf. Ref. 14 and *Chem. Zentr.*, **58**, 1005 (1887).

A similar type of isomerism is found in ring compounds, the ring taking the place of the rigid double bond (Fig. 1-4). This kind of isomerism has been called "geometric (or geometrical) isomerism."

Whereas the type of geometrical isomerism occurring in ethylenes is not normally associated with optical activity,† since the plane of the double bond

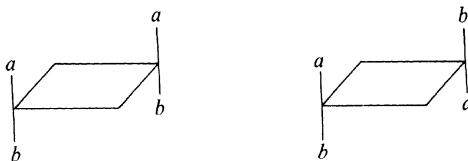


Fig. 1-4. Geometrical isomerism in ring compounds.

(plane of the paper) is also a plane of symmetry, the type of geometrical isomerism observed in cyclic compounds is often associated with optical activity. This is seen by a comparison of *cis*- and *trans*-crotonic acid (Fig. 1-5) on one hand and *cis*- and *trans*-2-methylcyclopropanecarboxylic acid (Fig. 1-5) on the other. The crotonic acids are geometrical isomers devoid of optical activity. The 2-methylcyclopropanecarboxylic acids are also geometrical isomers, but in addition they have non-superimposable mirror images, and therefore both the *cis* and the *trans* compounds exist as a pair of isomers that rotate the plane of polarized light to an equal extent in opposite directions.

It is evident, then, that the division of stereoisomerism into optical and geometrical isomerism is not a clear-cut one and that the two types of isomerism do, in fact, merge in certain cases. Nevertheless, for the purpose of organization, we shall, in this book, deal first with optical isomerism, then with the dual type of isomerism found in ring compounds, and lastly with purely geometrical isomerism.

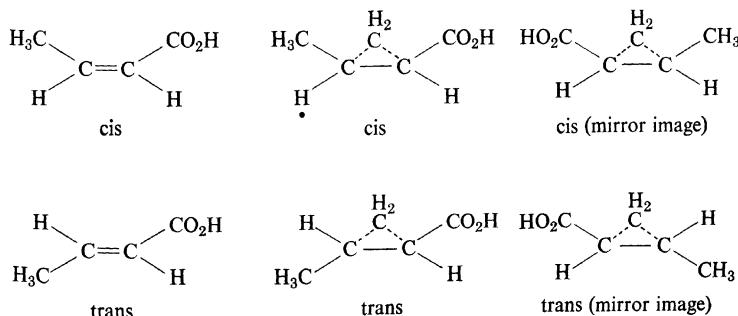


Fig. 1-5. Crotonic acids and 2-methylcyclopropanecarboxylic acids.

† Unless there is some other site in the molecule giving rise to optical isomerism as well, e.g., in  $\text{CHCl}=\text{CH}-\overset{*}{\text{CH}}(\text{CH}_3)\text{C}_2\text{H}_5$ , where there is the possibility of geometrical isomerism about the double bond and of optical isomerism involving the starred carbon.

**General References**

- <sup>10</sup> G. W. Wheland, "Advanced Organic Chemistry," 3d ed., John Wiley & Sons, Inc., New York, 1960, chaps. 6-8.
- <sup>11</sup> J. Hine, "Physical Organic Chemistry," 2d ed., McGraw-Hill Book Company, Inc., New York, 1962.
- <sup>12</sup> E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, Inc., New York, 1959.
- <sup>13</sup> C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1953.
- <sup>14</sup> G. M. Richardson, ed., "The Foundations of Stereochemistry," American Book Company, New York, 1901.
- <sup>15</sup> L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corporation, New York, 1961, chap. 3.

## Chapter 2

### OPTICAL ISOMERISM

#### 2-1. Polarimetry

Optical isomerism manifests itself by the rotation that certain molecules impart to the plane of polarized light when in the gaseous, liquid, or molten state or in solution.<sup>†</sup> This rotation is observed and measured by a rather simple instrument, known as a polarimeter. This is not the place to deal in any detail with the experimental aspects of polarimetry.<sup>4</sup> Suffice it to say that polarimetric readings are obtained by matching light intensities in the field of the instrument; if this is done visually using a sodium lamp ( $\lambda = 589 \text{ m}\mu$ ) as a light source, observations are good to about  $\pm 0.005^\circ$ . Attachments are available to permit photoelectric matching of the polarimeter; this speeds up the procedure and also makes possible accurate determinations of optical rotation at wavelengths longer and shorter than that of the sodium D line where the human eye becomes less sensitive. When photoelectric recording devices are combined with monochromators attached to a polychromatic light source, a continuous reading of optical rotation over a wide range of wavelengths becomes possible. This technique will be discussed in Chap. 14.

The observed angle of rotation of an optically active liquid, gas, or solution is denoted by the symbol  $\alpha$ . In the use of a polarimeter, it is important to realize that no immediate distinction can be made between rotations of  $\alpha \pm 180n^\circ$  ( $n$  any integer), for if the plane of polarization is rotated in the field by  $180^\circ$ , the new plane will appear to coincide with the old one. Thus, for example, no distinction would appear between rotations of  $+50^\circ$ ,  $+230^\circ$ ,  $+410^\circ$ , or  $-130^\circ$ . In order to make the distinction, it is necessary to measure the rotation at at least one other concentration. Since optical rotation is proportional to concentration (see below), if solutions of the above rotations were diluted to one-tenth of their original concentrations, their rotations would become  $+5^\circ$ ,  $+23^\circ$ ,  $+41^\circ$ , and  $-13^\circ$ , values which are all clearly distinct. Readings taken at two different concentrations almost always determine  $\alpha$  unequivocally. For a pure liquid, the required dilution may be effected with racemic material.

*Note:* All references above 2 are listed in General References at the end of the chapter.

<sup>†</sup>As already mentioned in Chap. 1, certain solids, such as quartz, may rotate the plane of polarized light as a result of their peculiar crystal structure. This type of rotation, which is unrelated to molecular properties, will not be considered further in this book.

Factors that affect the magnitude of optical rotation, in addition to the nature of the sample, are sample thickness (i.e., cell length), sample concentration (or density, in the case of a pure liquid), solvent, temperature, and wavelength. The relation of  $\alpha$  to cell length ( $l$ ) is linear and that to concentration ( $c$ ) is approximately linear, so that  $\alpha = [\alpha] \cdot l \cdot c$ , where  $[\alpha]$  is a proportionality constant depending on the nature of the sample, temperature, solvent, and wavelength of light. When  $l$  is measured in decimeters and  $c$  in grams per milliliter,  $[\alpha]$  is called "specific rotation":

$$[\alpha] = \frac{\alpha}{l \text{ (dm.) } c \text{ (g./ml.)}}$$

The dependence on wavelength and temperature is usually indicated by subscripts and superscripts, respectively; thus  $[\alpha]_D^{25}$  means the specific rotation of a substance at 25°C. measured at the wavelength of the sodium D line.<sup>†</sup> Solvent dependence, as well as a minor dependence of  $[\alpha]$  on concentration (which is not entirely taken into account by the concentration term in the formula), is denoted by information in parentheses appended to the value of the specific rotation; thus  $[\alpha]_{546}^{20} - 76.3 \pm 0.3^\circ$  ( $c = 5.77$  g./100 ml., ethanol) denotes a specific rotation measured with light of wavelength 546 m $\mu$  at 20° in absolute ethanol at a concentration of 5.77 g./100 ml.<sup>‡</sup> When the rotation of a pure liquid is cited, no concentration term is, of course, called for, since the density is constant at the given temperature; the word "neat" is often used in the parentheses to specify that the measurement refers to a pure liquid. Thus  $[\alpha]_D^{25} + 40^\circ$  (neat) refers to the specific rotation of a pure liquid measured with sodium D light at 25°C. If the density of this particular liquid is 1.10 at 25°, an alternative way of reporting this rotation would be by the observed rotation:  $\alpha_D^{25} + 44^\circ$  (neat,  $l = 1$  dm.). Note that, since observed rotation is dependent on cell length, the cell length must now be stated also.

The relation between specific rotation and structure will be discussed at some length in Chap. 14. Suffice it to say at this point that some of the changes of specific rotation associated with temperature, solvent, and concentration changes are related to changes in intermolecular hydrogen bonding and/or the degree of association and dissociation. For example, a sample of atrolactic acid, C<sub>6</sub>H<sub>5</sub>C(CH<sub>3</sub>)OHCO<sub>2</sub>H, which is dextrorotatory (i.e., rotates the plane of polarized light to the right) in benzene is levorotatory (i.e., rotates to the left) in ether.<sup>1</sup> Presumably in benzene there are strong intermolecular association forces (which would be expected to vary with concentration as well as temperature) whereas in ether there may be strong hydrogen bonding between the acidic hydrogen of the acid and the ether oxygen of the solvent.

Since optical rotatory power is a property of molecules, if two substances

<sup>†</sup> Because of the temperature dependence of both  $c$  and  $\alpha$ , most polarimeter cells are constructed so that they can be readily thermostated.

<sup>‡</sup> The concentration of solutions in polarimetry is usually expressed in grams per 100 milliliters even though the formula as given above requires it to be expressed in grams per milliliter. Often the formula above is reserved for pure liquids and a formula  $[\alpha] = 100\alpha/l \cdot c'$  is employed for solutions,  $c'$  now being expressed in grams per 100 milliliters.

<sup>1</sup> E. Eliel, unpublished observation.

have unequal molecular weights but are alike with respect to the power of rotating the plane of polarized light, the substance of smaller molecular weight has the larger specific rotation, simply because it has more molecules per unit weight. (Specific rotation, it may be recalled, is the rotation produced by 1 g. of material in 1 ml. of liquid in a 1-dm. tube.) In order to compensate for the effect of differing molecular weights (which, from the theoretical point of view, is quite unimportant) one defines a new term "molecular rotation" obtained by multiplying specific rotation by molecular weight (thus compensating for the above-indicated disadvantage of larger molecules) and then dividing by 100. (The division by 100 is included arbitrarily in the definition of molecular rotation in order to keep its numerical values manageable small.) Molecular rotation is expressed by the symbols  $[M]$  or  $[\phi]$ . Thus

$$[M] = [\phi] = \frac{[\alpha] \cdot \text{mol. wt.}}{100} = \frac{\alpha}{l \text{ (dm.) } c \text{ (moles/100 ml.)}}$$

## 2-2. Molecular Dissymmetry

Van't Hoff and Le Bel related the phenomenon of optical rotation to the presence of asymmetrically substituted carbon atoms (henceforth called, for short, "asymmetric atoms") in the molecule.<sup>†</sup> They realized, however, that there could exist optically active compounds having no asymmetric atoms (cf. Chaps. 6, 7, and 11) and that in some instances compounds having two or more asymmetric carbon atoms cannot be obtained optically active (Sec. 3-3). Thus it is desirable to go back to the earlier idea of Pasteur, namely, that optical activity is a consequence of *molecular dissymmetry*. In fact, the necessary and sufficient condition for a molecule to show optical activity is that such a molecule not be superimposable with its mirror image.<sup>‡</sup> A molecule superimposable with its mirror image cannot be optically active, whereas any molecule not superimposable with its mirror image (allowing for internal rotation) necessarily shows optical activity.<sup>¶</sup>

<sup>†</sup> Other kinds of atoms, such as silicon, nitrogen, phosphorus, and sulfur, may give rise to asymmetry. For example, quaternary ammonium salts of the type  $\text{RR}'\text{R}''\text{R}'''\text{N}^+\text{X}^-$  and analogous phosphonium salts, sulfoxides,  $\text{RR}'\text{SO}$ , and trialkylsilanes,  $\text{RR}'\text{R}''\text{SiH}$ , have been obtained optically active. Compounds of this type will not be treated explicitly in this book; for further information on some of them the reader is referred to pp. 400-443 in Ref. 5. The stereochemistry of inorganic coordination compounds has been summarized by F. Basolo, B. P. Block, and Th. D. O'Brien in chaps. 8-10 of J. C. Bailar, ed., "Chemistry of the Coordination Compounds," Reinhold Publishing Corporation, New York, 1956; by R. S. Nyholm in W. Klyne, ed., "Progress in Stereochemistry," vol. 1, Academic Press, Inc., New York, 1954, chap. 9; and by R. J. Gillespie and R. S. Nyholm in W. Klyne and P. B. D. de la Mare, eds., *ibid.*, vol. 2, 1958, chap. 8.

<sup>‡</sup> To make the condition sufficient, it may be necessary in some cases to allow the molecule to undergo internal rotation about single bonds before or after the imaginary reflection; cf. Ref. 2 and the discussion at the end of this section.

<sup>¶</sup> Some caution is required in translating this statement from the molecular realm to the macroscopic realm of the observable. A macroscopic assembly of large numbers of molecules is not necessarily optically active, even though each one of the molecules is. For it may happen that, in such an assembly, there are approximately equal numbers of molecules rotating the plane of polarized light in one direction and in the other, and the result (if the rotations are of equal magnitude) is that no net over-all rotation is observed. Such an assembly is known as a "racemic modification." This matter is of paramount importance, inasmuch as optical rotation is always observed in an assembly of large numbers of molecules, never in an individual molecule or a few molecules. Chapter 4 deals extensively with this question.

According to group theory, the symmetry properties of a given molecule tell us whether or not the molecule is superimposable with its mirror image. A molecule that has a plane of symmetry, a center of symmetry, or an alternating axis of symmetry† is superimposable with its mirror image, but a molecule that has no element of symmetry, or one that has only a simple axis

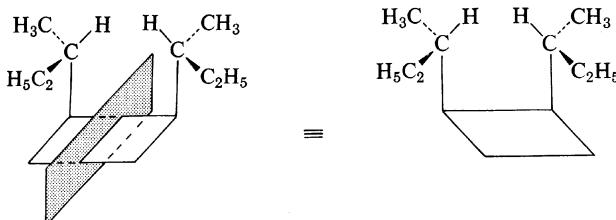


Fig. 2-1. Molecule with plane of symmetry.

of symmetry (and none of the above-mentioned three elements), is not superimposable with its mirror image. It follows that there are usually two ways of deciding whether a given molecule is optically active. One is to construct a model of the molecule and then to build a mirror image of this model; if the model and its image are superimposable, the molecule is not optically active, otherwise it is. Or one may look for symmetry elements in the molecule; if it has a plane (cf. Fig. 2-1), center (cf. Fig. 2-2), or alternating axis (cf. Fig. 2-3) of symmetry, it is not active, but if it has none of these elements, it is active, even though it may have a simple axis of symmetry (Fig. 2-4).‡

The examples shown in Figs. 2-1 to 2-4 are deliberately chosen from molecules having two recurrent structural elements, namely, a cyclobutane ring with two or four *sec*-butyl,  $\text{CH}_3-\text{CH}-\text{C}_2\text{H}_5$ , substituents. Taken individually, the *sec*-butyl substituent has an asymmetric carbon. Nevertheless, of the four structures shown in Figs. 2-1 to 2-4, only one (Fig. 2-4) shows optical

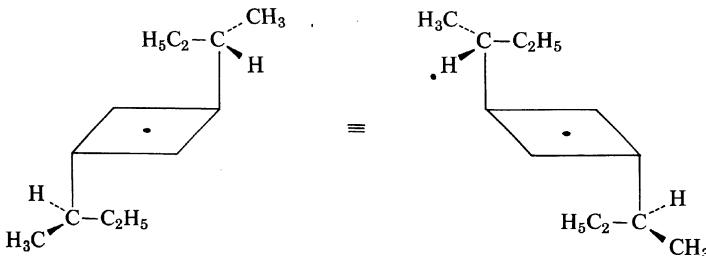


Fig. 2-2. Molecule with center of symmetry.

† The alternating axis of symmetry is actually sufficient inasmuch as a plane of symmetry is equivalent to a onefold alternating axis and a center of symmetry is equivalent to a twofold alternating axis.

‡ An exception is pointed out at the end of this section.

activity. The molecule shown on the left in Fig. 2-1 has a plane of symmetry† bisecting the ring in the manner shown. Its mirror image (Fig. 2-1, right) is superimposable with the original molecule by a simple translation to the left. The molecule shown in Fig. 2-2 has a center or point of symmetry‡ at the center of the ring. Its mirror image (Fig. 2-2, right) may be superimposed with

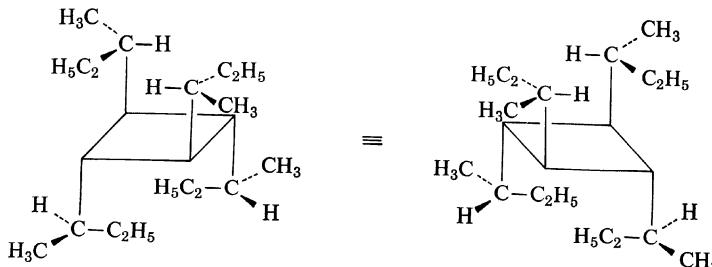


Fig. 2-3. Molecule with alternating axis of symmetry (fourfold).

the original molecule by turning the ring upside down. The molecule in Fig. 2-3 has a fourfold alternating axis of symmetry,¶ passing through the center of the ring and at right angles to it. Its mirror image (Fig. 2-3, right) is superimposable with the original molecule by turning the ring upside down and rotating it 90° around the axis. Finally, the molecule in Fig. 2-4 has a twofold (simple) axis of symmetry.§ It is not superimposable with its mirror image (Fig. 2-4, right), and both the molecules shown in Fig. 2-4 are optically active.

Molecules of the type shown in Fig. 2-4 which are non-superimposable mirror images are called "enantiomorphs" or "enantiomers" (also known as

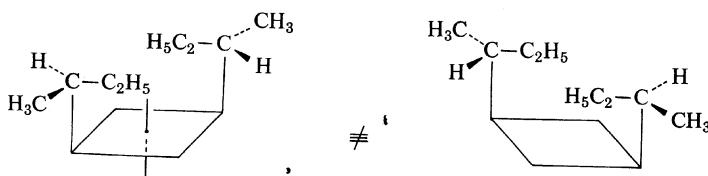


Fig. 2-4. Molecule with simple axis of symmetry (twofold) (optically active).

† A plane of symmetry is a plane such that, if a line from any element on one side of the plane is drawn perpendicular to the plane and the line extended to an equal distance on the other side of the plane, an identical element will be found at the end of the line. Putting it more simply, one half of the molecule is the mirror image of the other half, the plane of symmetry being the plane of the (imaginary) mirror.

‡ A center of symmetry is a point such that, if a line is drawn from any element to this point and then extended an equal distance beyond the point, another identical element will be found at the end of the line.

¶ An  $n$ -fold alternating axis of symmetry is an axis such that, when the structure possessing this axis is rotated around the axis by an angle of  $2\pi/n$  and then reflected across a plane at right angles to the axis, another, identical structure results.

§ An  $n$ -fold axis of symmetry is an axis such that, when a structure possessing this axis is rotated by an angle of  $2\pi/n$  around the axis, another, identical structure results.

"optical antipodes" or "antimers"); they rotate the plane of polarized light in opposite directions but have the same absolute value of the specific rotation.

The reader should construct models of the molecules shown in Figs. 2-1 to 2-4 and convince himself both of the presence of the indicated elements of symmetry and of the superimposability (or non-superimposability) of the appropriate models with their respective mirror images.

Wheland<sup>16</sup> has drawn attention to the fact that, since a molecule may be optically active even though it has a simple axis of symmetry, it is not correct to say that optically active molecules lack the elements of symmetry. Therefore, the terms "optically active" and "asymmetric" as applied to molecules should not properly be used in the same context. A new term is called for to denote the absence of an alternating (but not necessarily of a simple) axis of symmetry; this term is "dissymmetric." A molecule that is dissymmetric lacks an alternating axis of symmetry and is usually optically active (see, however, below). A dissymmetric (and therefore usually optically active) molecule may or may not be asymmetric (i.e., lack a simple axis of symmetry). A symmetric molecule is one which possesses an alternating axis of symmetry and is therefore optically inactive. Table 2-1 summarizes these relationships.

Table 2-1  
Symmetry Designations

Term	Alternating axis	Simple axis	Optical activity
Symmetric	Present <sup>a</sup>	May or may not be present	Inactive
Dissymmetric	Absent	May or may not be present	Usually active
Asymmetric	Absent	Absent	Usually active

<sup>a</sup> Onefold alternating axis corresponds to plane of symmetry; twofold alternating axis corresponds to center of symmetry.

Although it is generally true that dissymmetric molecules are optically active, a molecule, (*dextro*)-menthyl (*levo*)-menthyl 2,6,2',6'-tetranitro-4,4'-diphenate (Fig. 2-5), has been synthesized<sup>2a</sup> which is inactive though devoid of any symmetry element. [The molecule cannot exist in the form in which the two phenyl rings are coplanar because of the steric interference of the bulky nitro groups in this form (cf. Chap. 6). This excluded form is the only arrangement of the molecule which possesses a plane—or other element—of symmetry.] The lack of activity of this molecule is attributed<sup>2b</sup> to the fact that the molecule and its mirror image, though not actually superimposable, can be readily made superimposable by rotation around the bonds linking the carboxylate groups to the rings. Other dissymmetric but inactive molecules of this type might, in principle, be found.

<sup>2(a)</sup> K. Mislow and R. Bolstad, *J. Am. Chem. Soc.*, **77**, 6712 (1955). <sup>(b)</sup> K. Mislow, *Science*, **120**, 232 (1954); *Trans. N.Y. Acad. Sci.*, **19**, 298 (1957).

### 2-3. Molecular Models

In trying to visualize the symmetry properties of the molecules depicted in Figs. 2-1 to 2-5, the reader may have felt the need for three-dimensional representations of these molecules. The only completely adequate way to visualize molecules in space is by means of three-dimensional models. Since the need for such models will recur throughout this book and, in fact, whenever one considers a problem in stereochemistry, a brief description of the available molecular models is called for.

There are essentially three types of models: those that merely represent the geometric relationship of the atoms in the molecule without being accurate as to interatomic distances; those that show interatomic distances correctly to scale without, however, showing the sizes of the atoms themselves; and those that are to scale with respect to both atomic and interatomic dimensions and therefore allow one to construct a true scale model of the molecule.

The first type of models—those showing geometric relationships only—are by far the least expensive. They are usually models of the ball-and-stick type (affectionately called "tinkertoys" by some chemists). They are very satisfac-

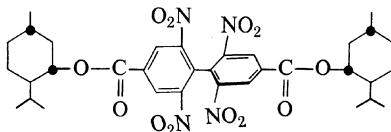


Fig. 2-5. (*dextro*)-Menthyl (*evo*)-menthyl 2,6,2',6'-tetranitro-4,4'-diphenate.

tory for depicting over-all molecular geometry as well as symmetry relationships and allow one to decide the number and kind of stereoisomers that may exist for a given structure. No practicing organic chemist should be without a set or two of these models. Sets are available using colored wooden spheres for atoms and wooden pegs for bonds† (with stout springs available for strained structures, such as the cyclobutane rings in Figs. 2-1 to 2-4) or using a smaller size of colored wooden spheres for atoms and stout springs for all bonds.‡ The latter sets are more compact but make a less rigid and therefore less easily manipulated model.

Where it is desirable to measure interatomic distances in a model, the model must be to scale as far as bond distances are concerned. The "Barton models," "Dreiding models," and "Cenco-Petersen models" are of this type. In the Barton models§ (scale 1 Å. ≡ 10 cm.) the carbon atoms are metal tetrahedra or (for doubly bonded atoms) triangular prisms and the bonds are rigid

† Available in the United States from E. H. Sargent and Co., 4647 W. Foster Avenue, Chicago 30, Ill.

‡ Available in the United States from Central Scientific Co., 1700 Irving Park Road, Chicago 13, Ill.

§ Available in the United States from Wilkens-Anderson Co., 4525 West Division Street, Chicago 51, Ill. The "bonds" in these models are rather flexible and tend to snap at the constricted (grooved) part.

metal rods which are grooved near the ends, the grooves being held in a predetermined place inside the atom models by means of screws in the latter. A less expensive wooden version of the Barton models is also available; † in these models the interatomic distances are not accurately to scale and the models are not suitable for quantitative measurements, but they are very good for class demonstrations because they are much less cluttered than the ball-and-stick models and show angular relationships more clearly.

In the Dreiding type‡ the atoms and bonds combined are constructed of four metal rods, two solid and two hollow, joined together at the center of the carbon atom at the correct tetrahedral angle. To join two atoms, the solid bond of one is inserted into the hollow bond of the other. The length of the bonds and the position of the stops inside the hollow bonds are such that the C—H and C—C distances are represented to scale by the unattached bonds and by two joined bonds, respectively. A carbon atom consisting of three coplanar rods at 120° angles to each other is used for double-bonded structures. Some hetero atoms are also available. These models are excellent for desk manipulation, although too small for demonstration in large classes ( $1 \text{ \AA.} \equiv 2.5 \text{ cm.}$ ).

The Cenco-Petersen molecular models|| are sturdy, large-scale models ( $1 \text{ \AA.} \equiv 5 \text{ cm.}$ ) in which the bonds are screwed into the spheres representing atoms. A variety of atoms (differing in bond angles), as well as bonds of different lengths, are available. Bonds may be set so that they rotate freely or they may be set rigidly.

In the third type of model in which both the atomic and the bonding dimensions are to scale, the atoms are usually represented as spheres sawed off at right angles to the direction of the bonds and equipped with snap locks that can be joined by snap fasteners. These models are particularly desirable when one wishes to know whether two atoms in a molecule can approach each other very closely, whether there is strain in a molecule due to overcrowding of certain atoms, etc. Both a small-scale version ("Fisher-Hirschfelder-Taylor models,"  $1 \text{ \AA.} \equiv 1 \text{ cm.}$ )§ and a somewhat larger-size version ("Stuart-Briegleb models,"  $1 \text{ \AA.} \equiv 1.5 \text{ cm.}$ )|| are available. The so-called "Catalin models" # are a variation of the Fisher-Hirschfelder-Taylor models in which the atoms (made of a phenolic resin) are joined by hard-rubber pegs instead of metal snaps. This imparts a somewhat greater flexibility to the models and allows the representation of moderately strained structures. Another way of increasing the flexibility of the models is used in the "Courtauld atomic models"†† (scale  $1 \text{ \AA.} \equiv 0.8 \text{ in.}$ ). In these models the snap-fastener

† From the Bennett Lumber and Manufacturing Co., Zeeland, Mich., U.S.A.

‡ Available in the United States from G.M. Instrument Co., 511 S. Prairie Street, Greenville, Ill.

|| Available in the United States from Central Scientific Co., 1700 Irving Park Road, Chicago 13, Ill.

§ Available in the United States from Fisher Scientific Co., 717 Forbes Ave., Pittsburgh 19, Pa.

|| Available in the United States from Arthur S. LaPine and Co., 6001 South Knox Avenue, Chicago 29, Ill.

# Available in the United States from Arthur F. Smith Co., 311 Alexander Street, Rochester, N.Y.

†† Available in the United States from The Ealing Corporation, 33 University Road, Cambridge, Mass.

socket is equipped with a spring which allows some lateral motion, and the atoms are separated by a rubber spacing collar. Another type of highly flexible models is the "Godfrey models"<sup>†</sup> (scale 1 A.  $\equiv$  1.65 cm.) in which pliability is achieved by making the atoms out of flexible polyvinyl chloride and the fasteners (bonds) out of polyethylene. Even cyclopropane may be represented by the Godfrey models. In the Courtauld and the Godfrey models the radii of the spherical surfaces of the atomic models are proportional to the actual van der Waals radii of the atoms, whereas in the Fisher-Hirschfelder-Taylor, Stuart-Briegleb, and Catalin models the radius of the atomic spheres is about 80% of the van der Waals radius. For example, in the Catalin models where the scale is 1 cm.  $\equiv$  1 A. in the bond lengths, the radius of the nitrogen-atom model is 1.20 cm., corresponding to a van der Waals radius of 1.5 A. Thus, the apparent crowding in these models is somewhat less severe than in the actual molecules. This is to compensate for the fact that the bond angles in the models (other than the Courtauld and Godfrey models) are rigid whereas the bond angles in the actual molecules can be deformed relatively readily.

Detailed, illustrated literature about these types of models may be obtained by writing to the suppliers.

#### General References

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- <sup>4</sup>W. Heller, Polarimetry, in A. Weissberger, ed., "Technique of Organic Chemistry," vol. I, pt. 3, 3d ed., Interscience Publishers, Inc., New York, 1960, pp. 2147-2333.
- <sup>5</sup>R. L. Shriner and R. Adams, Optical Isomerism, in H. Gilman, ed., "Organic Chemistry," vol. I, 2d ed., John Wiley & Sons, Inc., New York, 1943, pp. 281-304.
- <sup>6</sup>G. W. Wheland, "Advanced Organic Chemistry," 3d ed., John Wiley & Sons, Inc., New York, 1960, chap. 6
- <sup>7</sup>R. L. Bent, "Stereoisomerism," *J. Chem. Educ.*, **30**, 328 (1953).

<sup>†</sup> Available from the Will Corporation, Rochester, N.Y., U.S.A.

## Chapter 3

### OPTICAL ISOMERISM DUE TO ASYMMETRIC CARBON ATOMS

#### 3-1. Compounds with One Asymmetric Carbon Atom

The simplest source of dissymmetry in an organic molecule is a carbon atom to which four other atoms or groups, each different from the other, are attached. Denoting these atoms or groups by a, b, c, and d, the general symbolism for such a carbon atom becomes Cabcd. One of the oldest known examples is lactic acid,  $\text{CH}_3\overset{*}{\text{C}}\text{HOHCO}_2\text{H}$ , in which the starred carbon atom is asymmetric, being substituted by a hydrogen atom, hydroxyl group, methyl group, and carboxyl group. It has long been known that the lactic acid produced in the living muscle when it performs work ("sarcolactic acid") is dextrorotatory, whereas part of the lactic acid formed by fermentation of lactose in the souring of milk ("fermentation lactic acid") is levorotatory. Synthetic lactic acid, as will be shown in Chap. 4, is a mixture of equal amounts of the dextrorotatory and levorotatory forms and does not affect the plane of polarized light.

Molecular models of (+)-lactic acid (dextrorotatory) and (-)-lactic acid (levorotatory) are shown in Figs. 3-1 and 3-2, along with three-dimensional line drawings of the compounds.<sup>†</sup> From the information given so far, it cannot be deduced which model corresponds to the dextrorotatory and which to the levorotatory form, but the representations in Figs. 3-1 and 3-2 are correct in this respect. The problem of which arrangement of the atoms in space corresponds to which isomer will be taken up in Chap. 5 under the heading of "configuration."

Since paper and blackboards are two-dimensional, it is inconvenient to represent molecules in their three-dimensional reality, and two-dimensional projection is frequently resorted to. Emil Fischer<sup>1</sup> in 1891 proposed a type of projection formula which is still in use. In this representation, the mole-

*Note:* All references above 17 are listed in the General References at the end of the chapter.

<sup>†</sup> The beginner in the field is strongly urged to build his own molecular models from the less costly sets described in Sec. 2-3. It is impossible for the novice to gain an understanding of stereochemistry without frequent reference to three-dimensional models.

<sup>1</sup> E. Fischer, *Ber.*, **24**, 2683 (1891).

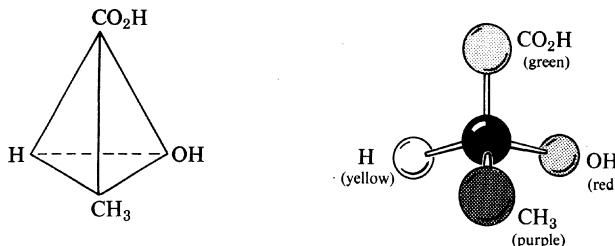


Fig. 3-1. (+)-Lactic acid. (The asymmetric carbon atom is at the center of the tetrahedron. To avoid cluttering the drawing, it is never shown.)†

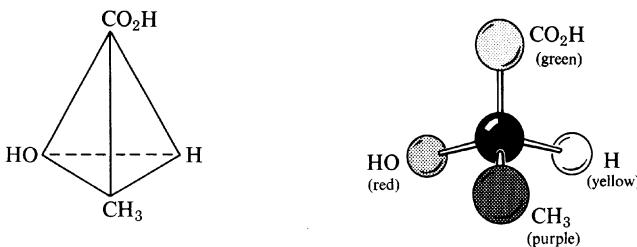


Fig. 3-2. (-)-Lactic acid.†

cule is so oriented that the asymmetric carbon is in the plane of the projection, the groups at the top and bottom are inclined equally below the plane of projection, and the groups on the left and right are similarly inclined equally above the plane of projection. The molecule is then projected in the shape of a cross, as shown in Fig. 3-3. Unfortunately, the orientation of the tetrahedron used for projection in Fig. 3-3 is different from the way in which the tetrahedron is ordinarily shown if represented three-dimensionally (Fig. 3-2); this is one of the several vicissitudes of stereochemical representation to which the newcomer has to become accustomed. Several other points in connection with Fig. 3-3 deserve attention. The projection formula, being two-dimensional, may never be lifted out of the projection plane and turned over. And, since the vertical bonds are in reality *below* the projection plane whereas

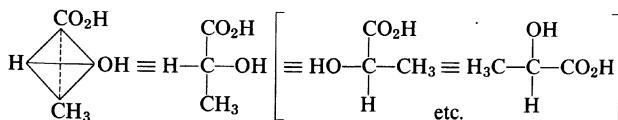


Fig. 3-3. Projection formula of (-)-lactic acid.

† The colors indicated in these figures represent typical colors of balls in ball-and-stick models. Symmetrical groups such as  $\text{CH}_3$ ,  $\text{OH}$ , and  $\text{CO}_2\text{H}$  are customarily represented by a single ball in the model.

the horizontal bonds are *above* this plane, it is not permissible to rotate the projection formula within the plane of the paper by either a 90° or a 270° angle, although it is all right to rotate it by a 180° angle. It is well to convince oneself of these limitations by means of actual models. Contemplation of models also indicates that, while substituents may not be switched in pairs, they may be rotated in groups of three, as shown in the bracket in Fig. 3-3.

If the asymmetrically substituted tetrahedral carbon atom is indeed responsible for optical rotatory power in the case of simple molecules such as lactic acid (as proposed by van't Hoff and by Le Bel in 1874),<sup>2,3</sup> then the interchange of two groups must lead from one enantiomer to the other.<sup>†</sup> This prediction was verified experimentally<sup>4</sup> by means of the series of reactions shown in Fig. 3-4.<sup>‡</sup> (The round-about transformation of the half-ester to the half-amide was resorted to since direct ammonolysis of the ester was unsuccessful.)

Numerous examples of active compounds of the type Cabcd are known, including hydroxy acids, such as lactic, malic, and mandelic acid; carbinols,

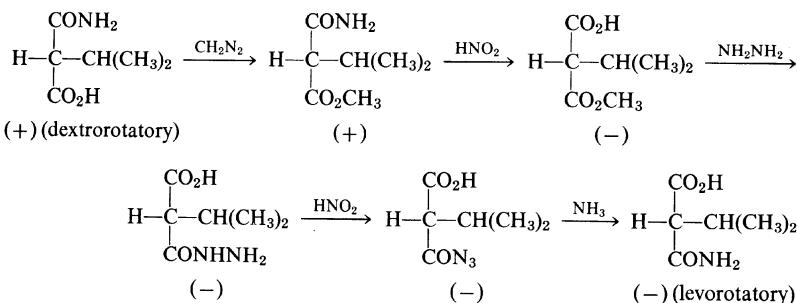
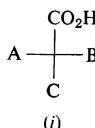


Fig. 3-4. Transformation of one enantiomer into the other.

such as butanol-2 and methylphenylcarbinol; amino acids, such as alanine, phenylalanine, tryptophan, and many others; halides, such as 2-bromoöctane; active amyl alcohol, hydratropic acid, atrolactic acid, etc. In most of these at least two of the four substituents are carbon-containing groups, such as alkyl or carboxyl groups. However, the compound chloroiododomethanesulfonic acid, CHClISO<sub>3</sub>H, in which none of the attached groups contains carbon,

† The reader should verify this statement by examination of models as well as by inspection of projection formulas.

‡ The arrangement of the groups around the asymmetric carbon in the (+)- and (-)-isopropylmalonamidic acids, unlike that of the lactic acids shown in Figs. 3-1 and 3-2, is not known. The representations chosen here are an enlightened guess based on an empirical rule that an acid of configuration (i) forms a more levorotatory salt when the polarizability order (Chap. 14) of the other three substituents is A > B > C (J. H. Brewster, private communication).



<sup>2</sup> J. A. Le Bel, *Bull. soc. chim. France*, [2]22, 337 (1874).

<sup>3</sup> J. H. van't Hoff, *Bull. soc. chim. France*, [2]23, 295 (1875). (The original version appeared in Dutch in 1874.)

<sup>4</sup> E. Fischer and F. Brauns, *Ber.*, 47, 3181 (1914).

has been resolved,<sup>5</sup> and there is some tenuous evidence<sup>6</sup> that fluorochlorobromomethane, CHFCIBr, in which a, b, c, and d are all individual atoms rather than groups, may be obtained in optically active form also.

Of particular interest is the fact that molecules in which asymmetry is due to isotopic substitution, such as RCHDR', have been obtained optically active,<sup>7</sup> as shown in Fig. 3-5. The specific rotation of optically pure ethylbenzene- $\alpha$ -d is at least 0.7 to 0.8°.<sup>8</sup> Other active deuterium compounds with

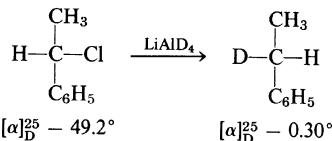
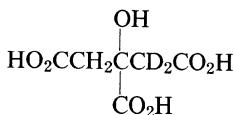


Fig. 3-5. Optically active compound of the RCHDR' type.

rotations of similar magnitude have been synthesized<sup>9</sup> in which it has been shown that the arrangement of the alkyl groups and the hydrogen atom around the asymmetric carbon is opposite in the deuterocarbon from what it was in the halide (as is implied in Fig. 3-5); i.e., the reduction involves inversion of configuration (cf. Chap. 5).

Not only may compounds of type RCHDR' be obtained optically active but also asymmetric compounds in which the isotope is remote from the asymmetric carbon, such as<sup>10a</sup>  $\text{CH}_3\text{CHOHCD}_3$  and<sup>10b</sup>



One compound of this type,  $\text{C}_6\text{H}_5\text{CHOHC}_6\text{D}_5$ , has even been resolved<sup>10c</sup> by the classical method of crystallization of diastereoisomeric derivatives (Sec. 4-4b)! The rotation of these compounds is of the order of a degree also; earlier reports that compounds of this type could not be obtained active<sup>11</sup> (e.g., in the catalytic deuteration of active  $\text{C}_6\text{H}_5\text{CHOHC}_6\text{H}_{11}$  and  $\text{C}_2\text{H}_5\text{CHOHC}\equiv\text{CH}$ ) presumably involved accidental racemization of the compounds during their attempted synthesis. The case of the  $\alpha,\alpha$ -dideuteroctric acid mentioned above is particularly striking because its specific rota-

<sup>5</sup> W. J. Pope and J. Read, *J. Chem. Soc.*, **105**, 811 (1914).

<sup>6</sup> K. L. Berry and J. M. Sturtevant, *J. Am. Chem. Soc.*, **64**, 1599 (1942).

<sup>7</sup> E. L. Eliel, *J. Am. Chem. Soc.*, **71**, 3970 (1949). See also E. R. Alexander and A. G. Pinkus, *ibid.*, **71**, 1786 (1949).

<sup>8</sup> A. Streitwieser, J. R. Wolfe, and W. D. Schaeffer, *Tetrahedron*, **6**, 338 (1959); H. J. Dauben and L. L. McCoy, *J. Am. Chem. Soc.*, **81**, 5404 (1959).

<sup>9</sup> G. K. Helmckamp and B. F. Rickborn, *J. Org. Chem.*, **22**, 479 (1957).

<sup>10(a)</sup> K. Mislow, R. E. O'Brien, and H. Schaefer, *J. Am. Chem. Soc.*, **82**, 5512 (1960). (b) C. Martius and G. Schorre, *Ann.*, **570**, 140 (1950). (c) Y. Pocker, *Proc. Chem. Soc.*, 140 (1961).

<sup>11</sup> See Ref. 20, pp. 302-304; also R. L. Burwell, F. Hummel, and E. S. Wallis, *J. Org. Chem.*, **1**, 332 (1936).

tion in ammonium molybdate solution is reported<sup>10b</sup> to be over 30°. Presumably a complex is formed which absorbs in the yellow region of the spectrum and gives rise to a Cotton effect (see Chap. 14) near the wavelength of the sodium D line.

### 3-2. Compounds with Two or More Unequal Asymmetric Carbon Atoms

Many natural products, such as certain carbohydrates, peptides, steroids, terpenes, alkaloids, etc., contain two or more asymmetric carbon atoms, and a thorough understanding of the stereochemistry of systems with more than one asymmetric center is therefore essential. When there are two distinct

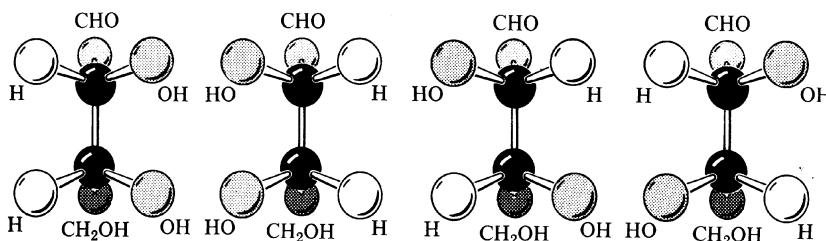


Fig. 3-6. The aldohexoses.

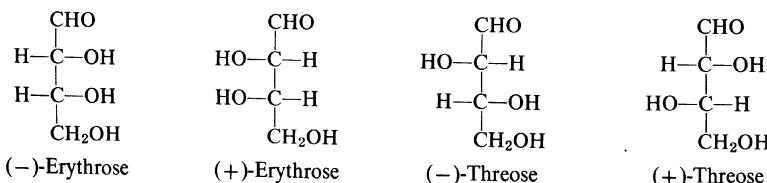


Fig. 3-7. Projection formulas of the aldohexoses.

asymmetric carbon atoms in a molecule, two arrangements of the groups are possible around each of them, and the total number of possibilities is  $2 \times 2$  or 4. Adding another asymmetric carbon atom with its two possible arrangements doubles the number of isomers again; thus the number of stereoisomers for a compound with three distinct asymmetric atoms is  $2 \times 4 = 2 \times 2 \times 2 = 2^3 = 8$ . In general, the number of stereoisomers for a compound with  $n$  distinct asymmetric atoms is  $2^n$ .

Examples of compounds with two asymmetric carbon atoms (starred) are the four-carbon sugars (tetroses),  $\text{CH}_2\text{OH}\overset{*}{\text{C}}\text{HOH}\overset{*}{\text{C}}\text{HOHCHO}$ . Models of the four possible isomers are shown in Fig. 3-6 and the corresponding projection formulas in Fig. 3-7. Also indicated in Fig. 3-7 are the names and signs of rotation of these compounds.

The projection formulas of compounds with two asymmetric atoms are obtained as follows: The model is so oriented that the asymmetric carbon

atoms (second and third carbon) lie in the projection plane and the groups on the two sides (hydrogen and hydroxyl) stick out *above* (or in front of) the projection plane. The remaining two groups (aldehyde group and primary alcohol group in the case of the tetroses) then automatically stick out *below* (or behind) the projection plane, and the model is ready for projection. In the case of the aldose sugars, the additional convention is followed that the aldehyde group is to be at the *top* of the formula so projected (No. 1 carbon) and the primary alcohol group at the *bottom* (No. 4 carbon in the case of the tetroses). In an abbreviated writing of the projection formulas, the aldehyde carbon is denoted by a blot or circle, the main carbon chain by a vertical line, and the secondary hydroxyl groups by horizontal lines; the hydrogen atoms are omitted altogether. This notation<sup>12</sup> is shown in Fig. 3-8 for the tetroses.

Inspection of either the models or the projection formulas of (−)- and (+)-erythrose shows that these molecules are mirror images of each other; i.e., (−)- and (+)-erythrose are enantiomers and have identical physical and chemical properties except for the direction in which they rotate the plane of polarized light. Similarly, (−)- and (+)-threose are enantiomers. On the other hand, comparing either of the erythroses with either of the threoses, one

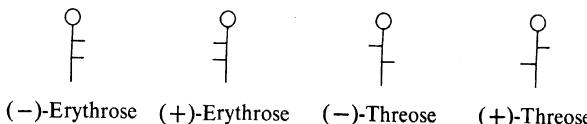


Fig. 3-8. Abbreviated projection formulas for aldohexoses.

finds that, although stereoisomers, they are not mirror images of each other. Such stereoisomers, some or all of which are dissymmetric but which are not mirror images of each other (and therefore not enantiomers), are called "diastereoisomers" (or "diastereomers"). It is evident that, in order to have diastereoisomers corresponding to a given structural formula, there must be at least two asymmetric atoms† in the given structure. If there is only one asymmetric atom,‡ there will only be two enantiomers.

Interestingly enough, whereas enantiomers have identical properties in a symmetric environment,‡ diastereoisomers may differ widely in both physical and chemical properties—in fact, many diastereoisomers differ among each

† This statement is oversimplified. It was pointed out in Chap. 2 that there are dissymmetric molecules without individual asymmetric atoms. Thus one can have enantiomers, and for that matter diastereoisomers, without asymmetric atoms. Actual cases will be considered in Chaps. 6, 7, and 11. To make the statement in the text universally correct, one should replace the words "asymmetric atoms" by "dissymmetric groupings." For a general definition of "dissymmetric grouping" the reader is referred to Ref. 21b, p. 219; specific examples will be pointed out later in this text.

‡ The qualification of the symmetric environment is necessary, for, as will be explained in Chap. 4, enantiomers differ in their reactivity toward dissymmetric reagents and behave differently in a dissymmetric physical environment.

other as much as ordinary (structural) isomers do. This difference between enantiomers and diastereoisomers, while puzzling at first thought, can be readily rationalized upon some reflection. In enantiomers, all intramolecular distances between corresponding groups are the same. Also, any symmetrical reagent approaching the two enantiomers in turn can always be so oriented that the approach is exactly the same in the two cases, i.e., that at a given intermolecular distance all the atoms of the approaching reagent have the same distance from all the atoms in one of the enantiomers as they would have in the other enantiomer. The situation is comparable to that of a man who has perfectly shaped hands and is perfectly ambidextrous; not only do any two fingers of one of his hands bear exactly the same relation to each other as the corresponding fingers of the other hand, but he is able to approach and handle any symmetrical tool (such as a hammer or pair of tweezers) equally well with one hand as with the other.<sup>†</sup> The same is not true of diastereoisomers. They may be likened to a hypothetical individual two of whose fingers (on one hand only) have been interchanged. Now the distance between fingers (corresponding to groups in the molecule) is no longer the same for the two hands. On the molecular scale, the different dis-

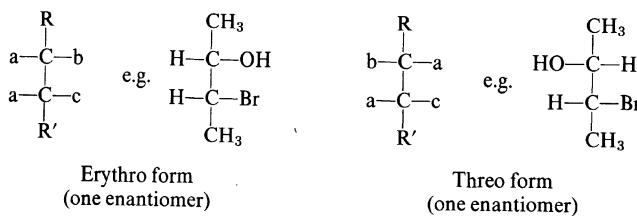


Fig. 3-9. Erythro-threo nomenclature.

tances between corresponding groups in diastereoisomers may produce differences in boiling point, melting point, solubility, spectral properties, etc., in such isomers. The free energy of the two diastereoisomers is also different, since such things as crowding between bulky substituents, hydrogen bonds within the molecule, etc., are not the same. Finally, toward an object (molecule) approaching from the outside, the fingers of the two hands (groups of the two diastereoisomeric molecules) no longer bear the same relationship; i.e., the individual can no longer be perfectly ambidextrous and likewise the diastereoisomeric molecules show differences in reactivity.

Molecules that contain two asymmetric atoms in particular have been used extensively in mechanistic studies, and a special nomenclature and special forms of notation for such systems have sprung up. The nomenclature is derived from the names of the four-carbon sugars, erythrose and threose, and applies to all systems of the type‡  $R-Cab-Cac-R'$ . If the two like groups  $a$  in the projection formula are on the same side, as the hydroxyl groups in

† The equivalence of the hands no longer holds when the external agent is dissymmetric; e.g., a left glove will fit only the left hand, not the right hand. This situation, as already mentioned, also has its parallel among molecular enantiomers; cf. Chap. 4.

‡  $R-C-C-R'$  is the main chain of the molecule.

erythrose, the isomer is called the "erythro" form; if they are on opposite sides, as the hydroxyl groups in threose, the isomer is called the "threo" form. Figure 3-9 indicates the general nomenclature and also gives a particular illustration involving 3-bromo-2-butanol.

As for notation, it might appear at first sight that the Fischer projection formulas, as illustrated in Figs. 3-7 and 3-9, should be adequate for the representation of compounds with two asymmetric atoms. However, in looking at the models from which such projection formulas are derived (e.g., Fig. 3-6), one realizes that these models (and therefore the projections) represent the molecule in the so-called "eclipsed" form (cf. Chap. 6), i.e., in the form in which  $C_2$  and  $C_3$  are so rotated with respect to each other that the groups attached to them approach each other as closely as possible. It turns out (Chap. 6) that in this form crowding between the substituents on  $C_2$  and  $C_3$  is at a maximum and that the real shape of the molecule is not like this at all but more closely corresponds to an arrangement where  $C_2$  and  $C_3$  are rotated with respect to each other by an angle of  $60^\circ$  so that their substituents are now as far apart as possible. In this arrangement the molecule is said to be in the "staggered" form (cf. Chap. 6). In considering reactions of a molecule,

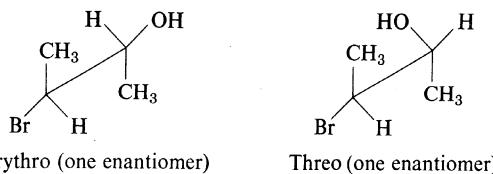


Fig. 3-10. Sawhorse formulas of the 3-bromo-2-butanols.

it is usually desirable to depict the molecule in its actual staggered form, rather than in the hypothetical eclipsed form shown in the Fischer projection. Of the various ways of representing molecules with two asymmetric atoms in their staggered form, the "sawhorse" representation<sup>13</sup> and the Newman projection formula<sup>14</sup> are, in the author's view, the clearest and most convenient.

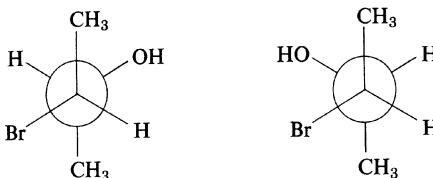
In the sawhorse representation, the molecule is simply shown in three dimensions, the bond between the asymmetric carbons being oriented diagonally backward and being exaggerated somewhat in length. Figure 3-10 shows the sawhorse formulas of the 3-bromo-2-butanol whose Fischer projections were given in Fig. 3-9. It should be noted that there are three different ways of staggering  $C_2$  and  $C_3$  with respect to each other; the formulas in Fig. 3-10 are arbitrarily disposed in such a way that the bulky methyl groups point as far away from each other as possible.

In the Newman projection formula, the molecule is viewed from front to back in the direction of the bond linking the asymmetric carbon atoms. These two atoms thus exactly eclipse each other and are represented by two superimposed circles (actually one circle only appears in the drawing). The

<sup>13</sup> See, for example, D. Y. Curtin, *Record Chem. Progr. (Kresge-Hooker Sci. Lib.)*, **15**, 111 (1954).

<sup>14</sup> M. S. Newman, *J. Chem. Educ.*, **32**, 344 (1955).

bonds and groups attached to the asymmetric carbon atoms are projected into a vertical plane; the bonds thus appear as the spokes of a wheel at angles of  $120^\circ$  for each carbon, the spokes for the rear carbon being displaced by an angle of  $60^\circ$  with respect to the bonds on the front carbon. In order to distinguish the two sets of bonds, the set for the front carbon is drawn to the center of the circle but that for the rear carbon ends at the periphery. New-



Erythro (one enantiomer)      Threo (one enantiomer)  
Fig. 3-11. Newman projection for the 3-bromo-2-butanol.

man projection formulas for the 3-bromo-2-butanol are shown in Fig. 3-11.

It is desirable that anyone dealing with stereochemical problems be able to translate rapidly one set of formulas into the other. In particular, one should be able to shift readily from the Fischer projection formula (which is the one most often used in books and articles) to either the sawhorse or Newman projection formula (which is the one most useful in assessing the chem-

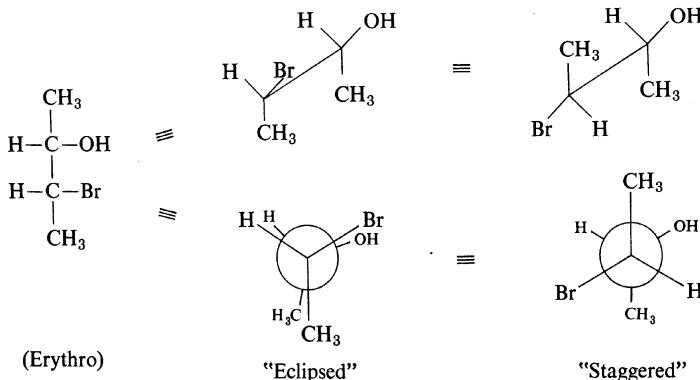


Fig. 3-12. Transformation from Fischer to sawhorse or Newman formula.

ical behavior of a molecule, since it more aptly depicts the actual molecular shape). One way of effecting the transformation is to build a model corresponding to the Fischer projection, rotate the model into the staggered form, and then draw the corresponding sawhorse or Newman projection. A quicker way, not requiring models, is shown in Fig. 3-12. Here the Fischer projection is directly translated into an "eclipsed sawhorse" or Newman pro-

jection, and the latter is then rotated by a  $180^\circ$  angle around the  $C_2-C_3$  bond to give the normal sawhorse or Newman projection.

A few further observations regarding the different representations may be helpful. The Fischer formula shows at a glance whether one is dealing with an erythro or threo form, but the sawhorse and Newman formulas do not and usually require at least a mental process of rotation around  $C_2-C_3$  until

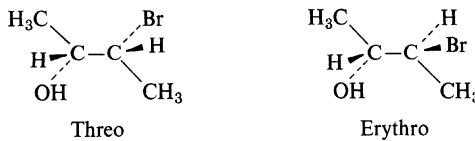


Fig. 3-13. Flying-wedge formulas of the 3-bromo-2-butanol isomers.

one can decide which is which. Also, the sawhorse formula is quite convenient to represent eclipsed as well as staggered forms, but the Newman projection is awkward for the representation of eclipsed forms (cf. Fig. 3-12).

Yet another way of showing compounds with two asymmetric centers is by means of "flying-wedge" formulas,<sup>15</sup> depicted for erythro- and threo-3-bromo-2-butanol in Fig. 3-13. These formulas, in which the molecule is depicted looking sideways at the bond joining the asymmetric carbon atoms, will not be used in this book.

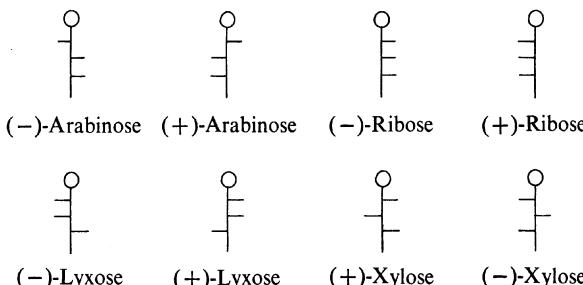


Fig. 3-14. Stereoisomeric aldopentoses.

Much of the early development of stereochemistry was stimulated by investigations of various sugars. It is therefore appropriate to conclude this section by an illustration of compounds with three and four asymmetric carbon atoms, using the aldopentoses and aldohexoses as examples. Figure 3-14 shows the eight stereoisomeric aldopentoses (four pairs of enantiomers), and Fig. 3-15 depicts one enantiomer of each of the eight pairs of diastereoisomeric aldohexoses (total number of stereoisomers: 16).†

† The spatial formulas in Figs. 3-8, 3-14, 3-15, and 3-16 are known to represent the correct arrangement in space of the groups attached to the asymmetric carbon atoms; cf. Chap. 5.

<sup>15</sup> For example, D. J. Cram, *J. Am. Chem. Soc.*, 74, 2129 (1952).

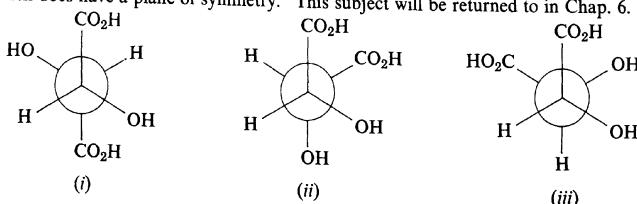
### 3-3. Compounds Containing Like Asymmetric Carbon Atoms

When a compound contains two or more asymmetric carbon atoms which are alike, meaning that the same atoms or groups are attached to both, the general formula for computing the number of stereoisomers (page 20) no longer applies. A case in point is tartaric acid, HO<sub>2</sub>C<sup>\*</sup>CHOH<sup>\*</sup>CO<sub>2</sub>H. Here the two asymmetric carbon atoms (starred) are alike in that each is linked to a hydrogen atom, a hydroxyl group, a carboxyl group, and a —CHO<sub>2</sub>H group. A molecule of this type is sometimes described by the symbolism AA, where A stands for an asymmetric carbon atom. At first sight, four different arrangements appear to be possible; the models and their Fischer projections are shown in Fig. 3-16. The first two formulas do, indeed, represent two active forms, (—)- and (+)-tartaric acid, which are enantiomeric to each other. The third and fourth formulas, however, represent the same molecule, since one can be obtained from the other by a rotation of 180° in the plane of the paper, such a rotation being permitted for a Fischer projection formula (cf. Fig. 3-3). Since the third and fourth formulas are at the same time identical and mirror images of each other, it follows that they represent one and the same, inactive molecule. (This can also be deduced from the fact that the molecule has a plane of symmetry: dotted line.) There is, thus, a tartaric acid diastereoisomeric with the active forms but itself inactive. This acid is called *meso*-tartaric acid, and inactive diastereoisomers of this type in general are called "meso forms."†

*meso*-Tartaric acid differs from either of its active diastereoisomers in physical and chemical properties in the same way and for the same reason that one active diastereoisomer differs from another (cf. page 21). Thus, *meso*-tartaric acid melts at 140° whereas the (+) and (—) forms melt at 170°; it is less dense, less soluble in water, and a less strong acid than the active isomers and has a higher dipole moment.

It is instructive to make models of the three tartaric acids and to inspect the individual asymmetric carbon atoms (best after separating them). One thus arrives at the conclusion that (—)-tartaric acid is made up of two asymmetric carbon atoms of like arrangement of the groups. Similarly, (+)-tar-

† It is of some interest that the projection of *meso*-tartaric acid shown in Fig. 3-16 as having a plane of symmetry corresponds to the eclipsed form and does not represent a prevalent state of the molecule. Rather, *meso*-tartaric acid exists mainly in the staggered forms shown in (i) to (iii) below. Of these (i) has a center of symmetry, and (ii) and (iii), though dissymmetric, are mirror images of each other. The absence of activity may be ascribed to the fact that (ii) and (iii) are present in equal amounts, that they are readily interconverted by internal rotation, and (less important) that during such rotation the molecule passes through the form shown in Fig. 3-16 which does have a plane of symmetry. This subject will be returned to in Chap. 6.



tartaric acid is made up of two asymmetric carbon atoms of like arrangement, the arrangement being opposite to that for the (-) enantiomer. *meso*-Tartaric acid, on the other hand, is made up of two asymmetric carbon atoms of *opposite* arrangement, a fact which can also be gleaned from the projection

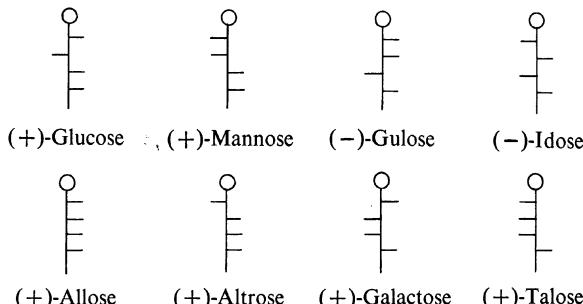


Fig. 3-15. Diastereoisomeric aldohexoses (one member of each pair of enantiomers shown).

formula if one separates the upper half from the lower along the dotted line (Fig. 3-16) and rotates it through a 180° angle. If the arrangement of the substituents about each of the asymmetric carbon atoms in (-)-tartaric acid is called† “S” and that in (+)-tartaric acid is called† “R,” then (-)-tartaric

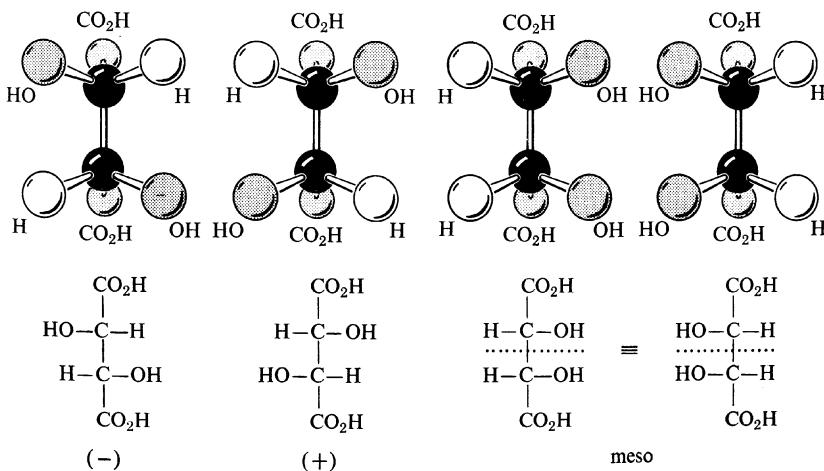


Fig. 3-16. The tartaric acids.

acid has the S,S arrangement, (+)-tartaric acid has the R,R arrangement, and *meso*-tartaric acid has the R,S (or S,R) arrangement.

† At this point, the symbols R and S may be taken to be simply means of denoting that the arrangements of the groups about the two asymmetric carbon atoms are opposite. Actually, the symbols have a more profound meaning which will be explained in Sec. 5-2.

Continuing with this type of symbolism, we may next consider the number of isomers in 2,3,4-trihydroxyglutaric acid, HO<sub>2</sub>C—CHOH—CHOH—CHOH—CO<sub>2</sub>H, which may be said to be of type ABA, since the molecule has two asymmetric carbon atoms which are alike (Nos. 2 and 4) and one other one (No. 3) which is asymmetric in some of the stereoisomers but not in all. Each asymmetric atom may, *a priori*, have the R or S arrangement. Thus one arrives at the possibilities shown in Fig. 3-17.

1 HO <sub>2</sub> C	2 —CHOH—	3 —CHOH—	4 —CHOH—	5 —CO <sub>2</sub> H	Isomer No.	Isomer Type
	R		R		1	Active } enantiomers
	S		S		2	Active }
R	r*		S		3	Meso
R	s*		S		4	Meso

\* Small letters are used because these atoms are "pseudoasymmetric"; see below and Sec. 5-2.

Fig. 3-17. The 2,3,4-trihydroxyglutaric acids.

In isomers 1 and 2 (which are mirror images of each other and therefore represent a pair of enantiomers) the central carbon atom (No. 3) is not asymmetric, since the two groups attached have the same configuration as well as structure. In isomers 3 and 4, the central carbon atom is asymmetric, but the molecule as a whole is not, since it has a plane of symmetry bisecting carbon atom No. 3 (see model or projection formula).

Therefore, isomers 3 and 4 are distinct but inactive; they represent two meso forms. The central carbon atom (No. 3) in isomers 3 and 4 is some-

HO <sub>2</sub> C	—CHOH—	—CHOH—	—CHOH—	—CHOH—	CO <sub>2</sub> H	No.	Isomer Type
R	R	R	R			1	Active } enantiomers
S	S	S	S			2	Active }
R	R	R	S			3	Active } enantiomers
S	S	S	R			4	Active }
R	R	S	R			5	Active } enantiomers
S	S	R	S			6	Active }
R	R	S	S			7	Meso
R	S	R	S			8	Meso
R	S	S	R			9	Active } enantiomers
S	R	R	S			10	Active }

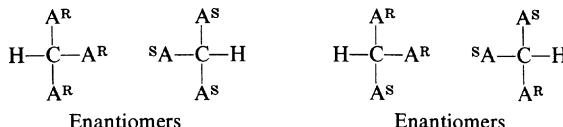
Fig. 3-18. The 2,3,4,5-tetrahydroxyadipic acids.

times said to be "pseudoasymmetric," meaning that its asymmetry is due to two of the attached groups being opposite in configuration. Such a pseudo-asymmetric atom does not give rise to dissymmetry in the molecule as a whole.

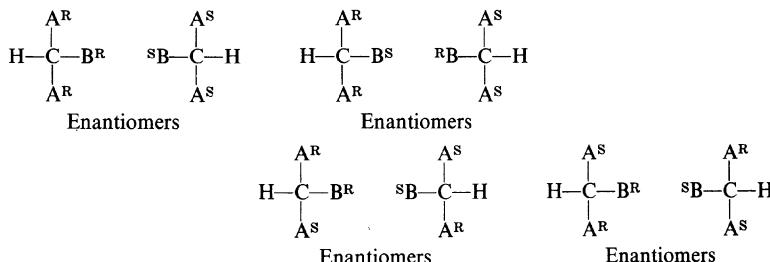
The isomerism of the 2,3,4,5-tetrahydroxyadipic acids (type ABBA), of importance as reference compounds in hexose chemistry, is summarized in Fig. 3-18. There are four pairs of enantiomers and two meso forms. It is instructive to work this out for oneself and to convince oneself that there are no other isomers.

### 3-4. Compounds with Asymmetric Carbon Atoms in Branched Chains

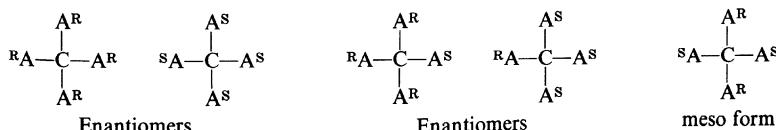
In the compounds discussed so far, the asymmetric carbons could always be arranged in one main chain. On rare occasions only does one encounter branched dissymmetric molecules, i.e., molecules in which the asymmetric

Fig. 3-19.  $\text{CHA}_3^*$  case.

carbon atoms cannot all be aligned in one chain. A general case would be a molecule of the type  $\text{CA}^*\text{B}^*\text{D}^*\text{E}^*$ , where the groups  $\text{A}^*$ ,  $\text{B}^*$ ,  $\text{D}^*$ , and  $\text{E}^*$  attached to the central carbon atom are all asymmetric and the central carbon atom is asymmetric also. Here there are, then, five asymmetric atoms, and the total number of stereoisomers is  $2^5$  or 32. Cases where two or more

Fig. 3-20.  $\text{CHA}_2^*\text{B}^*$  case.

of the asymmetric groups attached to the central carbon atom are alike are more complicated, for, depending on the arrangement of the like asymmetric groups, the central carbon atom is or is not itself asymmetric. Thus, in the  $\text{CHA}_3^*$  case shown in Fig. 3-19, the central carbon atom is never asym-

Fig. 3-21.  $\text{CA}_4^*$  case.

metric and only two pairs of enantiomers are possible. On the other hand, in the  $\text{CHA}_2^*\text{B}^*$  case (Fig. 3-20) the central carbon atom *may* become asymmetric and the number of stereoisomers is therefore larger than in the simple  $\text{ABA}$  case discussed earlier (Fig. 3-17). The  $\text{CA}_4^*$  case shown in Fig. 3-21 is of

special interest. The isomer on the right of the figure is clearly identical with its mirror image (both being  $C_4H_8A_8$  with the central carbon atom not asymmetric); yet it has neither plane nor center of symmetry. Inspection of the model shows that this molecule has a fourfold alternating axis of symmetry (cf. Chap. 2). A molecule of this type possessing no other element of sym-

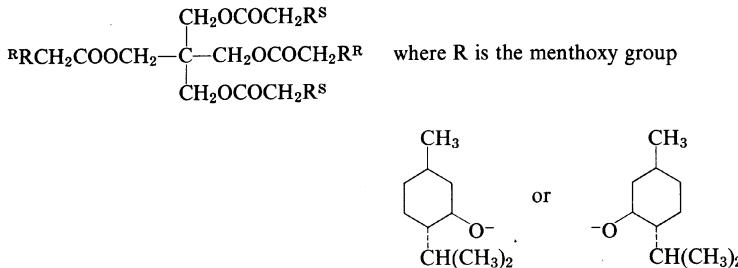


Fig. 3-22. Molecule possessing fourfold alternating axis of symmetry.

metry than an alternating axis (Fig. 3-22) has indeed been prepared<sup>16</sup> and shown to be optically inactive.

Mathematical formulas for computing the number of stereoisomers in branched structures have been developed.<sup>17</sup>

#### General References

<sup>18</sup> G. M. Richardson, ed., "The Foundations of Stereochemistry," American Book Company, New York, 1901.

<sup>19</sup> F. Ébel in K. Freudenberg, ed., "Stereochemie," Franz Deuticke, Leipzig, 1932, pp. 587-602; K. Freudenberg, *ibid.*, pp. 662-668.

<sup>20</sup> R. L. Shriner and R. Adams, Optical Isomerism, in H. Gilman, ed., "Organic Chemistry," 2d ed., John Wiley & Sons, Inc., New York, 1943, pp. 224-240.

<sup>21</sup> (a) G. W. Wheland, "Advanced Organic Chemistry," 3d ed., John Wiley & Sons, Inc., New York, 1960; (b) *id.*, 2d ed., 1949.

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<sup>16</sup> G. E. McCasland, R. Horvat, and M. R. Roth, *J. Am. Chem. Soc.*, **81**, 2399 (1959); for an earlier example, see G. E. McCasland and S. Proskow, *ibid.*, **78**, 5646 (1956).

<sup>17</sup> J. K. Senior, *Ber.*, **60B**, 73 (1927).

## Chapter 4

### RACEMIC MODIFICATIONS

#### 4-1. Nature of Racemic Modifications

It was pointed out in Chap. 2 that the individual molecules of most substances are optically active<sup>†</sup> if they are dissymmetric. Nevertheless, the substance in bulk may not be optically active, because it may be constituted of approximately equal numbers of dextrorotatory (+) and levorotatory (−) molecules so that the average rotation is zero. Such an assembly of molecules, one half of which are mirror images of the other half, is called a "racemic modification"<sup>‡</sup> and is denoted by the symbol ( $\pm$ ). The term "racemic modification" evidently does not apply to individual molecules; rather it is a statistical concept which arises when large numbers of molecules are considered. [To make this point clear to oneself, one might imagine a lazy Maxwellian demon,<sup>¶</sup> sitting between two lakes of one and the same optically active substance, except that the substance in one lake is dextrorotatory, that in the other levorotatory. The demon is then instructed to assemble a mole of the substance in a glass by picking individual molecules at random out of the two lakes. It is clear that the first molecule that he picks will be either dextrorotatory or levorotatory and there is a 50-50 chance that the first two molecules he picks will be of the same rotation. Even after he has picked 20 molecules, there is a fair chance that he will have significantly more of one kind than of the other. But after he has picked  $6.02 \times 10^{23}$  molecules, one can be quite sure that any fluctuation in favor of one kind of molecule or the other will be so minor as to be experimentally undetectable and the material in the glass will not rotate the plane of polarized light.]

In this chapter, the formation of racemic modifications will be considered in Sec. 4-2; their properties, especially in the solid state, in Sec. 4-3; and the important process of separating the dextrorotatory and levorotatory molecules, known as "resolution," will be described in Sec. 4-4.

*Note:* All references above 81 are listed in the General References at the end of the chapter.

<sup>†</sup> Unfortunately, this statement is of doubtful operational significance, inasmuch as the optical activity of an individual molecule has never been observed and possibly never will be.

<sup>‡</sup> The term "dl pair" is also frequently used. "Racemic mixture" has been erroneously used in the same context but actually has a more restricted meaning; see below.

<sup>¶</sup>A lazy Maxwellian demon is one who accomplishes only what would happen on its own account anyway.

### 4-2. Formation of Racemic Modifications

a. **By Mixing.** The most obvious and trivial way of forming a racemic modification is by intimate mixing of exactly equal amounts of the dextrorotatory (+) and levorotatory (-) isomers. This process is associated with an entropy of mixing, since the racemic modification represents a more random state of affairs than the separate enantiomers. The entropy of mixing is calculated by the usual formula  $\Delta S = -R(x_1 \ln x_1 - x_2 \ln x_2)$  (assuming ideal behavior†).

In the case of a racemic modification,  $x_1 = x_2 = \frac{1}{2}$ , whence  $\Delta S = -R \ln \frac{1}{2} = R \ln 2 = 1.4$  cal./deg. mole. The free-energy change in producing the racemic modification from the enantiomers is therefore  $\Delta F = -T \Delta S = -0.42$  kcal./mole at room temperature.‡ The entropy of mixing is positive because racemization by mixing (like any mixing) leads from a more ordered to a more random (or disordered) state.

The formation of a racemic modification by mixing is sometimes resorted to if racemic material, obtained by synthesis (see below), is to be compared with available dextrorotatory and levorotatory material presumed to be of

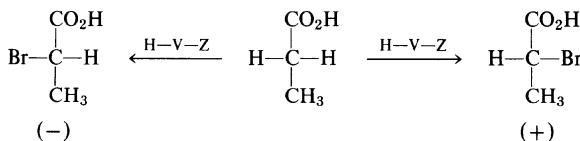


Fig. 4-1. Bromination of propionic acid.

the same species. As will be seen later, the ( $\pm$ ) material will, of course, have the same melting point as that of an intimate mixture of equal amounts of the (+) and (-) isomers of the same chemical species.

b. **By Synthesis.** Any synthesis of dissymmetric molecules, starting from either symmetric molecules or a racemic modification and using no optically active reagents or catalysts and no asymmetric physical influence (cf. Sec. 4-4*d* and *f*), always produces a racemic modification (i.e., an equal number of the two enantiomeric types of product molecules). This point may be better appreciated by looking at the two common ways of producing an asymmetric carbon in a molecule: by displacement and by addition. The first method is exemplified by the bromination of propionic acid to  $\alpha$ -bromopropionic acid by the Hell-Vollhard-Zelinsky method (Fig. 4-1). Since each of the two alpha-hydrogens bears the same relationship¶ to the other and to the rest of the

† Ideal behavior in a mixture means that interaction between unlike molecules in the mixture is the same as interaction between the (like) molecules of the individual pure components. For enantiomers, such an assumption is probably excellent for gases and dilute solutions, fair for pure liquids, but not applicable to solids (see below).

‡ Assuming that mixing is a thermoneutral process, i.e.,  $\Delta H = 0$ . This is certainly the case if ideal behavior is encountered. For a possible exception, see A. Ladenburg, *Ber.*, **28**, 163 (1895); also C. J. McGinn, *J. Phys. Chem.*, **65**, 1896 (1961).

¶ In reality, the two relations are of the mirror-image type. Thus in going from one hydrogen in the projection formula to the carboxyl group, one moves up and right, but from the other hydrogen one moves an equal distance up and left. In the absence of any dissymmetric influence, however, the terms right and left are devoid of significance on the molecular scale. This point will be returned to later (Sec. 4-4*g*).

molecule, each is replaced at the same rate as the other and equal numbers of (+) and (-) molecules of  $\alpha$ -bromopropionic acid result. The second method is exemplified by the addition of hydrogen cyanide to acetaldehyde to give lactonitrile (Fig. 4-2). Here approach from either side of the carbonyl is equally facile and therefore equal numbers of molecules of the two enantiomeric forms of lactonitrile,  $\text{CH}_3\text{CHOHCN}$ , result.

c. By Racemization. Racemization is the process of producing a racemic modification starting with *one* of the pure enantiomers. Since the two enantiomers have the same free energy (Chap. 3), the equilibrium mixture will correspond to a 50-50 composition; i.e., it will be a racemic modification. Since the concentration of the pure enantiomer is reduced to one-half of its original value when racemization occurs, the free-energy change associated with racemization is  $\Delta F = RT \ln \frac{1}{2} = -RT \ln 2$ . It will be seen that this is equal to the free-energy change associated with forming a racemic modification by mixing. In mixing, one starts with equal amounts of the (+) and (-) forms, in racemization with either form by itself; however, this makes no difference to the free-energy change. Given that racemization is an energetically favored process, the question remains whether a convenient pathway can be

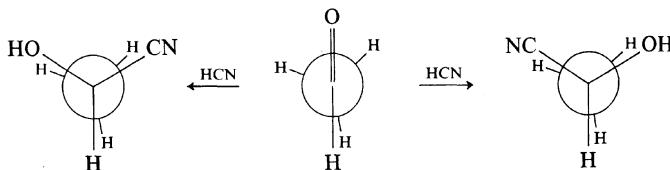


Fig. 4-2. Addition of hydrogen cyanide to acetaldehyde.

found for equilibrium to be established, or, in other words, whether the activation energy for interconversion of the enantiomers is prohibitively high or not.

If racemization is considered a reversible transformation of the (+) into the (-) form, the kinetic expression for a reversible reaction applies. Let  $a$  be the initial concentration of the given enantiomer,  $x$  the amount changed into the opposite enantiomer after time  $t$ , and  $k$  the rate constant for both the forward and the reverse reaction (in this particular instance the two rate constants are equal). Then

$$\frac{dx}{dt} = k(a - x) - kx = k(a - 2x)$$

The integrated form of this equation is

$$k = \frac{2.3}{2t} \log \frac{a}{a - 2x}$$

In practice, the concentration of the active species is followed by optical rotation, and since optical rotation is proportional to the concentration of the active species:  $\alpha_0 \propto a$  and  $\alpha_t \propto (a - 2x)$ , where  $\alpha_0$  is the initial rotation and  $\alpha_t$  is the rotation after time  $t$ , the rate constant for racemization is given by

$$k = \frac{2.3}{2t} \log \frac{\alpha_0}{\alpha_t}$$

Some authors, instead of considering racemization a reversible interconversion of the enantiomers, i.e.,  $(+)$   $\rightleftharpoons$   $(-)$ , consider it an irreversible transformation of one of the enantiomers into the racemic modification:  $(+)$   $\rightarrow$   $(\pm)$ . In this case the kinetics of an irreversible first-order reaction applies:  $dy/dt = k'(a - y)$ , where  $a$  has the same meaning as before and  $y$  is the amount of material racemized at time  $t$ . Integration gives  $k' = (2.3/t) \log a/(a - y)$ , and since the initial rotation  $\alpha_0$  is proportional to  $a$  and the rotation  $\alpha_t$  is proportional to  $a - y$  (active material minus racemized material), this may be expressed as

$$k' = \frac{2.3}{t} \log \frac{\alpha_0}{\alpha_t}$$

It should be noted that  $k'$  and  $k$  are not the same; in fact  $k' = 2k$ , that is, the rate of racemization is twice the rate of interconversion of the enantiomers. This is reasonable; for each  $(-)$  molecule formed from a  $(+)$  molecule, *two* molecules are "racemized," since the  $(+)$  molecule so formed counterbalances the rotation of another (unchanged)  $(-)$  molecule. When reading the literature, it is obviously important to discern whether rate constants for loss of activity refer to interconversion of enantiomers or to formation of the racemic modification. The latter type of rate constant is more frequently encountered.

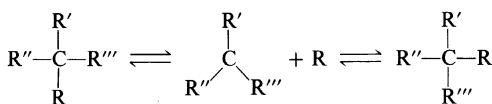


Fig. 4-3. Process of racemization.

Whether racemization will take place at a reasonable rate depends on the system under consideration. Several chemical methods for reaching the racemization equilibrium may be distinguished.

*i. Thermal Racemization.* One general method of racemizing an optically active material is by breaking, temporarily, one of the four bonds to an asymmetric carbon. If, in the subsequent re-formation of the bond, the group separated exchanges places with one of the remaining groups, the dissymmetric molecule is converted to its enantiomer (Fig. 4-3).†

If the bond is to be broken homolytically, i.e., in such a way that one of the electrons of the bond stays with carbon and the other with the group separated, considerable energy (namely, that equivalent to the bond-dissociation energy) must be expended and high temperatures are required. This is apt to lead to chemical changes more deep-seated than simple racemization, and well-authenticated cases of thermal racemization by homolytic cleavage are quite rare. The racemization of  $\alpha$ -phenethyl chloride,  $\text{C}_6\text{H}_5\text{CHClCH}_3$ , upon distillation at atmospheric pressure may be of this type, although this has not been clearly established. Relatively facile thermal racemization may occur in special cases when one enantiomer can be converted to the other by

† It is not immediately obvious why and how such an exchange of places occurs, but in fact it does. This point will be considered in detail in Chap. 13.

stretching and bending bonds rather than by actually breaking them. Such cases are considered in Chap. 6.

*ii. By Anion Formation.* A second way of bringing about the process depicted in Fig. 4-3 is by heterolytic cleavage, in such a way that the electron pair of the bond broken stays with the R'R''R'''C group. This group is thus converted to an anion. The group R separated without its electrons is usually a proton. In other words, the process involves the temporary separation of a mildly acidic hydrogen. Several examples are shown in Fig. 4-4.

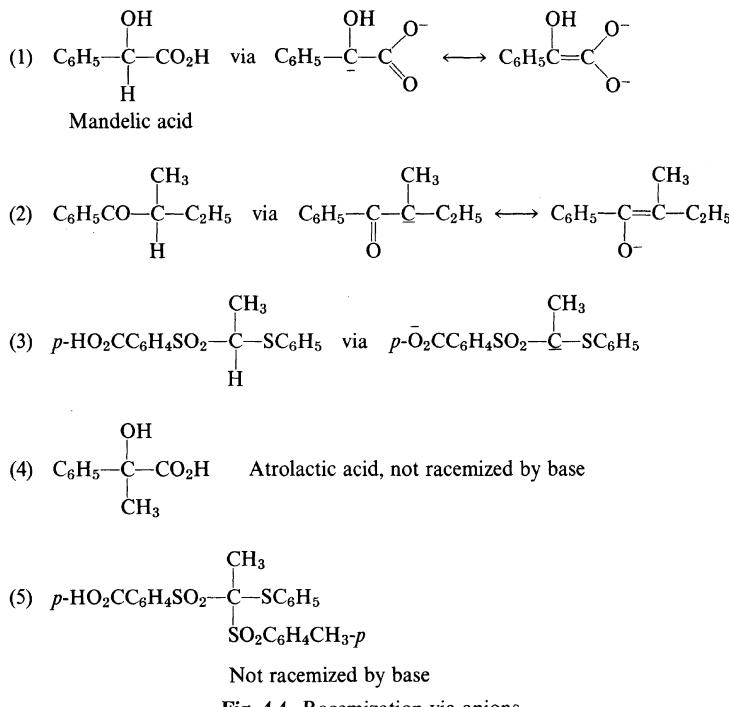


Fig. 4-4. Racemization via anions.

The base used to remove the proton is, in most cases, methoxide or ethoxide. Only those compounds (1 to 3) having an acidic hydrogen attached to the asymmetric carbon are racemized by a base; where there is no acidic hydrogen attached to the asymmetric carbon (4,5) no base-induced racemization occurs. The more labile and acidic the hydrogen, the greater, in general, is the ease of racemization. The hydrogen on the asymmetric carbon in the disulfone  $p\text{-HO}_2\text{CC}_6\text{H}_4\text{SO}_2\overset{*}{\text{CH}}(\text{CH}_3)\text{SO}_2\text{C}_6\text{H}_5$  is so acidic and the compound is therefore converted to the carbanion so readily that all attempts at resolving it have failed.

In a particularly elegant demonstration that racemization by base involves the anion as intermediate, it was shown<sup>1</sup> that the rate of racemization of active phenyl *sec*-butyl ketone in dioxane-D<sub>2</sub>O medium using NaOD as base was equal to the rate of deuterium exchange.<sup>1a</sup> Previously it had been shown<sup>2</sup> that the rate of racemization by sodium acetate is equal to the rate of bromination in the presence of the same catalyst. These observations are rational-

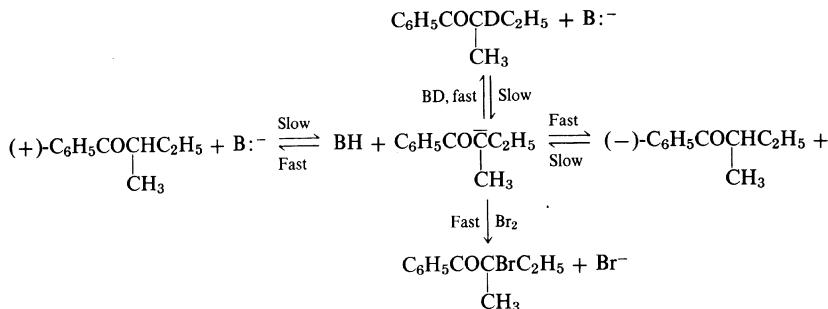


Fig. 4-5. Rates of racemization, deuterium exchange, and bromination of phenyl *sec*-butyl ketone in presence of base.

ized readily by assuming that all three processes (racemization, deuterium exchange, halogenation) proceed through a common intermediate—presumably the anion—which is formed in a rate-determining step (Fig. 4-5).

*iii. By Cation Formation.* Another way of bringing about racemization by the type of process depicted in Fig. 4-3 is to remove (temporarily) the group

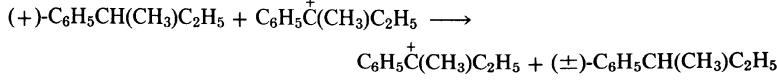
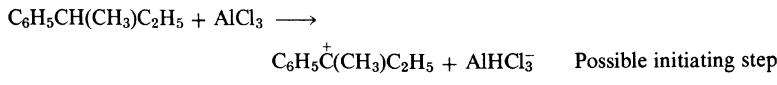
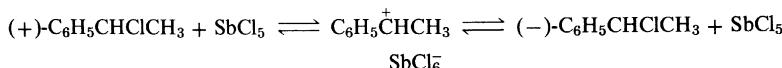


Fig. 4-6. Racemization via carbonium ions.

R with its pair of electrons and to leave R'R''R'''C<sup>+</sup> as a carbonium ion. Usually, this type of racemization is brought about by a Lewis acid which

<sup>1</sup>S. K. Hsü, C. K. Ingold, and C. L. Wilson, *J. Chem. Soc.*, 78 (1938).

<sup>1a</sup>See also D. J. Cram, B. Rickborn, C. A. Kingsbury, and P. Haberfield, *J. Am. Chem. Soc.*, 83, 3678 (1961).

<sup>2</sup>S. K. Hsü and C. L. Wilson, *J. Chem. Soc.*, 623 (1936).

abstracts R:<sup>-</sup>. Examples are the racemization of  $\alpha$ -phenethyl chloride by means<sup>3</sup> of antimony pentachloride and of 2-phenylbutane by aluminum chloride (Fig. 4-6).<sup>4</sup> Mercuric chloride, zinc chloride, and stannic chloride are also effective catalysts for the racemization of  $\alpha$ -phenethyl chloride, but chlorides devoid of Lewis acid activity, such as lithium chloride and tetramethylammonium chloride, are ineffective.

*iv. By Reversible Formation of Stable Inactive Intermediates.* The carbonium ions and carbanions involved in the above-described racemizations are

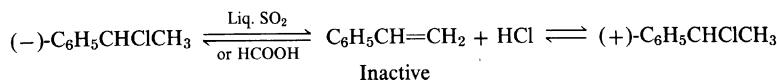
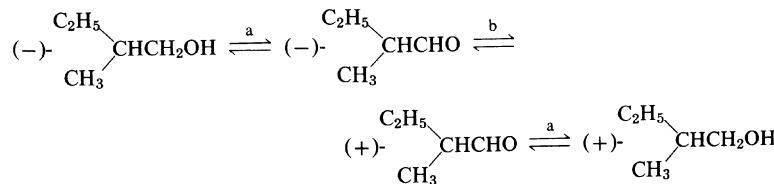
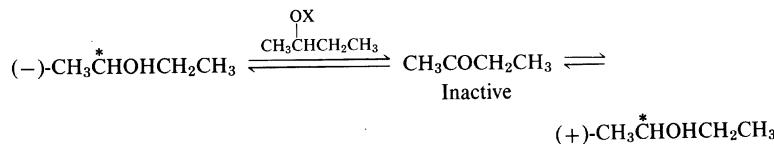


Fig. 4-7. Racemization of  $\alpha$ -phenethyl chloride.

probably true intermediates but of very short half-life. In contrast, this section will be concerned with the reversible formation of symmetric intermediates which are stable entities in their own right. An example is the racemization of  $\alpha$ -phenethyl chloride upon dissolution in liquid sulfur dioxide or formic acid; this has been shown to proceed by a dehydrohalogenation-hydrohalogenation process<sup>5</sup> (Fig. 4-7). Racemization of alcohols in the presence of sodium or aluminum alkoxides is another case in point; this reaction requires the presence of a trace of carbonyl compound (usually formed by air oxidation) and



<sup>a</sup> Alkoxide.

<sup>b</sup> Base.

Fig. 4-8. Racemization of 2-butanol and 2-methyl-1-butanol by alkoxides.

is known to involve a carbinol-carbonyl equilibrium (cf. page 72) (Fig. 4-8). A special case, also shown in Fig. 4-8, concerns the racemization of active amyl alcohol by sodium (actually sodium amyloxide) at 200°; in this case the

<sup>3</sup> K. Bodendorf and H. Böhme, *Ann.*, **516**, 1 (1935).

<sup>4</sup> E. L. Eliel, P. H. Wilken, and F. T. Fang, *J. Org. Chem.*, **22**, 231 (1957); cf. R. L. Burwell and A. D. Shields, *J. Am. Chem. Soc.*, **77**, 2766 (1955).

<sup>5</sup> E. D. Hughes, C. K. Ingold, and A. D. Scott, *Nature*, **138**, 120 (1936).

alcohol is reversibly oxidized to the corresponding aldehyde, which, in turn, is racemized by the anion-forming mechanism described above.<sup>6</sup>

Racemization through reversible formation of a ketene has been observed<sup>7</sup> in the case of 2,4-dichloro-3-phenylcyclobutene upon heating in chloroform solution (Fig. 4-9). Enolization (which would lead to a cyclobutadiene structure) is ruled out in this case by the observation that no H-D exchange on the cyclobutene occurs when racemization is effected in  $\text{CH}_3\text{CO}_2\text{D}$  as a solvent. When the solvent is ethanol, ketene formation becomes irreversible and an ethyl ester is formed at the same rate at which racemization occurs (Fig. 4-9).

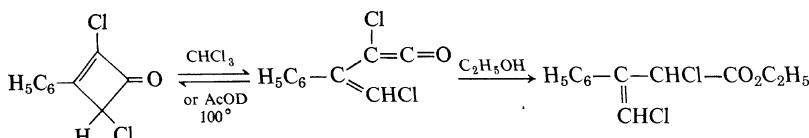


Fig. 4-9. Racemization through ketene intermediate.

v. *By Walden Inversion.* The racemization of 2-iodooctane by potassium iodide in refluxing acetone involves a process known as "Walden inversion":  $(+)-\text{CH}_3\text{CHIC}_6\text{H}_{13} + \text{I}^- \rightleftharpoons \text{I}^- + (-)-\text{CH}_3\text{CHIC}_6\text{H}_{13}$ . This process will be considered in detail in Sec. 5-4f.

d. *By Chemical Transformation.* It is possible to change a dissymmetric molecule to its enantiomeric form without ever breaking any of the bonds leading to the asymmetric atom.<sup>†</sup> An example has been shown in Fig. 3-4.

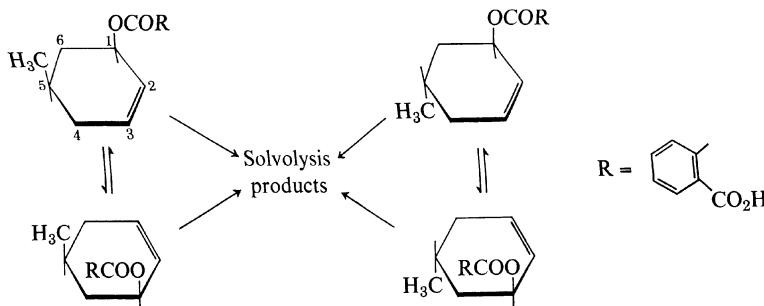


Fig. 4-10. Racemization by rearrangement.

If such a change is brought about in reversible fashion, it will lead to racemization. A case in point<sup>8</sup> is the racemization of 5-methyl-2-cyclohexenyl acid phthalate in aqueous acetone at 100° (Fig. 4-10). Two simultaneous processes take place, namely, solvolysis (to a mixture of 5-methyl-1,3-cyclo-

<sup>†</sup> More properly we should speak of a "dissymmetric grouping," not an asymmetric atom.

<sup>6</sup> Cf. Ref. 83, p. 866.

<sup>7</sup> E. F. Jenny and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 2005 (1956).

<sup>8</sup> H. L. Goering and E. F. Silversmith, *J. Am. Chem. Soc.*, **77**, 1129 (1955).

hexadiene, phthalic acid, and 5-methyl-2-cyclohexenols) and rearrangement of the phthalate group from the 1 to the 3 position. Inasmuch as this rearrangement converts the molecule to its mirror image, it leads to racemization without any other observable change. The  $(-)$ -*cis*-phthalate is converted to  $(\pm)$ -*cis*-phthalate whereas the  $(-)$ -*trans*-phthalate gives  $(\pm)$ -*trans*-phthalate. No interconversion of the *cis* to the *trans* series, and vice versa, is observed. The racemizing rearrangement is believed to involve an ion pair in which the phthalate anion is associated with one or another of the faces of the molecule (Fig. 4-11).† Racemization is evidently due to change of configuration at the No. 5 carbon, even though no bond to this carbon is ever broken. Also configuration at the newly created asymmetric carbon C<sub>3</sub> is opposite to that at C<sub>1</sub> in the starting material.

e. **Epimerization, Mutarotation, and Asymmetric Transformation.**<sup>91</sup> Although epimerization, mutarotation, and asymmetric transformation do not constitute racemization, they are closely related to racemization and will be taken up in this section.

i. **Epimerization.** Epimerization is defined as change in configuration (arrangement of the groups) at *one* asymmetric atom in a compound having

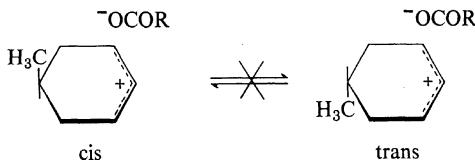
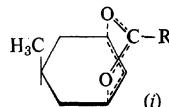


Fig. 4-11. Ion pairs involved in 5-methyl-2-cyclohexenyl acid phthalate rearrangement.

more than one such atom. Except in very unusual circumstances, epimerization of an optically active compound does not involve racemization, since only one of several asymmetric atoms is affected. Rather, epimerization involves interconversion of diastereoisomers. Even a racemic modification may be subjected to epimerization if it contains more than one asymmetric center. In this case, epimerization involves partial conversion to a diastereoisomeric racemic modification. An example is shown in Fig. 4-12. Treatment of  $(-)$ -menthone (1) with a base will effect a partial change of configuration at C<sub>4</sub>, the asymmetric center adjacent to the carbonyl group (cf. page 35), but will leave the arrangement at C<sub>1</sub> unchanged. The product of the transformation is  $(+)$ -isomenthone (2). Because (1) and (2) are diastereoisomers rather than enantiomers, in general, they differ in free energy and therefore equilibrium does not correspond to a 50-50 mixture of the two diastereoisomers. In the case of the menthones, the equilibrium constant<sup>8a</sup> is

† The evidence presented here does not exclude a cyclic transition state of type *i*. However, such a transition state does not readily explain the effect of the solvent dielectric constant on the rate of racemization (Ref. 8) and is excluded on other grounds; cf. H. L. Goering and J. T. Doi, *J. Am. Chem. Soc.*, **82**, 5850 (1960).



<sup>8a</sup> J. Read, G. J. Robertson, and A. M. R. Cook, *J. Chem. Soc.*, 1276 (1927).

close to 2.3, so that equilibrium corresponds to about 70% (1) and 30% (2). Since (3) and (4) have the same free energies as their respective enantiomers, the equilibrium of (3) and (4) is the same as that of (1) and (2), namely, 70% (3) and 30% (4). Since ( $\pm$ )-menthone is a mixture of equal parts of (1) and (3) and ( $\pm$ )-isomenthone is a mixture of equal parts of (2) and (4), the equilibrium of ( $\pm$ )-menthone and ( $\pm$ )-isomenthone is the same (70-30) as that of their pure enantiomers (1) and (2) [or (3) and (4)].

Diastereoisomers that differ in configuration at only one asymmetric center<sup>†</sup> are sometimes called "epimers"; thus menthone and isomenthone are epimers.<sup>‡</sup>

*ii. Mutarotation and First-order Asymmetric Transformation.* In 1846, Dubrunfaut discovered that, when glucose is dissolved in water and the optical activity of the solution observed, there is a gradual change in rotation from an initial value corresponding to  $[\alpha]_D^{20}$  of +111° to an equilibrium value of  $[\alpha]_D^{20}$  of +52.5°. Lowry, in 1899, coined the name "mutarotation" for this

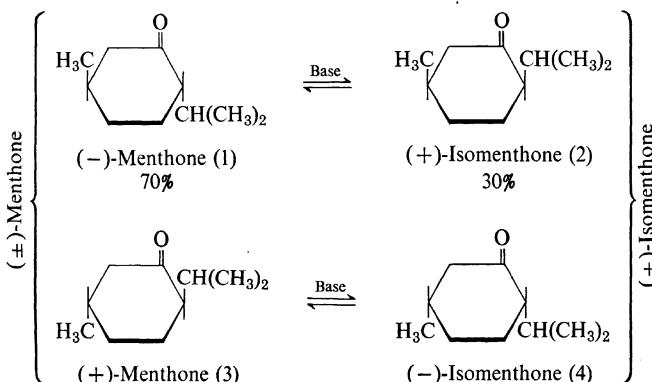


Fig. 4-12. Epimerization of menthone and isomenthone.

phenomenon. Mutarotation, then, is the spontaneous change, with time, in the rotation of freshly prepared solutions of certain optically active substances. Eventually, their rotation reaches an equilibrium value, generally different from zero. Mutarotation may be the result of either a spontaneous epimerization or a spontaneous structural change. In the case of (+)-glucose, mutarotation involves a change of configuration at the No. 1 carbon (the so-called "anomeric center") owing to an opening and reclosing of the hemiacetal

<sup>†</sup> The term "asymmetric center" is sometimes used to denote a focal point of asymmetry, such as an asymmetrically substituted atom; it is synonymous with "dissymmetric grouping" mentioned earlier.

<sup>‡</sup> Originally, the terms epimers and epimerization were coined in the sugar series, epimers being sugars differing in configuration at the No. 2 carbon, such as glucose and mannose (Fig. 3-15). Since this is the center adjacent to the potential aldehyde group in the sugar, epimerization of such sugars may, in principle, be effected by a base. In actual fact, this reaction is very unclean, and epimerization of an aldohexose is best carried out by oxidation to the corresponding gluconic acid, epimerization of the acid by means of pyridine, lactonization, and reduction back to an aldohexose mixture: E. Fischer, *Ber.*, 23, 799 (1890).

ring (Fig. 4-13). The intermediate open-chain aldehyde form is present in negligibly small concentration. Equilibrium corresponds to 38% of the  $\alpha$  and 62% of the  $\beta$  form.

Figures 4-14 and 4-15 illustrate mutarotation due to structural changes. In the gluconolactones (Fig. 4-14) mutarotation is caused by partial hydroly-

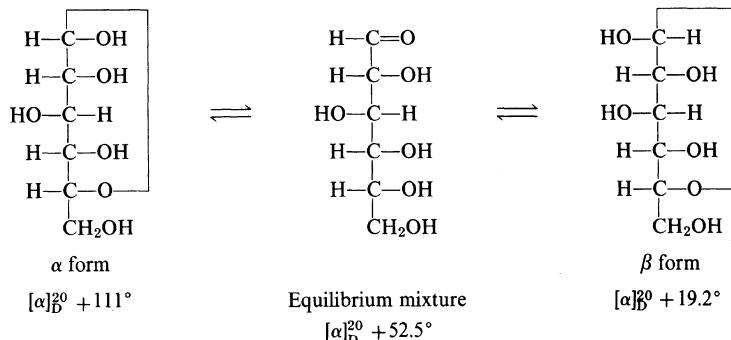


Fig. 4-13. Mutarotation of (+)-glucose.

sis to gluconic acid in aqueous solution.<sup>8b</sup> In aniline camphor-10-sulfonate (Fig. 4-15) it is due to isomerization to a ketimine or anil.<sup>8c</sup>

In general, the rate of mutarotation depends on temperature, solvent, and catalyst. The mutarotation of glucose is known to be acid-base catalyzed. Temperature and solvent also affect the position of the equilibrium.

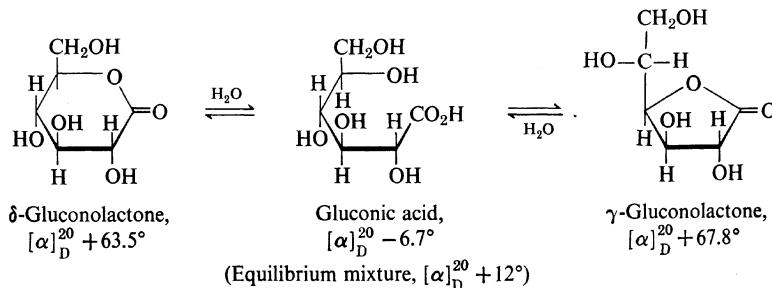


Fig. 4-14. Mutarotation of the gluconolactones.

First-order asymmetric transformation is closely related to mutarotation, but whereas mutarotation is defined phenomenologically, first-order asymmetric transformation is defined by origin as a spontaneous epimerization in solution. Thus, all mutarotations due to configurational (rather than struc-

<sup>8b</sup> K. Rehorst, *Ber.*, **61**, 163 (1928).

<sup>8c</sup> R. S. Schreiber and R. L. Shriner, *J. Am. Chem. Soc.*, **57**, 1306 (1935).

tural) changes involve first-order asymmetric transformations,<sup>†</sup> and first-order asymmetric transformations usually manifest themselves in mutarotation. The different origin of the two terms is largely a historical one.<sup>†</sup> In many cases, asymmetric transformation involves not the dissolution of a single pure diastereoisomer but the formation and transformation of a mixture of diastereoisomers in solution. Suppose that a racemic acid, ( $\pm$ )-A, is brought together in solution with an optically active base (-)-B. If A has an optically labile (epimerizable) center, mutarotation due to first-order asymmetric transformation will be observed in the solution, once the reagents are mixed. The general principle of the method as well as an actual example is illustrated in Fig. 4-16. When ( $\pm$ )-chlorobromomethanesulfonic acid was treated with an equivalent of active 1-hydroxy-2-aminohydridane in dilute acetone solution, the resulting solution exhibited mutarotation. The rotation at equilibrium indicated<sup>9</sup> that the solution contained 81% of the salt of one enantiomer of the acid and 19% of the salt of the other enantiomer.<sup>‡</sup> Evidently the acid is very easily converted to its enolate (the  $\alpha$ -hydrogen being highly acidic), and therefore epimerization of the two diastereoisomeric salts occurs; one

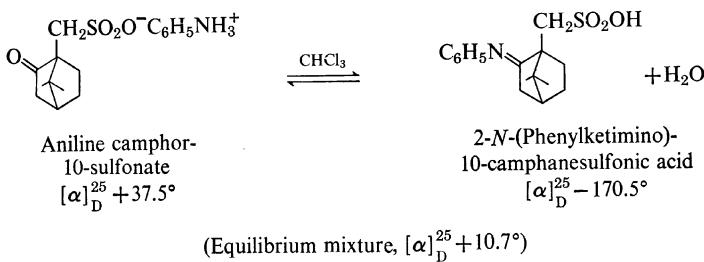


Fig. 4-15. Mutarotation of aniline camphor-10-sulfonate.

<sup>†</sup> The term has a somewhat unfortunate history. It was first coined by R. Kuhn [*Ber.*, 65, 49 (1932)] who used it for the salt of an optically stable base with an optically labile acid. This salt was converted, in solution, to a mixture of unequal amounts of two diastereoisomers, but no pure diastereoisomer could be isolated, and the acid, on being liberated from its salt, reverted to the racemic form faster than its rotation could be measured. Kuhn contrasts such "asymmetric transformations of the first kind" with those "of the second kind," where pure diastereoisomers can be isolated and the labile material recovered in an, at least fleetingly, active state. This distinction is not, however, a useful one, since there is no clear-cut division between optically stable and optically labile compounds but rather a gradual transition from one to the other (see especially Chap. 6). The terms will therefore be used here in the sense of M. M. Jamison and E. E. Turner [*J. Chem. Soc.*, 437 (1942)], first-order asymmetric transformations referring to transformations in solution and second-order ones (page 63) referring to cases where one diastereoisomer actually crystallizes. There is also a difficulty in translation; Kuhn's "erster Art" was translated into English as "first-order," whereas the proper meaning is "of the first kind."

<sup>‡</sup> The salt of the (-) acid as well as the salt of the ( $\pm$ ) acid could be obtained in crystalline form by working in more concentrated solution. By studying the mutarotation of these salts and extrapolating to zero time, the rotation of the pure salts was obtained, and from this the position of the equilibrium mixture could be calculated.

salt happens to be more stable than its diastereoisomer by a factor of 4. All attempts to liberate the active acid from its salts failed, for the same labile hydrogen that causes rapid epimerization of the salts also causes rapid racemization of the free acid.

First-order asymmetric transformations are particularly common in the biphenyl series, and further examples will be found in Chap. 6.

#### 4-3. Properties of Racemic Modifications

In the gaseous or liquid state and in solution, a racemic modification is usually an ideal or nearly ideal mixture of equal numbers of enantiomeric molecules.<sup>†</sup> The usual physical laws applicable to ideal mixtures apply, and since the physical properties of the enantiomers (except toward such asymmetric entities as polarized light) are identical, they are also identical with the

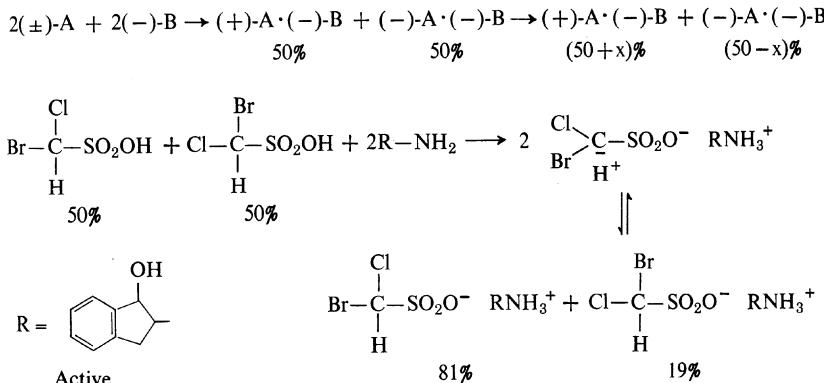


Fig. 4-16. First-order asymmetric transformation.

properties of the racemic modification.<sup>10</sup> Thus racemic modifications have the same boiling points as the pure enantiomers (except for the aforementioned slight deviation from ideality in a few cases); they also have the same refractive index and density in the liquid state<sup>10</sup> and the same infrared spectrum either in the liquid state or in solution.

The same is not true in the solid (crystalline) state.<sup>11</sup> Intercrystalline forces between molecules are highly specific and sensitive to even minor changes in geometry. Therefore, in the solid state, although a molecule of the dextrorotatory form bears the same relation to another molecule of the (+) form as a molecule of the levorotatory form bears to another (-) mole-

<sup>†</sup> Significant deviations from ideality have been observed in some optically active liquids capable of hydrogen bonding; see, for example, F. B. Thole, *J. Chem. Soc.*, **103**, 19 (1913); C. J. McGinn, *J. Phys. Chem.*, **65**, 1896 (1961).

<sup>10</sup> H. Mauser, *Chem. Ber.*, **90**, 299 (1957).

<sup>11</sup> H. Mauser, *Chem. Ber.*, **90**, 307 (1957).

cule, the interrelation of  $(-)$  and  $(+)$  molecules is different. As a result, in the solid state, deviations from ideal behavior are generally encountered. The following three cases may arise:

a. **Racemic Mixtures.** It may happen that in a crystal each enantiomer has greater affinity for molecules of the same kind than for molecules of the other enantiomer. In that case, once a molecule of the  $(+)$  form is laid down in the crystal, only  $(+)$  molecules will grow on it [and similarly for  $(-)$  molecules]. Thus, the macroscopic crystal (or, at least, the unit cell) will correspond to either the  $(+)$  or the  $(-)$  form. The racemic modification will thus be a gross mixture of crystals of the two forms, and one speaks of a "racemic mixture" (also occasionally called "conglomerate").

Since a racemic mixture is a mixture of crystals of the  $(+)$  and  $(-)$  forms, its properties are, in most respects, similar to those of the pure enantiomers. In particular, this applies to the X-ray powder diagram and the infrared spectrum in the solid state. However, the melting point of a racemic mixture

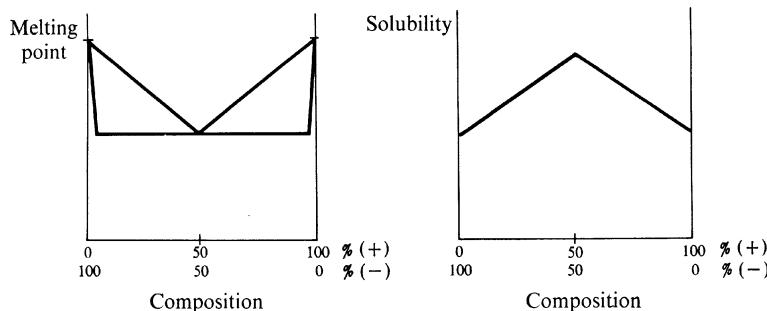


Fig. 4-17. Melting-point and solubility diagrams of racemic mixtures.

(like that of any typical mixture) is lower than that of the pure components and its solubility is higher. Melting point and solubility diagrams of a racemic mixture and the two pure enantiomers are shown in Fig. 4-17. The racemic mixture corresponds to a eutectic which, in this particular case, always occurs at the 50-50 composition mark. An example of a racemic mixture is  $(\pm)$ -sodium ammonium tartrate, provided that the salt is crystallized from water at a temperature below  $27^\circ\text{C}$ .

b. **Racemic Compounds.** A rather more common situation than that described above is that the molecules of one enantiomer have greater affinity for those of the opposite enantiomer than for their own kind. In that case, opposite enantiomers pair up in the unit cell of the crystal which will thus contain equal numbers of  $(+)$  and  $(-)$  molecules (sometimes just one of each kind). In this case we obtain a true compound in the stoichiometric sense, since any macroscopic crystal upon subdivision (down to the level of the unit cell, though not, of course, down to the molecular level) always gives fragments containing equal numbers of molecules of the two enantiomers. A compound of this type (which exists only in the solid state) is called

a "racemic compound" or a "racemate." Racemic compounds have lower enthalpies than the pure enantiomers. Being true compounds, they differ in most physical properties from the enantiomers; for example, they have different infrared spectra in the solid state, different X-ray powder diagrams, different melting points, and different solubilities. The melting-point diagram for an optically active material that forms a racemic compound is shown in Fig. 4-18; the melting point of the compound lies at a maximum of the curve which may be either higher or lower than the melting point of the pure enantiomers. The corresponding solubility curve is also shown in Fig. 4-18.

A number of cases are known where one and the same racemic modification forms a mixture below a certain temperature and a compound above it, or vice versa. Examples are sodium ammonium tartrate which forms a conglomerate *below* 27°C. but a racemate if crystallized above that temperature, and rubidium tartrate which forms a racemic mixture *above* 40° but a compound below that temperature. In some cases, this change in affinity of like

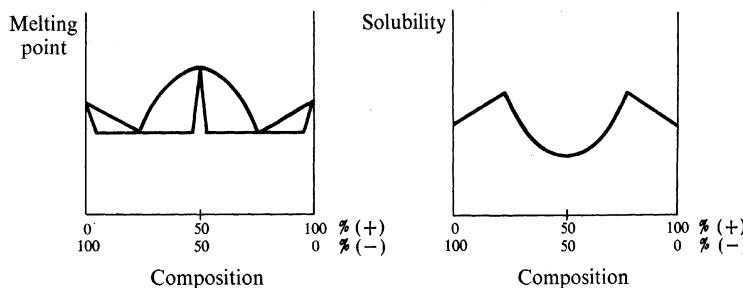


Fig. 4-18. Melting-point and solubility diagrams of racemic compounds. (The compound may melt at a lower point than the pure enantiomers in some cases.)

and unlike molecules to each other with temperature may be accounted for by a change in the number of solvent molecules in the crystal. Thus, sodium ammonium tartrate crystallizes as a mixture (below 27°) with four molecules of water but as a compound (above 27°) with only two. The change in the number of water molecules in the crystal evidently changes the relative ease of fitting like and unlike enantiomers together.

c. **Racemic Solid Solutions.** In some instances, racemic modifications show nearly ideal behavior even in the solid state, meaning that there is little difference in affinity between molecules of like or opposite configuration. In that case, the arrangement of the molecules in the solid is random and one obtains a "racemic solid solution" or mixed crystal. Such solid solutions are identical with the enantiomers in all respects; even the melting point and solubility of the racemic solid solution either are the same as those of the enantiomers or differ from them only very slightly. A melting-point diagram of a racemic solid solution is shown in Fig. 4-19. The solid horizontal line represents an ideal case; in actual fact the curve may be slightly concave upward or downward (dashed lines). ( $\pm$ )-Camphor oxime is obtained as a

racemic solid solution if crystallized above 103°C., although below that temperature it forms a racemic compound.

A racemic compound may be distinguished from a mixture or solid solution by a comparison of its infrared spectrum in the solid state with that of the enantiomers. Only the compound shows a different spectrum. Sometimes the differences are quite profound. For example, the active acid phthalate of *p*-ethylphenylmethylcarbinol (Fig. 4-20) shows evidence of *intra-*

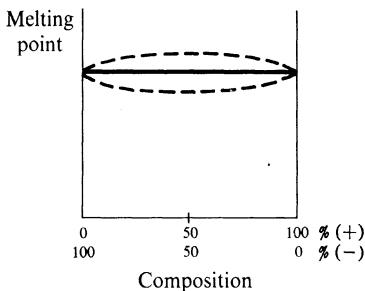


Fig. 4-19. Melting-point diagram of racemic solid solution.

molecular hydrogen bonding only, whereas the racemate shows evidence of strong *intermolecular* hydrogen bonding, presumably between molecules of the (+) and (-) forms.<sup>12</sup>

Another way of distinguishing the three racemic forms is by making use of the melting-point or solubility diagrams.<sup>13</sup> Admixture of one of the pure enantiomers to a racemic mixture increases the melting point, whereas the same process in the case of a compound leads to a depression. In the case of a solid solution, not much change results from such admixture. (For reli-

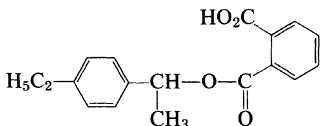


Fig. 4-20. *p*-Ethylphenylmethylcarbinyl acid phthalate.

able results, it is often necessary to determine the melting points of several different mixtures, which in essence means tracing part of the diagrams of Fig. 4-17, 4-18, or 4-19.) Also, it might be noted that a saturated solution of a racemic mixture or solid solution is saturated also with respect to either enantiomer, but the same is not true for all racemic compounds. Thus, if to a saturated solution of the racemic modification a few crystals of one of the

<sup>12</sup> E. L. Eliel and J. T. Kofron, *J. Am. Chem. Soc.*, **75**, 4585 (1953).

<sup>13</sup> H. W. B. Roozeboom, *Z. physik. Chem.*, **28**, 494 (1899); see also Ref. 11.

enantiomers are added, the crystals will dissolve (and the solution will become optically active) only if one is dealing with a compound.<sup>†</sup>

Yet another way of distinguishing the racemic forms is by examination of the unit cell through X-ray crystallography.<sup>14</sup> The unit cell of the compound contains equal numbers of enantiomeric molecules, whereas in the mixture or solid solution it contains only molecules of one enantiomer or the other, but not both.

#### 4-4. Resolution of Racemic Modifications

By "resolution" of a racemic modification is meant the separation (not usually in quantitative recovery) of the two enantiomers<sup>‡</sup> in the pure state. This process is of considerable practical importance, for, as indicated in Sec. 4-2*b*, synthetic processes usually lead to racemic modifications. On the other hand, many of the chemicals occurring in both plants and animals are found there as pure enantiomers. Any total synthesis of such naturally occurring compounds must, therefore, involve a resolution step.

Of the several methods of resolution which will be described in this section, only resolution via conversion to diastereoisomers (Sec. 4-4*b*) and resolution by biochemical methods (Sec. 4-4*e*) are generally useful. The other methods are included mainly because of their considerable theoretical interest.<sup>¶</sup>

a. **Resolution by Mechanical Separation of Crystals.** When one is dealing with a racemic *mixture*, macroscopic crystals of either the (+) or the (-) form are usually present. Provided that the crystals are visually distinct, it should be possible to pick them apart by means of tweezers and thus to effect resolution. The first resolution ever to be brought about was achieved in this way by Louis Pasteur in 1848.<sup>15</sup> Pasteur prepared the sodium ammonium salt of racemic tartaric acid and allowed it to crystallize in large crystals by slow evaporation of the aqueous solution. He then picked apart the two kinds of crystals, making use of the fact that they were hemihedric, i.e., showed dissymmetry in the crystal state. All crystals having the dissymmetric facets disposed in one orientation belonged to one enantiomer, whereas the mirror-image crystals, whose dissymmetric facets were disposed in the opposite orientation, belonged to the other enantiomer (cf. Fig. 1-1). When the two batches of crystals were separately redissolved, the resulting solutions rotated the plane of polarized light to an equal extent in opposite directions. It is fortunate (and perhaps fortuitous) that Pasteur allowed his

<sup>†</sup> Provided that the compound is less soluble than the enantiomers, as in the case shown in Fig. 4-18.

<sup>‡</sup> Sometimes the term is employed even though only one of the enantiomers is obtained pure. When some separation of the enantiomers occurs but neither is obtained completely free of the other, one speaks of "partial resolution."

<sup>¶</sup> Sometimes the best route to an optically active compound is synthesis (by conventional means) from optically active precursors rather than resolution. Examples are given in Chap. 5 (Sec. 5-5).

<sup>14</sup> For example, K. Pettersson, *Arkiv Kemi*, 7, 347 (1954).

<sup>15</sup> L. Pasteur, *Ann. chim. et phys.*, [3]24, 442 (1848).

solutions to evaporate spontaneously in the cool Parisian climate, for, as indicated in Sec. 4-3, sodium ammonium tartrate crystallizes as a racemic mixture only below 27°; above this temperature it crystallizes as a compound which cannot, of course, be separated mechanically.

The method of mechanical separation is rarely a practical way of separating enantiomers. It is tedious, it cannot be applied to racemic compounds or solid solutions, and it can be applied only to those mixtures in which the crystals of the enantiomers are visually distinct. Although it is now recognized that crystals of dextrorotatory and levorotatory enantiomers always show hemihedrism and are mirror images of each other (as crystals as well as molecules), the distinctive crystal faces are often so poorly developed as to be useless from the practical standpoint.

A more useful variation of mechanical separation is the method of inoculation, originally discovered by Gernez.<sup>16</sup> If a saturated solution of a racemic mixture is carefully inoculated with a pure crystal of one of the enantiomers (with respect to which the solution is supersaturated; cf. Fig. 4-17), the crystal will grow and an appreciable amount of one active form may thus be separated from the racemic mixture. This type of resolution is also applicable to racemic compounds, provided that the compound is more soluble than either of the pure enantiomers. If no crystal of either pure enantiomer is available for inoculation, a crystal of another optically active substance may sometimes serve as a seed. For example, (+)-sodium ammonium tartrate can be crystallized from a solution of the racemic modification not only by inoculation with a crystal of the (+) salt but also by inoculation with (-)-asparagine,  $\text{H}_2\text{NCOCH}_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ . Sometimes inoculation may even be effected with an optically inactive substance; for example,<sup>17</sup> active asparagine has been crystallized from solutions of the racemic modification by inoculation with crystals of glycine,  $\text{H}_2\text{NCH}_2\text{CO}_2\text{H}$ .<sup>†</sup> In a few instances, spontaneous crystallization‡ of active material from solutions of the *dl* form has been observed.<sup>18</sup>

Crystallization methods by themselves are rarely practical methods of resolution, but they are often used in a practical way in conjunction with other methods. For example, phenylmethylcarbinyl hydrogen phthalate,

<sup>†</sup> The success of this experiment has been attributed (Ref. 17) to the possibility that glycine, although a symmetric molecule, might, like quartz, form dissymmetric crystals. In fact, although the ordinary or alpha modification of glycine is symmetric [G. Albrecht and R. B. Corey, *J. Am. Chem. Soc.*, **61**, 1087 (1939)], another crystalline modification, called gamma, exists which is dissymmetric [Y. Itaka, *Acta Cryst.*, **11**, 225 (1958)].

<sup>‡</sup> Surprisingly, K. Vogler and M. Kofer [*Helv. Chim. Acta*, **39**, 1387 (1956)] have reported the resolution of 3,3-diethyl-5-methyl-2,4-diketopiperidine which forms a racemic solid solution by this method.

<sup>16</sup> M. Gernez, *Compt. rend.*, **63**, 843 (1866). See also G. Amiard, R. Joly, and L. Velluz, U.S. Patent 2,734,919 (1956), *Chem. Abstr.*, **50**, 16857b (1956); British Patents 829,938 and 829,939 (to E. I. du Pont de Nemours and Co.) (1960), *Chem. Abstr.*, **54**, 17283f (1960). H. E. Zaugg, *J. Am. Chem. Soc.*, **77**, 2910 (1955).

<sup>17</sup> I. Ostromisslensky, *Ber.*, **41**, 3035 (1908).

<sup>18</sup> (a) R. C. Ferreira, *Nature*, **171**, 39 (1953); (b) E. Havinga, *Biochim. et Biophys. Acta*, **13**, 171 (1954).



after being resolved to the extent of about 95% or so by means of brucine (Sec. 4-4*b*) is dissolved in carbon disulfide and seeded with a small crystal of the racemic compound. In this particular case, the racemic compound is less soluble than the enantiomers (cf. Fig. 4-18) and so most of the excess of it left in the resolved phthalate crystallizes out. The mother liquor is decanted and petroleum ether added to it, whereupon the enantiomeric phthalate crystallizes in turn. In other cases, where a racemic mixture is formed or where the racemic compound is more soluble than the enantiomers, the active form may be purified by crystallization, any residual racemic material remaining in the mother liquor (cf. Fig. 4-17). This is a very common way of further purifying active material which has already been partially resolved to a considerable extent by one of the methods to be discussed below.

**b. Resolution by Formation of Diastereoisomers.<sup>94</sup> Second-order Asymmetric Transformations.** When a racemic modification is allowed to interact with an optically active material to give a derivative (such as a salt), in actual fact two diastereoisomeric derivatives result. For example, in a reaction of a racemic acid ( $\pm$ )-A with an active base, (-)-B, the individual molecules of the acid are either (+) or (-), and, therefore, the individual molecules of the salt formed are either (+)-A·(-)-B or (-)-A·(-)-B. These two types of salt molecules are evidently no longer enantiomers, but diastereoisomers. Therefore, they have different properties and may, in general, be separated on the basis of this difference in properties. Although distillation<sup>19</sup> and chromatographic separation<sup>20, 95</sup> have been employed,† the most efficient method of separating such diastereoisomers is by crystallization. This is because, as already mentioned, crystal structure is apt to be particularly sensitive to minor variations in molecular architecture (such as the difference between diastereoisomers).

Several conditions should be fulfilled by a good resolving agent. First, the compound between the resolving agent and the substance to be resolved should be easily formed and should also be easily broken up, for once one of the diastereoisomers, e.g., (-)-A·(-)-B, is obtained in the pure state, it must be decomposed chemically so that pure (-)-A may be recovered. This condition is generally met by salts, which are usually formed readily by mixing the organic acid and base in a solvent and may be decomposed, following resolution, by treatment with mineral acid (if the organic acid is to be recovered) or mineral base (if the organic base is desired). It is easiest, therefore, to resolve acids (carboxylic or sulfonic) or amines. Other substances, to be resolved, must often be transformed first into an acid, as will be explained further below, or else synthesized from a resolved acid or base

† Gas chromatography in particular may provide a useful separation method for diastereoisomers. It has been applied to the resolution of ( $\pm$ )-camphor through separation of the ketals formed with (-)-2,3-butanediol: J. Casanova and E. J. Corey, *Chemistry & Industry (London)*, 1664 (1961).

<sup>19</sup> M. E. Bailey and H. B. Hass, *J. Am. Chem. Soc.*, 63, 1969 (1941).

<sup>20</sup> M. M. Jamison and E. E. Turner, *J. Chem. Soc.*, 611 (1942).

(Sec. 5-5). Secondly, the compound between the resolving agent and substance to be resolved must be nicely crystalline,<sup>†</sup> and there must be an appreciable difference in solubility between (+)-A·(-)-B and (-)-A·(-)-B.<sup>‡</sup> Whether this condition is fulfilled depends on both the nature of A and B and the solvent chosen. Unfortunately, resolution is, in this respect, still very much a matter of trial and error, and even in the papers of experienced investigators one is apt to find, from time to time, a statement that a certain compound resisted resolution by any one of a large number of combinations of resolving agents and solvents that were tried. The best hint that can be given for resolution of, let us say, an acid A is to use a base B and a solvent which have been found successful in the past in the resolution of a similar acid A'. The difficulty with this hint lies in the word "similar." For example, it might have been thought that mandelic acid, C<sub>6</sub>H<sub>5</sub>CHOHCO<sub>2</sub>H, and atrolactic acid, C<sub>6</sub>H<sub>5</sub>C(CH<sub>3</sub>)OHCO<sub>2</sub>H, are similar, but whereas the former may be readily resolved by means of the commercially available (-)-ephedrine in aqueous alcoholic solution, the same resolving agent fails for atrolactic acid, and one has to resort to the (not commercially available) α-phenethylamine. Sometimes, even though (+)-A·(-)-B and (-)-A·(-)-B are, individually, nicely crystalline salts of well-differentiated solubility in a given solvent, resolution of (±)-A by (-)-B in the same solvent fails because of formation of a double salt (+)-A·(-)-B·(-)-A·(-)-B (in principle, similar to other types of double salts).<sup>¶</sup> This case occurs, for example, in the attempted resolution<sup>21</sup> of β-pipecoline (Fig. 4-21) by means of tartaric acid.<sup>§</sup>

<sup>†</sup> It is well to keep in mind that the process of resolution involves crystallization of the desired substance, for example, (-)-A·(-)-B, in the presence of an *equal amount* of an undesirable impurity, (+)-A·(-)-B!

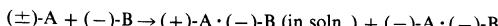
<sup>‡</sup> Occasionally, it is possible to crystallize one diastereoisomer from a solution supersaturated with respect to both. For example, when α-phenethyl hydrogen phthalate,



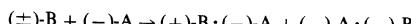
is treated with brucine in acetone solution, the salt of the (-)-phthalate with brucine precipitates more readily. Once this is filtered off, however, the filtrate deposits crystals of the (+)-phthalate brucine salt. When crystallization is not carried out carefully, both diastereoisomeric salts may crystallize together, thus spoiling the resolution process.

<sup>¶</sup> In other cases, only partial resolution can be achieved because a salt of the type 2(+)-A·(-)-B·(-)-A·(-)-B (or similar type) crystallizes.

<sup>§</sup> Because of the possibility of formation of such complexes, one cannot conclude that successful resolution of (±)-A with, say, (-)-B implies that (±)-B can be resolved with, say, (-)-A (Ref. 96). For assume:



where the latter salt crystallizes out. Also,



Now (+)-B·(-)-A has the same solubility as (+)-A·(-)-B (since they are enantiomers), and it would appear at first sight that, if the first resolution succeeds because (-)-A·(-)-B is less soluble than (+)-A·(-)-B, the second resolution should also succeed. The flaw is that (-)-A·(-)-B is a dissymmetric molecule and therefore may form a molecular complex with (+)-B·(-)-A (precluding resolution) although it does not form a complex with (-)-B·(+)-A. Thus, no prediction can, in principle, be made regarding the feasibility of resolving (±)-B with (-)-A (Ref. 96).

<sup>21</sup> A. Ladenburg, *Ber.*, 27, 75 (1894).

A third condition for a resolving agent is that it be either cheap or readily prepared or else readily and nearly quantitatively recoverable after completion of the resolution. If this condition is not fulfilled, the resolution, at least on a large scale, becomes excessively tedious or expensive. Among the bases, many alkaloids, such as brucine, strychnine, ephedrine, etc., are relatively inexpensive and also readily recoverable after resolution.<sup>†</sup> Quinine seems to be an exception in that it has a tendency to deteriorate on attempted recovery. Among the acids, (+)-10-camphorsulfonic acid is relatively inexpensive. (+)-Tartaric acid is so cheap that recovery may be forgone. On the other hand, active malic acid is very expensive and, since it is also hard to recover (being quite water-soluble), it is not a useful resolving agent except on a small scale.

A useful basic resolving agent which can be prepared readily in the laboratory is  $\alpha$ -phenethylamine,  $C_6H_5CH(NH_2)CH_3$ . The *dl* form of this material is commercially available (1960). Resolution according to the original procedure<sup>22</sup> required the very expensive (−)-malic acid and was prohibitive on a large scale. An improved procedure<sup>23</sup> used pyroglutamic acid (pyrrolidone-5-carboxylic acid; cf. Fig. 4-23) which can be prepared by a carefully controlled pyrolysis of the relatively cheap (+)-glutamic acid,



but is difficult to recover from the resolution. Finally, a very simple resolution of  $\alpha$ -phenethylamine using the cheap (+)-tartaric acid has been devel-

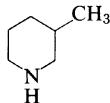


Fig. 4-21.  $\beta$ -Pipecoline.

oped,<sup>24</sup> and the active amine may now be considered readily available. The amine may also be resolved via the insoluble complex that the (+)-antipode forms with 2,3,4,6-tetraacetyl-D-glucose.<sup>24a</sup>

A fourth, though not absolutely indispensable, condition for a resolving agent is that it should be available in the optically pure state. For, in principle, the substance to be resolved cannot be obtained in a higher state of optical purity than the resolving agent by mere crystallization of diastereoisomers. Suppose that a basic resolving agent (−)-B is 90% optically pure, i.e., that it consists of 90% (−)-B and 10% ( $\pm$ )-B. This means that, of any

<sup>†</sup> The salt of the alkaloid with the acid resolved by it is decomposed by pouring it, in alcoholic solution, into dilute aqueous hydrochloric acid and filtering or extracting the organic acid liberated. The alkaloid stays in the aqueous-alcoholic layer as hydrochloride and may be liberated and recovered by addition of ammonia.

<sup>22</sup> A. W. Ingersoll, *Org. Syntheses*, Coll. Vol. II, p. 506 (1943), after J. M. Lovén, *Ber.*, **29**, 2313 (1896).

<sup>23</sup> R. J. Dearborn and J. A. Stekol, U.S. Patent 2,528,267 (1950), *Chem. Abstr.*, **45**, 2984c (1951).

<sup>24</sup> W. Theilacker and H. G. Winkler, *Chem. Ber.*, **87**, 690 (1954).

<sup>24a</sup> B. Helferich and W. Portz, *Chem. Ber.*, **86**, 1034 (1953).

100 molecules, 95 are  $(-)$ -B and 5 are  $(+)$ -B.<sup>†</sup> If 200 molecules of  $(\pm)$ -(A) are combined with 200 molecules of this base, one will actually have 100 molecules of  $(+)$ -A, 100 molecules of  $(-)$ -A, 190 molecules of  $(-)$ -B, and 10 molecules of  $(+)$ -B. Assuming statistical combination, one will then get 95 molecules of  $(+)$ -A  $\cdot$   $(-)$ -B, 95 molecules of  $(-)$ -A  $\cdot$   $(-)$ -B, 5 molecules of  $(+)$ -A  $\cdot$   $(+)$ -B, and 5 molecules of  $(-)$ -A  $\cdot$   $(+)$ -B. Suppose, further, that  $(+)$ -A  $\cdot$   $(-)$ -B is the less soluble diastereoisomer and that  $\frac{3}{5}$  of it or  $\frac{3}{5} \times 95$  or 57 molecules of this diastereoisomer are recovered after several recrystallizations. Now, since  $(-)$ -A  $\cdot$   $(+)$ -B is enantiomeric with  $(+)$ -A  $\cdot$   $(-)$ -B, it has just the same solubility as the latter, and therefore  $\frac{3}{5}$  of it or  $\frac{3}{5} \times 5$  or 3 molecules will be found in the final crystallizate along with 57 molecules of  $(+)$ -A  $\cdot$   $(-)$ -B. After decomposition of the salt, there will be 57 molecules of  $(+)$ -A and 3 molecules of  $(-)$ -A; i.e., 95% of all molecules will be  $(+)$ -A and 5% will be  $(-)$ -A. But this means that resolution has proceeded to the extent of 90%.<sup>‡</sup> i.e., to the extent of the optical purity of the resolving agent.

In practice, this limitation is not always a serious one. To begin with, one does not always need optically pure materials; i.e., it may not be necessary to achieve complete resolution. Secondly, after extensive resolution has been achieved, the enantiomers can often be further purified by crystallization, as described in Sec. 4-4a.

Most naturally occurring resolving agents (such as alkaloids) are readily obtained optically pure, but resolving agents prepared in the laboratory, especially if liquids, such as  $\alpha$ -phenethylamine, can be obtained optically pure only with some difficulty.

In the following paragraphs, the resolution of specific types of organic compounds will be discussed. The list of resolving agents is not meant to be exhaustive—only the more common types are mentioned. No specific directions for the resolution of individual compounds will be given here; for these the reader is referred to some of the reference works listed at the end of the chapter (e.g., Ref. 94) and to the original literature.<sup>¶</sup>

*i. Acids.* The alkaloids brucine, strychnine, ephedrine, quinine, quinidine, cinchonine, cinchonidine, and morphine have been frequently used to resolve optically active acids. Certain synthetic bases, such as  $\alpha$ -phenethylamine, menthylamine (prepared from natural, optically active menthol), and amphetamine are also useful. The formulas of most of these are shown in Fig. 4-22.

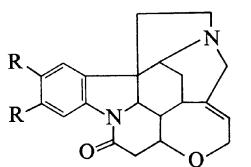
*ii. Bases.* The camphor derivatives camphor-10-sulfonic acid,  $\alpha$ -bromocamphor- $\pi$ -sulfonic acid, hydroxymethylene camphor, and camphoric acid; the menthol derivative menthoxyacetic acid; and the naturally occurring

<sup>†</sup> The reader should note the general proposition that  $x\%$  of racemic modification and  $(100 - x)\%$  of an active form, say the  $(-)$  form, correspond to  $x/2$  molecules of the  $(+)$  form and  $(100 - x/2)$  molecules of the  $(-)$  form. This is, of course, because the racemic modification is only a statistical aggregate and has no meaning on the molecular scale. In the limiting case, when  $x = 100$ , i.e., one is dealing only with the racemic modification, there are 50 (i.e., 100%) molecules of the  $(+)$  form and 50 ( $100 - 100\%$ ) molecules of the  $(-)$  form.

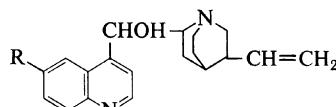
<sup>‡</sup> Considering 95 molecules of  $(+)$ -A and 5 molecules of  $(-)$ -A as 90 parts of  $(+)$  isomer and 10 parts of  $(\pm)$  isomer.

<sup>¶</sup> Resolution is still largely an experimental art. Sometimes procedures in the literature are difficult to repeat, and frequently a skilled experimenter may devise techniques superior to those previously described.

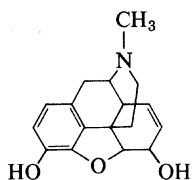
active forms of tartaric acid and malic acid have been used for resolution, among other acids. Also useful are diacetyltaurine, obtained by acetylation of taurine; pyrrolidine-5-carboxylic acid, obtained by pyrolysis of naturally occurring optically active glutamic acid; and certain acetyl derivatives of amino acids.<sup>25</sup> Glutamic acid itself, having one free as well as one zwitterionic carboxyl group, may function as an acidic resolving agent; it is used in the commercial resolution of lysine.



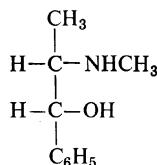
$R = H$  Strychnine  
 $R = CH_3O$  Brucine



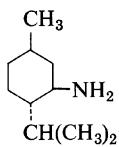
$R = H$  Cinchonine, cinchonidine  
 $R = CH_3O$  Quinine, quinidine



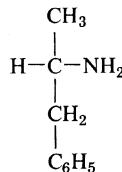
Morphine



(-)-Ephedrine



Menthylamine



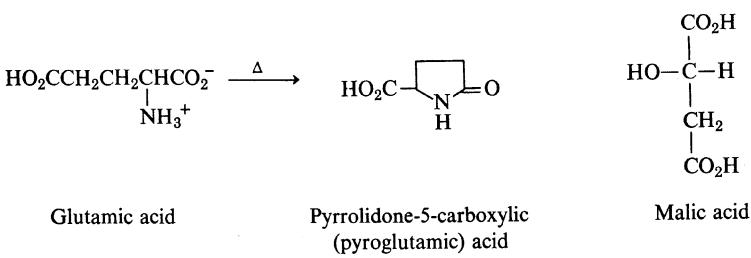
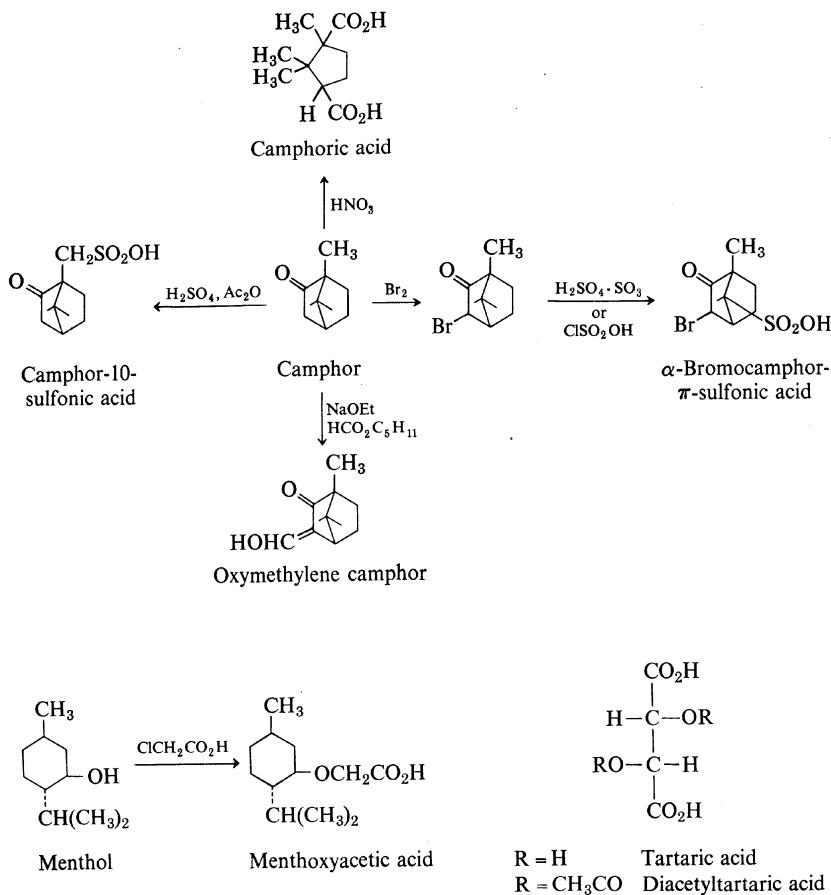
Amphetamine

Fig. 4-22. Formulas of common basic resolving agents.

The formulas of some of these resolving agents are shown in Fig. 4-23.

*iii. Amino Acids.* Because of their dipolar character, amino acids cannot usually be resolved, as such, using either optically active acids or active bases as resolving agents. A few exceptions are known; thus phenylglycine,  $C_6H_5CH(NH_2)CO_2H$ , has been resolved using camphor-10-sulfonic acid (which is a very strong acid). Some basic amino acids, which contain a free as well as a zwitterionic amine function, have been resolved by means of

<sup>25</sup> H. D. DeWitt and A. W. Ingersoll, *J. Am. Chem. Soc.*, 73, 5782 (1951).

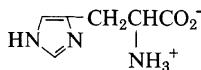


**Fig. 4-23.** Formulas of common acid resolving agents.

organic acids; thus (+)-tartaric acid has been employed to resolve ( $\pm$ )-histidine (Fig. 4-24), and ( $\pm$ )-lysine may be resolved by means of (+)-glutamic acid.

Commonly, however, amino acids are resolved in the form of their acyl derivatives, which are no longer endowed with zwitterionic properties and may therefore be resolved as typical acids. The classical example is alanine which was resolved in the form of its benzoyl derivative (Fig. 4-24) by Emil Fischer.<sup>26</sup> Crystallization of the brucine salt yielded the benzoyl derivative of (-)-alanine, whereas the strychnine salt gave the derivative of (+)-alanine. In the removal of the benzoyl group from the resolved derivative (by acid hydrolysis), some racemization occurred (note that the hydrogen on the asymmetric carbon is activated by the adjacent carbonyl group; cf. page 35). This difficulty can be largely avoided by subjecting the formyl derivative (Fig. 4-24) to resolution. Removal of the formyl group is effected under very mild conditions and does not lead to racemization of the resolved material.

*iv. Alcohols.*<sup>86</sup> Alcohols are most often resolved by prior conversion to their acid phthalate or succinate esters, formed by treating the alcohol with



Histidine

*N*-Benzoylalanine*N*-Formylalanine

Fig. 4-24. Some amino acids and derivatives thereof.

phthalic or succinic anhydride and pyridine. These half-esters are then resolved as typical acids, e.g., by means of the alkaloids brucine and cinchonidine. The pure diastereoisomeric salts, obtained after repeated recrystallization, are decomposed in the usual way (best by dissolution in methanol, pouring into dilute aqueous hydrochloric acid, and extraction of the phthalate precipitated with ether). The half-ester is then either saponified by treatment with hot aqueous sodium hydroxide, or, if there is any danger of racemization by base, the alcohol may be recovered from the half-ester by lithium aluminum hydride reduction. The phthalyl alcohol formed as a by-product in the case of hydride reduction of acid phthalates is very high-boiling so that the resolved alcohol can usually be separated from it by vacuum distillation. The by-product in the reduction of succinates is the very water-soluble 1,4-butanediol. The chemistry of these processes (phthalate case) is summarized in Fig. 4-25.

An alternative method of resolving alcohols and phenols is to convert them to esters of optically active acids. The usefulness of this method is

<sup>26</sup> E. Fischer, *Ber.*, **32**, 2451 (1899).

limited because relatively few esters are satisfactorily crystalline. Tartranilic acid, methyl isocyanate, and menthoxyacetyl chloride (all derivatives of naturally occurring active substances) are among the reagents that have been used to resolve alcohols; the formulas of these compounds and the derivatives that they form with alcohols are shown in Fig. 4-26.  $3\beta$ -Acetoxy- $\Delta^5$ -etiochenic acid (Fig. 4-26) forms nicely crystalline esters;<sup>26a</sup> a convenient preparation of this acid has been described.<sup>26b</sup>

Alcohols have also been resolved through the formation of glycosides, using as resolving agent acetobromoglucose.<sup>26c</sup>

v. *Aldehydes and Ketones.* The need for optically active carbonyl compounds does not arise frequently, and if it does, they are often best obtained by synthesis (cf. Sec. 5-5). A few derivatives of naturally active substances, such as menthylsemicarbazide, menthyldihydrazine, and tartramic acid hydrazide (Fig. 4-27) have been used to resolve carbonyl compounds. The

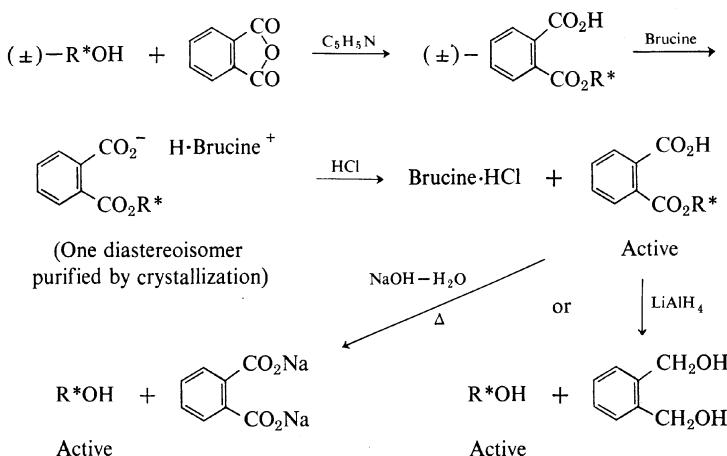
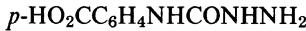


Fig. 4-25. Resolution of alcohols.

compounds that these reagents form with carbonyl compounds are all of the hydrazone type. They are sometimes hard to cleave without danger of racemization of the carbonyl moiety, especially if the active center is enolizable, i.e., if it is adjacent to the carbonyl function and bears a hydrogen, as in phenyl *sec*-butyl ketone,  $C_6H_5COCH(CH_3)C_2H_5$ .

An alternative way of resolving carbonyl compounds, akin to the resolution of alcohols described above, involves their conversion into 4-carboxyphenylsemicarbazones by means of 4-(4-carboxyphenyl)semicarbazide,



<sup>26a</sup> R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

<sup>26b</sup> C. Djerassi and J. Staunton, *J. Am. Chem. Soc.*, **83**, 736 (1961).

<sup>26c</sup> C. Neuberg, K. P. Jacobson, and J. Wagner, *Fermentforschung*, **10**, 491 (1929); B. Helferich and R. Hiltman, *Ber.*, **70**, 308 (1937).

These semicarbazones, which are acidic, are then resolved by means of brucine and, after resolution, are hydrolyzed back to the (optically active) carbonyl precursor.<sup>26d</sup>

*vi. Miscellaneous.* Compounds devoid of functional groups, such as saturated hydrocarbons, or possessing only weakly reactive functional groups, such as unsaturated and aromatic hydrocarbons, ethers, alkyl halides, and a variety of sulfur compounds† present a special problem in resolution. Often

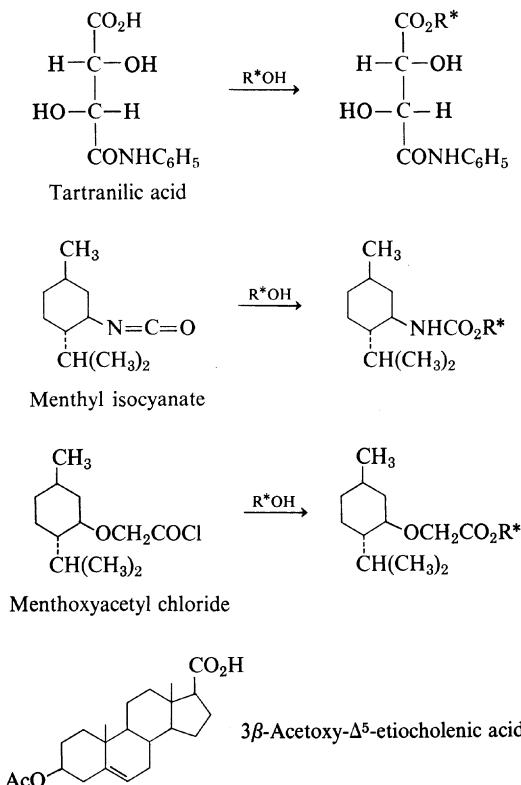


Fig. 4-26. Further resolving agents for alcohols.

† It is recognized, of course, that olefins, aromatics, and alkyl halides are perfectly respectable reagents in such reactions as addition, electrophilic substitution, and nucleophilic displacement, respectively. Up to now, however, these processes have not been exploited for purposes of resolution, either because appropriate optically active reagents are not available or because the reactions cannot be reversed at all readily.

<sup>26d</sup> J. K. Shillington, G. S. Denning, W. B. Greenough, T. Hill, and O. B. Ramsay, *J. Am. Chem. Soc.*, **80**, 6551 (1958).

it is better to synthesize such compounds in the active form, starting out with naturally active or resolved starting materials (cf. Sec. 5-5). A few special methods of resolution applicable to such compounds (and some others) are, however, available.

**RESOLUTION VIA MOLECULAR COMPLEXES.** When a *dl* pair is treated with a dissymmetric reagent with which it can form a crystalline complex compound, it may happen that the resulting two diastereoisomeric complexes are of different solubility and that one will precipitate in preference to the other. Decomposition of the complex by heating, dissolution, chromatography, or chemical treatment will then yield one of the enantiomers of the original substrate. Thus digitonin, a steroidal saponin, has been used to resolve terpineol,<sup>27</sup> (+)-2-naphthylcamphylamine has been used to resolve *N*-sec-butylpicramide,<sup>28</sup> and  $\alpha$ -(2,4,5,7-tetranitrofluorenylideneaminoöxy)propionic acid has been used to resolve 1-naphthyl sec-butyl ether.<sup>29</sup> The formulas of some of these resolving agents and the substances resolved are shown in Fig. 4-28.

A somewhat different type of resolution has been effected through the so-called clathrate or inclusion complexes. This type of complex is formed

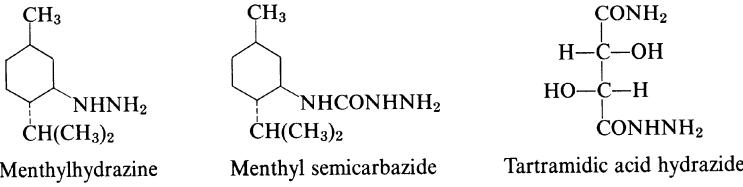


Fig. 4-27. Resolving agents for carbonyl compounds.

from a component that crystallizes in such a way as to leave a hole into which the other component may fit if it is of suitable size. The formation of the complex seems to depend on relative molecular dimensions rather than on any particular chemical affinity. One compound which has been used in this way is desoxycholic acid (Fig. 4-28), used in the resolution of camphor and the partial resolution of dipentene.<sup>30</sup> The inclusion compounds of desoxycholic acid are called "choleic acids."

A more unusual substance used for the same purpose is tri-*o*-thymotide (Fig. 4-29).<sup>31</sup> This molecule has the shape of a three-bladed propeller and may therefore exist in two enantiomeric forms. In solution it racemizes rapidly by transformation of one form into the other, but, upon crystallization, it may again be obtained optically active through preferential crystal-

<sup>27</sup> A. Windaus, F. Klähnhardt, and R. Weinhold, *Z. physiol. Chem.*, **126**, 308 (1923).

<sup>28</sup> R. Weiss and A. Abeles, *Monatsh.*, **59**, 238 (1932).

<sup>29</sup> M. S. Newman, W. B. Lutz, and D. Lednicer, *J. Am. Chem. Soc.*, **77**, 3420 (1955); M. S. Newman and W. B. Lutz, *ibid.*, **78**, 2469 (1956).

<sup>30</sup> H. Sobotka, *Naturwiss.*, **19**, 595 (1931); H. Sobotka and A. Goldberg, *Biochem. J.*, **26**, 905 (1932).

<sup>31</sup> H. M. Powell, *Nature*, **170**, 155 (1952).

lization of one of the enantiomers as a solvate (a kind of spontaneous resolution). When it is crystallized from a solvent possessing an asymmetric carbon atom, such as 2-bromobutane,  $\text{CH}_3\text{CHBrCH}_2\text{CH}_3$ , the crystals, in addition to containing only one form of the thymotide, also contain a predominance of one enantiomer of the solvent 2-bromobutane, which may thus be partially resolved.

An even more surprising case<sup>32</sup> is the resolution of 2-chlorooctane,  $\text{CH}_3\text{CHClC}_6\text{H}_{13-n}$ , by means of urea,  $\text{H}_2\text{NCONH}_2$ . Urea is not, of course, an asymmetric molecule but it crystallizes in spiral-shaped asymmetric crys-

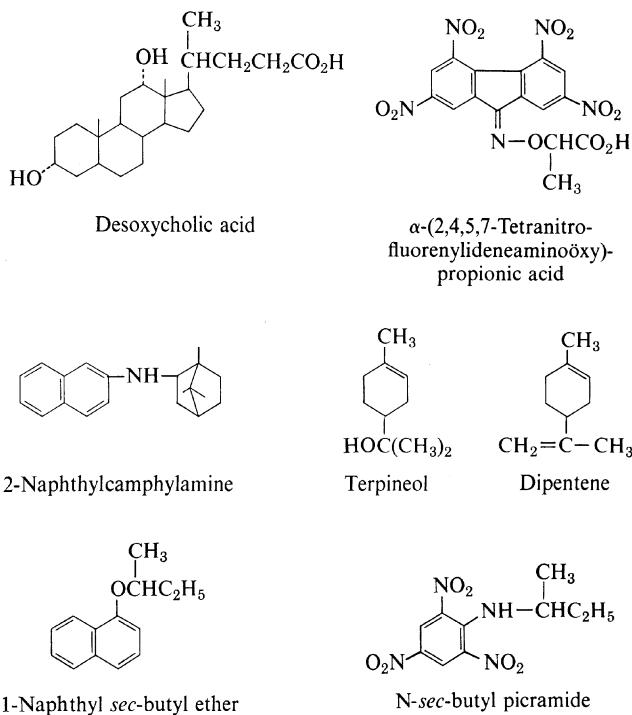


Fig. 4-28. Resolution by complex formation; reagents and compounds resolved.

tals. Depending on the "handedness" (hemihedric properties) of the crystal, one or another of the enantiomers of 2-chlorooctane will fit preferentially into the lattice and will thus be enriched in the inclusion compound. This type of resolution is somewhat hard to effect, since it depends on the preferential formation of one type of hemihedric urea crystal over the other (for which there is no a priori reason) by fortuitous inoculation with only one type of seed followed by undisturbed crystal growth.

<sup>32</sup> W. Schlenk, *Experientia*, 8, 337 (1952).

The above-mentioned inclusion compounds are "lattice inclusion compounds"; i.e., the canals in which the guest molecules are contained are formed by the crystal lattice of the host. There is another type, so-called "molecular inclusion compounds," in which the canals are within one host molecule. This evidently requires a large molecule, and one that has been used in resolution is cyclodextrin.<sup>33</sup> Ethyl mandelate,  $C_6H_5CHOHCO_2C_2H_5$ , and ethyl phenylchloroacetate,  $C_6H_5CHClCO_2C_2H_5$ , are among the compounds which have been resolved via their cyclodextrin inclusion compounds.<sup>33</sup>

Some further aspects of resolution by crystallization of diastereoisomers must now be considered. One of the principal difficulties of this method is that generally only one diastereoisomer (the less soluble one) can be obtained from solution in the pure state. The other diastereoisomer is apt to stay in the mother liquor contaminated with a residue of the less soluble material, and decomposition of such a mixture will evidently not give enantiomerically pure material. Thus, the common situation in resolution is that one enantiomer may be obtained pure or nearly so whereas the other is recovered in a

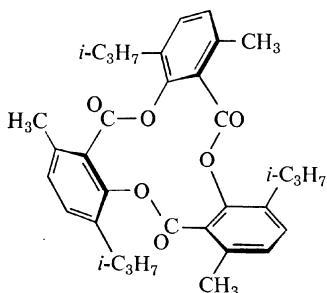


Fig. 4-29. Tri-*o*-thymotide. (From M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley & Sons, Inc., New York, 1956. By permission of the publishers.)

far from optically pure state. From the practical point of view this is not always too serious a drawback, since it is rarely necessary to have both enantiomers pure. However, sometimes one *does* want both enantiomers pure, and in any case, if both are obtained pure, this provides a useful check on the optical rotation of the substance (cf. Sec. 4-5).

Sometimes, such as in the case of  $\alpha$ -phenethyl hydrogen phthalate, the second diastereoisomer may crystallize from the mother liquor in a state of relatively high purity after the first diastereoisomer has been removed. In other cases, crystallization of the second diastereoisomer can be brought about by distilling off the original solvent and adding a new solvent. Such cases are, however, rare.

One obvious way (first suggested by Marckwald<sup>34</sup>) of obtaining the second enantiomer in a pure state is to use the antipode of the original resolving

<sup>33</sup> F. Cramer, *Angew. Chem.*, **64**, 136 (1952); F. Cramer and W. Dietsche, *Chem. Ber.*, **92**, 378 (1959).

<sup>34</sup> W. Marckwald, *Ber.*, **29**, 43 (1896).

agent. For if  $(+)-A \cdot (-)-B$  is less soluble than  $(-)-A \cdot (-)-B$  in the resolution of  $(\pm)-A$  by  $(-)-B$ , by the same token  $(-)-A \cdot (+)-B$  will be less soluble than  $(+)-A \cdot (+)-B$ . Thus,  $(+)-B$  may be used to complete the resolution of the impure  $(-)-A$  recovered from the mother liquors of the resolution of  $(+)-A$  [by  $(-)-B$ ]. The serious drawback of this method is that many resolving agents are natural products and their enantiomers are not usually available. Synthetic resolving agents, such as  $\alpha$ -phenethylamine, are useful for the application of Marckwald's method but suffer from the difficulty that both enantiomers of the resolving agent must first be prepared in the pure state.

In most cases, it is necessary to use a second resolving agent to complete the resolution of the impure second enantiomer. To do this, the first resolving agent is removed from the mother liquor of the original resolution by stripping solvent and adding acid (to remove basic resolving agent) or base (to remove acidic resolving agent), and the impure second enantiomer is recovered by filtration or extraction. A new resolution is then carried out in the usual way, by the same method of trial and error as the original resolution, but with the advantage that the material to be resolved is already enriched in the desired enantiomer and that therefore in the second resolution, unlike the original one, the desired diastereoisomer is formed in excess

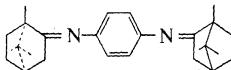


Fig. 4-30. *p*-Phenylene-bis-iminocamphor.

over the undesired one. Quite a number of resolutions have been completed in this way.

Two further variations of the resolution procedure, that devised by Pope and Peachey<sup>35</sup> and that studied by Ingersoll and coworkers,<sup>36</sup> are used only rarely; for a detailed summary the reader is referred elsewhere.<sup>37</sup>

**RESOLUTION BY CHROMATOGRAPHY.**<sup>35, 37</sup> If an optically active adsorbent, say  $(-)-A$ s., is used for chromatographing a raceme,  $(\pm)-X$ , the individual molecules form adsorbates  $(-)-A$ s.  $\cdot$   $(-)-X$  and  $(-)-A$ s.  $\cdot$   $(+)-X$ . Since these adsorbates are diastereoisomeric, they are not equally stable; i.e., one enantiomer (the one forming the less strong adsorbate) passes through the column faster than the other. Partial resolution may thus be achieved. An example<sup>38</sup> is the resolution of *p*-phenylene-bis-iminocamphor (Fig. 4-30) on a lactose column. The method is particularly useful to decide whether a given compound is a *dl* pair or an inherently inactive species. If its solution, upon percolation through a column of active adsorbent (assumed to be completely insoluble in the solvent used), becomes active, the material is a *dl* pair. Failure to obtain an active eluate is not conclusive; it means either that the sub-

<sup>35</sup> W. J. Pope and S. J. Peachey, *J. Chem. Soc.*, **75**, 1066 (1899).

<sup>36</sup> For example, A. W. Ingersoll and J. R. Little, *J. Am. Chem. Soc.*, **56**, 2123 (1934).

<sup>37</sup> Ref. 85, pp. 257-258.

<sup>38</sup> G. M. Henderson and H. G. Rule, *Nature*, **141**, 917 (1938); *J. Chem. Soc.*, 1568 (1939).

strate possesses symmetry or that this particular method of resolution failed completely. This type of resolution should be distinguished from resolution by separating diastereoisomers on an ordinary (inactive) column, such as alumina (page 49). It may better be regarded as equilibrium asymmetric transformation (Sec. 4-4c).

Instead of using an optically active adsorbent, it is possible to modify the surface of an inactive adsorbent by treatment with an active compound in such a way that the inactive adsorbent will acquire selectivity for one enantiomer over the other. Thus a column of silica gel made by reaction of sodium silicate with (+)-camphorsulfonic acid was found<sup>38a</sup> to adsorb (+)-camphorsulfonic acid in preference to the (-) enantiomer. When a solution of ( $\pm$ )-camphorsulfonic acid was passed through such a column, the first eluate was considerably enriched in the (-) form.

Types of chromatography other than that on a column have been successfully used in resolution. Paper chromatography<sup>39</sup> on No. 4 Whatman filter paper led to separation of ( $\pm$ )-2,3-dihydroxy- $\beta$ -phenylalanine,



into two distinct spots.<sup>39c</sup> The adsorbent here is, of course, the optically active cellulose. Attempted resolution of racemic amines on optically active ion-exchange resins was initially unsuccessful,<sup>40a</sup> but more recently separations have been claimed, for example, of the enantiomers of ( $\pm$ )-mandelic acid on a resin prepared from chloromethylated styrene-divinylbenzene copolymer treated with (-)- $\alpha$ -phenethylamine.<sup>40b</sup> Gas chromatography has also been adapted to the separation of enantiomers, partial resolution of 2-butanol (among other substances) having been achieved on a stationary phase of (-)-ethyl tartrate.<sup>40c</sup>

OTHER METHODS OF PHYSICAL SEPARATION. Resolution of racemates of optically stable<sup>†</sup> compounds by crystallization from optically active solvents is usually unsuccessful.<sup>41a</sup> Success may, however, be achieved in cases where the solvent and the substrate to be resolved can associate at two different sites,<sup>‡</sup> for example, in the resolution of 2,3-dibromo-1,4-butanediol through crystallization from (+)-diisopropyl tartrate.<sup>41b</sup>

A somewhat unusual method of resolution is dialysis through an optically active membrane,<sup>42</sup> which has been used to separate the enantiomers of tartaric acid.

<sup>†</sup> As distinct from the optically labile compounds to be described in the next section.

<sup>‡</sup> A similar condition—association at more than one site—may be necessary for successful resolution by chromatography; cf. C. E. Dalgliesh, *J. Chem. Soc.*, 3940 (1952), and H. Krebs, J. A. Wagner, and J. Diewald, *Chem. Ber.*, **89**, 1875 (1956).

<sup>38a</sup> R. Curti and U. Colombo, *J. Am. Chem. Soc.*, **74**, 3961 (1952).

<sup>39</sup>(a) M. Kotake, T. Sakan, N. Nakamura, and S. Senoh, *J. Am. Chem. Soc.*, **73**, 2973 (1951); (b) M. Mason and C. P. Berg, *J. Biol. Chem.*, **195**, 515 (1952); (c) C. E. Dalgliesh, *J. Chem. Soc.*, 3940 (1952).

<sup>40</sup>(a) J. F. Bunnett and J. L. Marks, *J. Am. Chem. Soc.*, **74**, 5893 (1952); (b) S. Tsuboyama and M. Yanagita, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **53**, 245 (1959); (c) G. Karagounis and G. Lippold, *Naturwiss.*, **46**, 145 (1959).

<sup>41</sup>(a) C. Buchanan and S. H. Graham, *J. Chem. Soc.*, 500 (1950); (b) A. Lüttringhaus and D. Berr, *Tetrahedron Letters*, no. 10, 10 (1959).

<sup>42</sup> V. O. G. Klingmüller and G. Gedenk, *Nature*, **179**, 367 (1957).

SECOND-ORDER ASYMMETRIC TRANSFORMATION.<sup>91</sup> The maximum theoretical yield of pure enantiomer in a resolution based on the original weight of ( $\pm$ ) material is obviously 50%, and yields of 25 to 30% are usually considered quite satisfactory. Nevertheless, resolutions have been described in which a nearly 100% yield of one form has been obtained as a crystalline diastereoisomer with the resolving agent. One of the early clear-cut cases is the resolution<sup>43</sup> of 2-(*p*-carboxybenzyl)hydrindanone-1 (Fig. 4-31). When the racemic form was treated with brucine in acetone solution at room temperature, one pure diastereoisomer precipitated in over 90% yield. Upon decomposition with mineral acid, this material gave the (+) enantiomer of the free acid I which, however, lost activity quite rapidly on standing. One is dealing here with a combination of resolution by preferential crystallization of one diastereoisomer and epimerization. The salt (+)-I·(-)-brucine is less soluble in acetone and crystallizes out, but as it does so, more (+)-I·(-)-brucine is formed from (-)-I·(-)-brucine by a process of epimerization involving the enolizable hydrogen marked in Fig. 4-31. The epimerization process itself involves an equilibrium (cf. page 39), but since

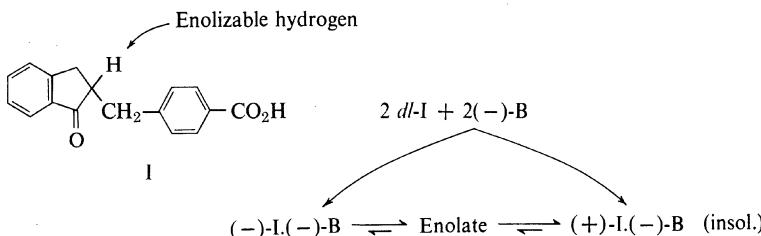


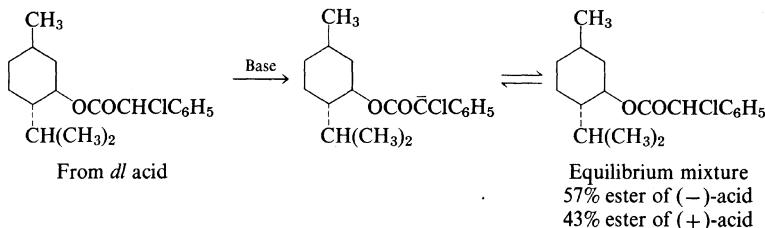
Fig. 4-31. Resolution of 2-(*p*-carboxybenzyl)hydrindanone-1.

one diastereoisomer is continuously removed from the solution by precipitation, the equilibrium between the diastereoisomers is continuously disturbed and eventually the entire material is converted to the less soluble form. This combination of epimerization and precipitation is known as "second-order asymmetric transformation." Second-order asymmetric transformation is involved also in the crystallization of mutarotating sugars such as glucose (cf. page 41). In solution, glucose is present as an equilibrium mixture of the  $\alpha$  and  $\beta$  forms (cf. Fig. 4-13). The position of equilibrium depends only slightly on solvent. When a solution of glucose is concentrated, however, the less soluble form crystallizes first, and this disturbs the equilibrium so that more of that form is produced in solution. This will crystallize again, and so on, crystals of entirely one form being obtained in this way. Which form crystallizes preferentially depends on the solvent: Crystallization from ethanol produces the  $\alpha$  isomer whereas crystallization from warm pyridine yields the  $\beta$  isomer.

c. **Resolution by Equilibrium Asymmetric Transformation.** By "equilibrium asymmetric transformation" we mean any change of configuration at one asymmetric atom of a compound having two or more such atoms which pro-

<sup>43</sup> H. Leuchs, *Ber.*, **54**, 830 (1921).

ceeds so as to establish a chemical or physical equilibrium; in other words, this is (cf. Sec. 4-2e) an epimerization leading to equilibrium. This term obviously includes first- (Sec. 4-2e) and second-order (Sec. 4-4b) asymmetric transformations. When equilibrium asymmetric transformation affects an asymmetric center which may subsequently be separated from the rest of the molecule, it constitutes a means of resolution.<sup>†</sup> The above-mentioned obtention of active 2-(*p*-carboxybenzyl)-1-hydrindanone (Fig. 4-31) is a case in point. Another example is the partial resolution of phenylchloroacetic acid



**Fig. 4-32.** Partial resolution of phenylchloroacetic acid by equilibrium asymmetric transformation.

by conversion to its menthyl ester followed by base-catalyzed epimerization (Fig. 4-32).<sup>43a</sup> The equilibrated ester contained 57% of the (–) acid and 43% of the (+) acid.<sup>‡</sup> Equilibrium asymmetric transformations may also take place in solutions of optically active solvents. Thus when *N*,4-dimethyl-*N*-acetyl-2-(*p*-toluenesulfonyl)aniline (Fig. 4-33) was dissolved in (+)-diethyl tartrate, the material which crystallized was slightly dextrorotatory when examined in an optically inactive solvent.<sup>41a</sup> Upon standing, the rotation of the solution decayed to zero, owing to spontaneous racemization. That this



**Fig. 4-33.** *N*,4-Dimethyl-*N*-acetyl-2-(*p*-toluenesulfonyl)aniline. (The reason for the activity of this material will be discussed in Chap. 6.)

is an asymmetric transformation rather than a preferential crystallization of one enantiomer is evidenced by the fact that it is not necessary to allow the material to crystallize from the diethyl tartrate solution. Total precipitation

<sup>†</sup> Elsewhere this has been called "equilibrium method of resolution." We feel that stressing the resolution aspect of this phenomenon in its definition is likely to obscure the underlying physicochemical process.

<sup>‡</sup> The acid was not recovered from the partly resolved ester in this instance, although in principle acid hydrolysis could have been used for this purpose.

of the solute by addition of water to the solution also produces active material.

**d. Resolution by Kinetic Asymmetric Transformation.**<sup>84</sup> By "kinetic asymmetric transformation" we mean the preferential formation, transformation, or destruction of one of two (or of several) stereoisomers in a given reaction because that one isomer is formed or reacts faster than all the others. In terms of chemical kinetics, this means that the free energy of activation for the reaction of the isomer in question is lower than that for all the other isomers. In general, such will be the case if the transition states corresponding to the reactions of the different stereoisomers are diastereoisomeric (not enantiomeric!) and therefore unequal in free energy (cf. Sec. 3-2).†

Three cases of kinetic asymmetric transformation may be distinguished, although all are based on the same principle. Two diastereoisomers may be formed or react at unequal rates without their asymmetric atoms being directly affected in the reaction under consideration. This has sometimes been called the "kinetic method of resolution," properly speaking. A second case arises when a reaction is involved which creates a new asymmetric center in a compound already possessing asymmetry or under the influence of an asymmetric reagent, catalyst, or physical influence. This case is often called "asymmetric synthesis" or "asymmetric induction." Finally a case may arise where enantiomers are destroyed at unequal rates by an asymmetric reagent. This case may be termed "asymmetric destruction."

*i. Kinetic Method of Resolution.* Diastereoisomers usually differ in free energy, and if they enter into a chemical reaction, the transition states for the isomers also usually differ in energy. Unless these energy differences happen to be the same in the ground and transition states, the activation energies for the diastereoisomers are also different. A case in point is the reaction of *cis*- and *trans*-1,2-cyclopentanediol with lead tetraacetate;<sup>43b</sup> the *cis* isomer reacts about 3000 times as fast as the *trans* compound.‡ The differences in ground state here are not likely to be large, and the big rate difference must be caused by differences in transition-state energy levels (Fig. 4-34).¶

The application of this principle to resolution will now be considered, using the case of methyl mandelate (Fig. 4-35) as an example. When ( $\pm$ )-menthol is esterified with ( $\pm$ )-mandelic acid, a molecule of the (+) acid may be linked to either (+) or (-) alcohol, and similarly for the (-) acid. Therefore there are actually four types of ester molecules, (+)(+), (+)(-), (-)(+), and (-)(-), as shown in Fig. 4-35, which form two pairs

† For a general treatment of the problem, it would be necessary to consider also the differences in free energy of the starting states, inasmuch as activation energy is a difference in energy between initial state and transition state; cf. Sec. 8-5 and Figs. 8-23 and 8-25. This complication does not arise in asymmetric synthesis and asymmetric destruction (Sec. 4-4*d*, *ii* and *iii* below) where the starting states are either one and the same or enantiomeric and thus equal in free energy.

This is an extreme case; usually the differences are not as large. The cause for these differences will be considered in more detail in Chaps. 6 and 8.

It is recognized that the case discussed here may be somewhat more complicated in that cyclic intermediates may be involved, and the equilibrium constant for the intermediates should also be considered in assessing relative reactivity of stereoisomers. This does not, however, affect the general principle involved.

of enantiomers. The two pairs, in turn, are diastereoisomeric (cf. Sec. 3-2). In the esterification, the diastereoisomers may (and probably will) be formed at unequal rates, for, although the ground state is the same for all possible combinations, the diastereoisomeric transition states differ in energy. As a result, if the reaction is interrupted before it is complete, or if insufficient menthol for complete esterification is used, one pair of enantiomers [the (+)(-) and (-)(+), as it happens] is formed in preference over the other. However, since enantiomers have the same free energy, they are formed at the *same* rate. The product, then, is a mixture of (+)(-) and (-)(+) ester (equal amounts) with a lesser proportion of the (+)(+) and (-)(-) isomers (again formed in equal amounts). Total saponification of such a mixture gives back equal amounts of (+) and (-) acid; thus no resolution has been achieved. The situation is different, however, if (-)-menthol is used in the esterification instead of the racemic alcohol. In this case only two diastereoisomers can result, namely, the (+)(-) and the (-)(-) ester,

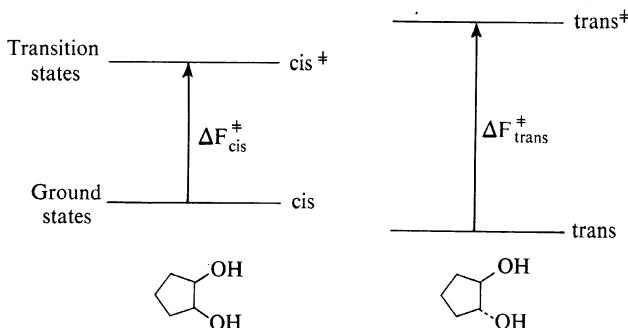


Fig. 4-34. Energetics of lead tetraacetate oxidation of *cis*- and *trans*-1,2-cyclopentane-diol.

and from what has been said above, the (+)(-) isomer will predominate when the reaction is stopped before completion. Hydrolysis of the ester mixture will thus return mandelic acid enriched in the (+) isomer, whereas the mandelic acid which remains unesterified will be predominantly (-). Partial resolution may thus be effected.<sup>44</sup>

Several variations of the kinetic method of resolution will now be considered. Instead of bringing together the asymmetric centers (at least two must be involved) in the key reaction, they may be separated. For example, when an equimolar mixture of the esters of (-)-menthol with (+)- and (-)-mandelic acid [obtained by total esterification of the racemic acid with (-)-menthol] is partially hydrolyzed, the acid liberated preferentially is the (+) isomer. The (-) isomer can be recovered by further hydrolysis of the residual ester. In principle, it is not necessary that the reaction effecting resolution should either bring together or separate the asymmetric centers involved. For example, one might envisage resolution of a racemic amino acid by partial acetylation of its (-)-menthyl ester. Since the (-)-menthyl

<sup>44</sup> W. Marckwald and A. McKenzie, *Ber.*, **32**, 2130 (1899).

esters of the (+)- and (-)-amino acid are diastereoisomers, they might be acetylated at different rates, so that one isomer might be enriched in the acylated material, the other in the unacylated residue. However, this particular kind of kinetic resolution does not seem to have been reduced to practice.<sup>†</sup>

The auxiliary asymmetric center required in the kinetic method may be

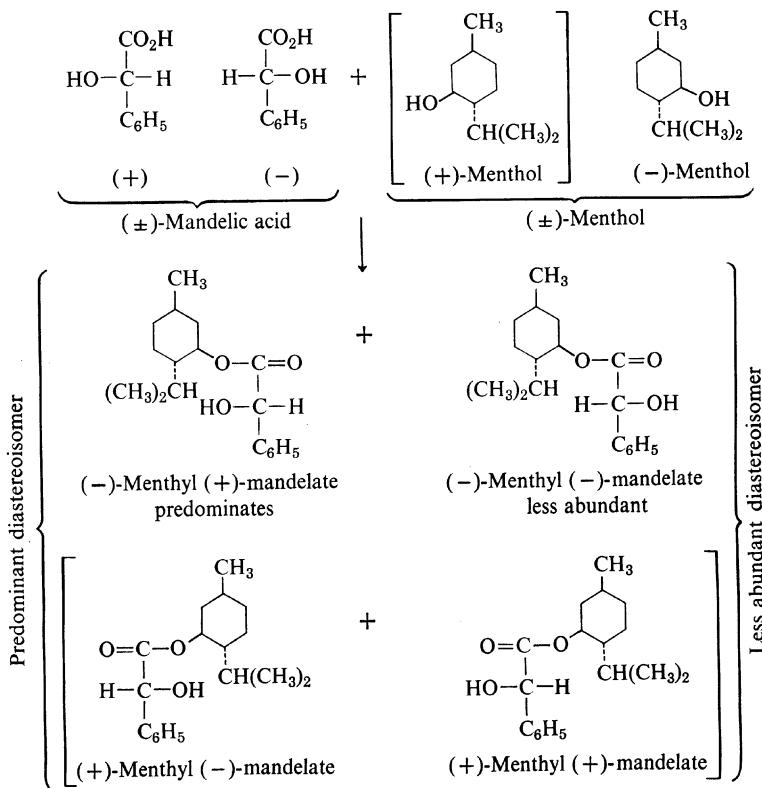
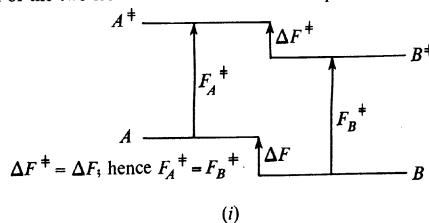


Fig. 4-35. Incomplete esterification of menthol with mandelic acid.

<sup>†</sup> Practical difficulties may arise because the differences between diastereoisomeric ground states and the corresponding transition states may be the same. In that case (i), the activation energies for reaction of the two isomers A and B would be equal.



present in the catalyst or solvent rather than in the substrate or reagent. Thus incomplete esterification of ( $\pm$ )-methylphenylcarbinol,  $C_6H_5CHOHCH_3$ , with acetic anhydride in the presence of brucine gives the levorotatory acetate,  $C_6H_5CHOAcCH_3$ , along with recovered dextrorotatory alcohol.<sup>45</sup> Incomplete hydrolysis of racemic ethyl phenylchloroacetate,



in the presence of cyclodextrin (cf. page 60) produces dextrorotatory phenylchloroacetic acid,  $C_6H_5CHClCO_2H$ , whereas the recovered ester is levorotatory.<sup>46</sup> Carbonation of racemic 2-butylmagnesium chloride,



in (+)-2,3-dimethoxybutane,  $CH_3CH(OCH_3)CH(OCH_3)CH_3$ , gives levorotatory methylethylacetic acid,  $CH_3CH(C_2H_5)CO_2H$ .<sup>47</sup> Here it seems to be necessary for one active ether molecule to coordinate with the organometallic reagent in two places for kinetic resolution to be effective, for methylethylacetic acid obtained by a method similar to the above in (-)-menthyl methyl ether was inactive.

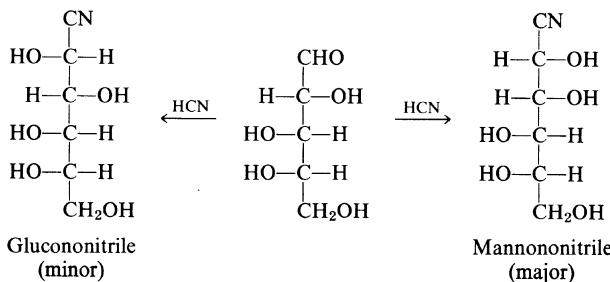


Fig. 4-36. Reaction of (+)-arabinose with hydrogen cyanide.

*ii. Asymmetric Synthesis.* Asymmetric synthesis or asymmetric induction† is only tenuously different from kinetic resolution. The difference is that the asymmetric atom, instead of being in the molecule to begin with, is introduced in the course of the reaction. An example is the synthesis of glucononitrile and mannononitrile from (+)-arabinose (Fig. 4-36). The two products are diastereoisomeric, and the transition states leading to them would also be expected to be diastereoisomeric and thus different in free energy. Since the starting state [(+)-arabinose] is the same for the two reactions, the activation energies are expected to differ, and the two products are formed at different

† There appears to be no agreement in the literature on the definition of these terms. In this book they are used interchangeably as meaning production of a new asymmetric atom or entire dissymmetric molecule under conditions where the resulting two stereoisomers are formed in unequal amounts.

<sup>45</sup> R. Wegler, *Ann.*, **498**, 62 (1932).

<sup>46</sup> F. Cramer and W. Dietsche, *Chemistry & Industry (London)*, 892 (1958); *Chem. Ber.*, **92**, 1739 (1959).

<sup>47</sup> H. L. Cohen and G. F. Wright, *J. Org. Chem.*, **18**, 432 (1953).

rates. In fact, mannonic acid nitrile predominates to such an extent that at one time it was believed to be the only product of the reaction.<sup>†</sup>

It is well to understand exactly what is involved in asymmetric synthesis. When a new asymmetric center is introduced in a molecule already possessing one or more asymmetric centers, a pair of diastereoisomers can always result, and for reasons already discussed, the two isomers are not usually formed in equal amounts.<sup>‡</sup> This is true whether the starting material was originally resolved or whether it is a *dl* pair. Thus, in the reduction of ( $\pm$ )-benzoin,  $C_6H_5CHOHCOC_6H_5$ , with lithium aluminum hydride, the major product is *meso*-hydrobenzoin,  $meso-C_6H_5CHOHCHOHC_6H_5$ , not its diastereoisomer; the same is true if one starts with (+)- or (-)-benzoin.

The difference in energy between diastereoisomeric transition states and the resulting preference of one diastereoisomeric product over the other is apt to be most marked when the newly created asymmetric center is close to an asymmetric center already in the molecule. For the particular case where the two centers are adjacent to each other and where asymmetry at the new center is created by an addition reaction to a double bond, *Cram's rule* predicts the predominant stereoisomer in the product.<sup>48</sup> The rule may be summarized in a diagram, as in Fig. 4-37, which refers to the particular case of

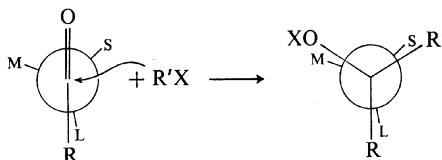


Fig. 4-37. Cram's rule.<sup>¶</sup>

an addition reaction (e.g., of hydride or an organometallic) to a carbonyl compound  $SML^C-COR$ . The rule states that when the asymmetric carbon ( $C$ ) is so oriented that the carbonyl function is flanked by the two smaller groups (M and S) attached to  $C$ , the reagent ( $R'X$ ) preferentially approaches the carbonyl group from the side of the smallest group S.<sup>¶</sup> The rule applies only to reactions that are kinetically controlled (cf. Sec. 7-3), i.e., where the product isolated is that formed in a rate-controlled process, not the more stable product formed in a subsequent equilibration.<sup>§</sup> Also, the rule specifi-

<sup>†</sup> It might be noted that, whereas a reaction leading to kinetic resolution must be interrupted short of completion, the same is not true of a reaction leading to asymmetric synthesis.

<sup>‡</sup> The introduction of an asymmetric center in a symmetric molecule in the absence of any asymmetric influence of course always leads to a *dl* pair (cf. Sec. 4-2b).

<sup>\*</sup> S is the smallest group on the asymmetric carbon  $C$ , M the medium-sized group, and L the largest group.

For example, in an aluminum isopropoxide (Meerwein-Ponndorf-Verley) reduction of a ketone, the product predicted by Cram's rule is that obtained after a short reaction time. Prolonged reaction leads to formation of the more stable diastereoisomer which is not necessarily that predicted by the rule.

<sup>48</sup> D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

cally does not apply to catalytic reduction, and it does not apply to cases where the small group S is a group such as hydroxy, alkoxy, or amino which may complex with the reagent R'X.<sup>49</sup> An example of the application of the rule is the reaction of  $\alpha$ -aminobenzyl phenyl ketone (as the hydrochloride) with excess *p*-chlorophenylmagnesium bromide (Fig. 4-38).† The predominant diastereoisomer produced is that predicted by the rule, phenyl being the large group, amino medium, and hydrogen small. The other diastereoisomer may be obtained in predominance by reversing the group already in the molecule and the group introduced in the reaction. In the present case this entails the reaction of  $\alpha$ -aminobenzyl *p*-chlorophenyl ketone (as the hydrochloride) with phenylmagnesium bromide (Fig. 4-38).‡

Asymmetric induction of the type described here does not necessarily involve optically active starting materials or products. However, it is obvious from what has been said before that, if the introduction of a new asymmetric center B into a molecule ( $\pm$ )-A gives a predominance of, let us say, (+)-A-(−)-B and (−)-A-(+)-B over the other diastereoisomer (+)-A-(+)-B and

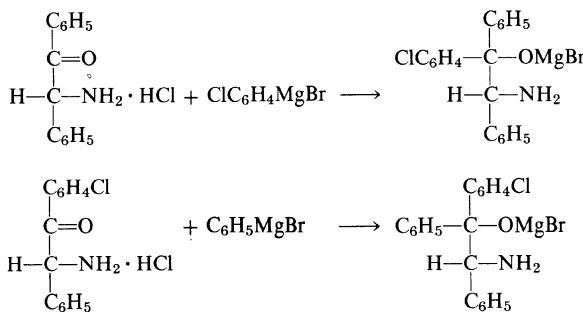


Fig. 4-38. Application of Cram's rule.

(−)-A-(−)-B, then, if one starts with an already resolved molecule, for example, (−)-A, one will get a predominance of (−)-A-(+)-B. If now in some way the part of the molecule containing the new asymmetric center B can be separated, this part will be optically active. Originally, the term "asymmetric synthesis" was limited to this particular type of case.<sup>50</sup> Numerous examples have been studied by McKenzie and coworkers. In McKenzie's first example,<sup>51</sup> the phenylglyoxylate ester of (−)-menthol was reduced with aluminum

† Correlation of the Fischer projection formulas used in Fig. 4-38 with the Newman projection formulas used in Fig. 4-37 is left as an exercise for the reader. Cf. Fig. 3-11.

‡ Despite its plausible geometric formulation, Cram's rule is only a *formal* rule based on empirical observation; it does *not* necessarily have any mechanistic implication. In fact, there are cases (Ref. 49) where the rule may lead to a correct prediction even though the transition state is manifestly different from what may be implied in Fig. 4-37.

<sup>49</sup> D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959); J. H. Stocker, P. Sidsunthorn, B. M. Benjamin, and C. J. Collins, *ibid.*, **82**, 3913 (1960).

<sup>50</sup> W. Marckwald, *Ber.*, **37**, 349 (1904).

<sup>51</sup> A. McKenzie, *J. Chem. Soc.*, **85**, 1249 (1904).

amalgam to the mandelate ester of (-)-menthol; the ester of (-)-mandelic acid predominated in the product over that of (+)-mandelic acid (Fig. 4-39). In later work the mandelic acid enriched in the (-) isomer was actually recovered from its methyl ester by hydrolysis. Prelog has recently stated<sup>52</sup> an empirical correlation between the arrangement of the groups (configuration) in the isomer formed predominantly in the type of synthesis studied by

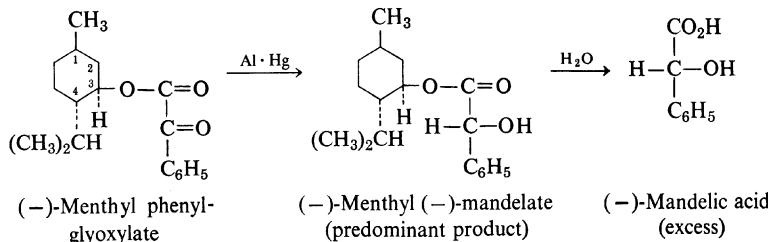
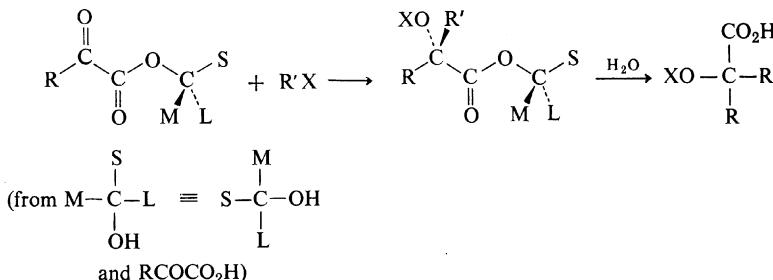


Fig. 4-39. Asymmetric synthesis of (-)-mandelic acid.

McKenzie and the corresponding arrangement in the optically active alcohol [e.g., (–)-menthol] used as an auxiliary reagent in the synthesis. The correlation, sometimes called *Prelog's rule*,<sup>52</sup> is summarized in Fig. 4-40.† In the statement of the rule, the arrangement of the groups in the starting material must be specified first, since there are several bonds around which the molecule may rotate. By convention, the molecule is so oriented that the two carbonyl groups are antiparallel and that the smallest group (S) in the alco-



**Fig. 4-40.** Prelog's rule.

hol portion is eclipsed with the ketone carbonyl. The reagent R' will then approach the ketone carbonyl group from the side of the smaller of the remaining two groups in the alcohol portion of the molecule, i.e., the side of the medium-sized group M. The case shown in Fig. 4-39 conforms with Prelog's rule if one considers that in the menthol molecule the

<sup>†</sup>This is also a *formal* representation without necessary mechanistic implications.

<sup>52</sup> V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).

small group S is H, the medium-sized group M is the methylene of the ring (at C<sub>2</sub>), and the large group L is the methine substituted with the isopropyl group (C<sub>4</sub>).† Prelog's rule has been very useful in assigning configurations to a variety of molecules; this aspect will be taken up further in Chap. 5. As in the case of Cram's rule, reversing the order in which the groups are introduced in the molecule reverses their arrangement in the preponderant product. Thus reaction of (−)-menthyl phenylglyoxylate,



with methylmagnesium bromide followed by hydrolysis gives predominantly (−)-atrolactic acid, C<sub>6</sub>H<sub>5</sub>C(CH<sub>3</sub>)OHCO<sub>2</sub>H, but reaction of (−)-menthyl pyruvate, CH<sub>3</sub>COCO<sub>2</sub>C<sub>10</sub>H<sub>19</sub>, with phenylmagnesium bromide gives predominantly the stereoisomeric (+)-atrolactic acid.

Several other types of asymmetric synthesis have been rationalized in terms of an optimal steric fit of the reagents involved. Examples are the Meerwein-Ponndorf-Verley reduction<sup>53</sup> of methyl isohexyl ketone,



with (+)-2-butanol, CH<sub>3</sub>CHOHC<sub>2</sub>H<sub>5</sub>, in the presence of aluminum 2-butoxide to give (+)-methylisohexylcarbinol, CH<sub>3</sub>CHOHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, and



Preferred

Fig. 4-41. Transition states for asymmetric Meerwein-Ponndorf reduction.

2-butanone, CH<sub>3</sub>COC<sub>2</sub>H<sub>5</sub>, and the reduction<sup>54</sup> of pinacolone, CH<sub>3</sub>COC(CH<sub>3</sub>)<sub>3</sub>, with (+)-2-methyl-1-butylmagnesium chloride, C<sub>2</sub>H<sub>5</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>MgCl, to give the magnesiocloride derivative of (+)-pinacolyl alcohol,



and 2-methyl-1-butene, C<sub>2</sub>H<sub>5</sub>C(CH<sub>3</sub>)=CH<sub>2</sub>. The probable transition states for these reactions are shown in Figs. 4-41 and 4-42. The preferred transition states are those where the larger groups (ethyl, isohexyl, *t*-butyl) are on opposite sides of the plane of the six-membered ring from each other.‡ An asymmetric synthesis of this type is to be expected only if the asymmetrically

† The reader will probably have to make a model for the case shown in Fig. 4-39 to convince himself that it conforms with the rule.

‡ Unfortunately, examination of the reduction of a wide variety of unsymmetric dialkyl ketones with optically active Grignard reagents has shown that the elegant picture shown in Fig. 4-42 represents an oversimplification: E. P. Burrows, F. J. Welch, and H. S. Mosher, *J. Am. Chem. Soc.*, **82**, 880 (1960).

<sup>53</sup> W. von E. Doering and R. W. Young, *J. Am. Chem. Soc.*, **72**, 631 (1950).

<sup>54</sup> H. S. Mosher and E. LaCombe, *J. Am. Chem. Soc.*, **72**, 3994 (1950).

substituted carbon is part of the cyclic transition state. Thus, no asymmetric reduction of pinacolone occurred with 3-methylamylmagnesium chloride,  $C_2H_5CH(CH_3)CH_2CH_2MgCl$ , even though the Grignard reagent was optically active.<sup>55</sup> In this case the asymmetric center does not form part of the ring in the cyclic transition state, and therefore there is no preference for one configuration of the pinacolyl alcohol formed over the other, the steric fit of the two diastereoisomeric transition states (and therefore their free energy) being the same. An interesting application<sup>56</sup> of this type of asymmetric

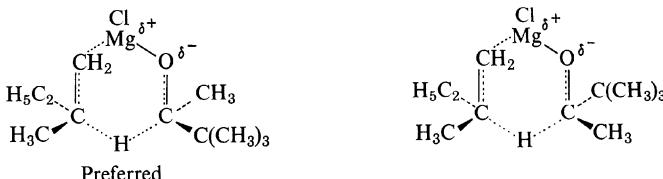


Fig. 4-42. Transition states for asymmetric Grignard reduction.

synthesis has been made in the reduction of butyraldehyde,  $CH_3CH_2CH_2CHO$ , with the magnesiobromide salt† of (+)-2-octanol-2-*d*,  $CH_3CDOHC_6H_{13}$ , which gave rise to *active* (−)-1-butanol-1-*d*,  $CH_3CH_2CH_2CHDOH$ , the activity being due to asymmetry at the primary carbon due to hydrogen and deuterium (cf. Sec. 3-1). An asymmetric synthesis somewhat similar to that discovered by McKenzie<sup>51</sup> and rationalized by Prelog,<sup>52</sup> but involving addition to a carbon-carbon rather than to a carbon-oxygen double bond, is the reaction of (−)-menthyl acrylate with diphenyldiazomethane to give, after

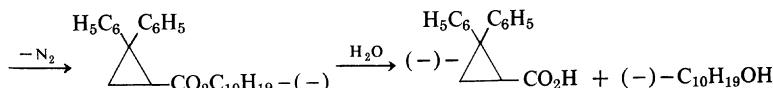
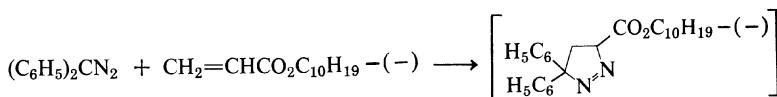


Fig. 4-43. Addition of diphenyldiazomethane to (−)-menthyl acrylate.

saponification, active 2,2-diphenylcyclopropanecarboxylic acid.<sup>57</sup> The reaction probably proceeds via an active pyrazoline (Fig. 4-43).

Asymmetric synthesis may also occur in the presence of an asymmetric catalyst or solvent rather than an asymmetric reagent. Thus, the synthesis of optically active phenylalanine (25% optically pure) has been claimed by

† This reduction is analogous to a Meerwein-Ponndorf reduction (with  $-OMgBr$  instead of  $-OAlX_2$ ) rather than to a reduction with a hindered Grignard reagent.

<sup>55</sup> H. S. Mosher and E. LaCombe, *J. Am. Chem. Soc.*, **72**, 4991 (1950).

<sup>56</sup> A. Streitwieser, *J. Am. Chem. Soc.*, **75**, 5014 (1953).

<sup>57</sup> F. J. Impastato, L. Barash, and H. M. Walborsky, *J. Am. Chem. Soc.*, **81**, 1514 (1959).

catalytic hydrogenation of ethyl  $\alpha$ -acetoximino- $\beta$ -phenylpyruvate, using a palladium catalyst supported on (optically active) silk fibroin followed by hydrolysis<sup>58</sup> (Fig. 4-44).

Active chloromandelic acid has been obtained from chlorobenzaldehyde via the cyanohydrin synthesis in the presence of cyclodextrin<sup>46</sup> (Fig. 4-45). The cyclodextrin appears to act as a solubilizing agent for the aldehyde. The reaction of methyl ethyl ketone with phenylmagnesium bromide<sup>59</sup> in (+)-2,3-dimethoxybutane gives 2-phenyl-2-butanol,  $C_6H_5C(CH_3)OHC_2H_5$ , of specific rotation  $[\alpha]_D^{20} + 3.04^\circ$ .

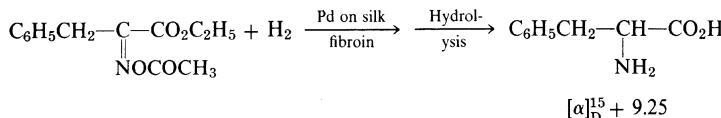


Fig. 4-44. Asymmetric hydrogenation.

*iii. Asymmetric Destruction.* When the asymmetry about one of the atoms (A) in two optically active diastereoisomers, (−)-A-(+)-B and (−)-A-(−)-B, is destroyed,<sup>†</sup> such destruction could take place at unequal rates in the two isomers, and the resulting product containing only the asymmetry due to B would then be optically active, even though originally the two diastereoisomers had been present in equal amounts. Cases of this type [in which (−)-A is chemically joined to ( $\pm$ )-B] do not seem to have been studied,<sup>‡</sup> but very

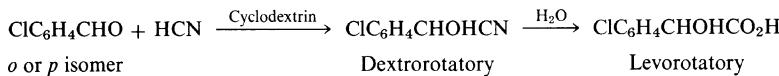


Fig. 4-45. Asymmetric synthesis in the presence of cyclodextrin.

similar cases, in which A is an asymmetric reagent or catalyst, are on record. Thus in the incomplete dehydration of ( $\pm$ )-phenylmethylcarbinol,



to styrene by means of (+)-camphorsulfonic acid, the recovered carbinol was weakly levorotatory.<sup>60</sup> In the dehydrohalogenation of the ( $\pm$ ) form of 1,2,3,4,5,6-hexachlorocyclohexane (cf. Chap. 7), which cannot readily be

<sup>†</sup> For example, asymmetry of the type  $R^*-CHOH-R'$  might be eliminated by oxidation to the ketone or dehydration to the olefin; asymmetry of the type  $R^*-CH(CO_2H)-R'$  might be eliminated by decarboxylation, etc. (The asymmetry in the group  $R^*$  would remain.)

<sup>‡</sup> A hypothetical example is the partial oxidation of (−)-menthyl ( $\pm$ )-mandelate,



The remaining ester, upon total saponification, should give rise to partially active mandelic acid. This would be the reverse of the asymmetric synthesis of active mandelic acid by reduction of (−)-menthyl phenylpyruvate (page 71).

<sup>58</sup> S. Akabori, S. Sakurai, Y. Izumi, and Y. Fujii, *Nature*, **178**, 323 (1956).

<sup>59</sup> N. Allentoff and G. F. Wright, *J. Org. Chem.*, **22**, 1 (1957).

<sup>60</sup> H. Wuyts, *Bull. soc. chim. Belges*, **30**, 30 (1921).

resolved by conventional means, with an insufficient amount of the optically active base brucine (Fig. 4-46), the remaining hexachloride became partly active.<sup>61</sup>

A case in which the catalyst (or catalyst support) supplies the asymmetric influence is provided by the observation<sup>62</sup> that partial decomposition (by dehydration or dehydrogenation) of racemic 2-butanol over nickel deposited on optically active quartz (cf. Sec. 1-2) at 550° causes the residual alcohol to become optically active. A similar example is the incomplete oxidation of 2,2'-dichlorobenzoin, 2-ClC<sub>6</sub>H<sub>4</sub>CHOHCOC<sub>6</sub>H<sub>4</sub>Cl-2', to the corresponding

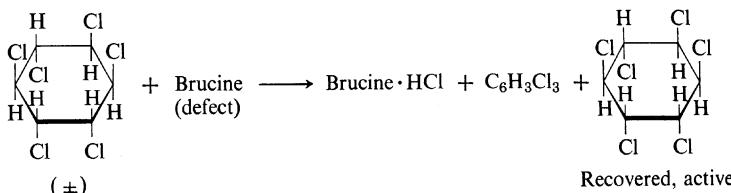


Fig. 4-46. Asymmetric dehydrohalogenation of (±)-1,2,3,4,5,6-hexachlorocyclohexane.

benzil by molecular oxygen in the presence of the catalyst cyclodextrin; the recovered starting material becomes dextrorotatory.<sup>46</sup> A more complicated case,<sup>63</sup> because it involves a substrate with several asymmetric centers, is the partial decarboxylation of (±)- $\alpha$ -carboxycamphor in the presence of the basic catalyst quinine (Fig. 4-47). In this case, not only is the recovered acid active, but so is the camphor obtained, since it still retains two of the original three asymmetric carbon atoms.

e. **Biochemical Asymmetric Transformation.** Under this heading we shall deal with the production of optically active compounds either by the inter-

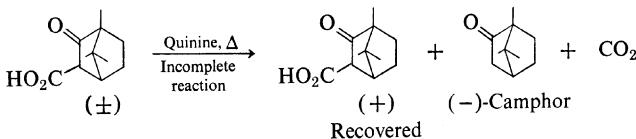


Fig. 4-47. Asymmetric decarboxylation of (±)- $\alpha$ -carboxycamphor.

vention of a living organism or by means of one of the catalyst systems, called enzymes, which may be isolated from living organisms. The distinction between biochemical methods of obtaining optically active compounds and other methods is, in many respects, an unfortunate one. In a sense, all the resolutions so far described are biochemical. The alkaloids, terpene derivatives, acids, etc., used in the common methods of resolution are mostly materials of natural origin, and even if they are either strictly synthetic, such as  $\alpha$ -phenethylamine, or natural products now accessible synthetically, such

<sup>61</sup>S. J. Cristol, *J. Am. Chem. Soc.*, **71**, 1894 (1949); cf. H. J. Lucas and C. W. Gould, *ibid.*, **64**, 601 (1942).

<sup>62</sup>G. M. Schwab, F. Rost, and L. Rudolph, *Kolloid-Z.*, **68**, 157 (1934).

<sup>63</sup>G. Bredig and K. Fajans, *Ber.*, **41**, 752 (1908); K. Fajans, *Z. physik. Chem.*, **73**, 25 (1910).

as strychnine,<sup>64</sup> somewhere in their synthesis some natural resolving agent must have been employed. Thus  $\alpha$ -phenethylamine may be resolved by natural (−)-malic acid or natural (+)-tartaric acid or (−)-pyroglutamic acid obtained by pyrolysis of natural (+)-glutamic acid; and in the synthesis of strychnine, the alkaloid quinidine is used in the resolution of one of the intermediates. Only the mechanical separation method (Sec. 4-4a) requires no other optically active agent, but then it requires the active intervention of the most highly developed of all biochemical systems, namely, man!<sup>†</sup> Another reason why the setting apart of biochemical methods is unfortunate is that it makes a qualitative distinction between enzyme systems and other dissymmetric molecules used in the preparation of dissymmetric products. For example, the reaction of benzaldehyde with hydrogen cyanide,



followed by hydrolysis to mandelic acid,  $\text{C}_6\text{H}_5\text{CHOHC}_2\text{H}$ , leads to an optically active product if carried out either in the presence of the enzyme emulsin<sup>65</sup> or in the presence of quinine or quinidine.<sup>66</sup> Yet the former process would be called biochemical and the latter an asymmetric synthesis! To be sure, quinine is now available synthetically<sup>67</sup> whereas emulsin is not, but this is not a distinction in principle, since there is no fundamental reason why enzymes should not one day be synthesized also.

In principle, the methods described in this section are merely special cases of kinetic asymmetric transformations (Sec. 4-4d). Nevertheless, there is one important quantitative (and practical) difference between the two methods: In the above asymmetric synthesis using quinine or quinidine, the excess of one enantiomer over the other in the product mandelic acid is less than 10%, but, using emulsin, the product is nearly optically pure. In other words, biochemical methods of obtaining active compounds are highly specific and therefore in many cases are of practical importance,<sup>‡</sup> whereas other kinetic asymmetric transformations are apt to be of theoretical interest only.<sup>¶</sup>

<sup>†</sup> The synthesis of dissymmetric molecules in the absence of other dissymmetric chemical species will be discussed in the next section (Sec. 4-4f).

<sup>‡</sup> Of the two practical methods of resolution, one—crystallization of diastereoisomers—depends on the high sensitivity of crystal shape to spatial arrangements of the molecules and on the resultant specificity in crystal growth and solubility. The other—the biochemical method—depends on the fact that polymeric molecules containing many asymmetric atoms (the proteins) are involved as catalysts; such molecules might be expected to show considerable specificity toward one enantiomer.

<sup>¶</sup> A notable and unique exception is the hydroboration-oxidation of olefins to optically active alcohols by means of di-isopinocampheylborane, the addition product of  $\alpha$ -pinene and diborane, which leads to products of optical purity of the order of 83 to 91%: H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 486 (1961); cf. page 361. Since the  $\alpha$ -pinene used in the synthesis was only about 90% optically pure, the “optical yield,” i.e., the ratio of optical purity of the product to optical purity of precursor, reagent, or catalyst, is close to 100% in this case. The optical yield of most other chemical asymmetric syntheses does not exceed 20 to 25% at best.

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<sup>64</sup> R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daenicker, and K. Schenker, *J. Am. Chem. Soc.*, **76**, 4749 (1954).

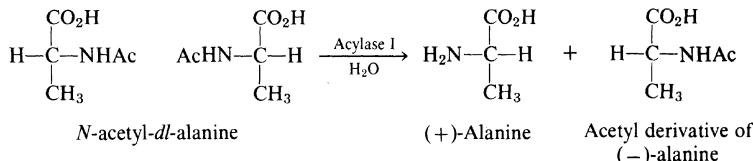
<sup>65</sup> L. Rosenthaler, *Biochem. Z.*, **14**, 238 (1908).

<sup>66</sup> G. Bredig and P. S. Fiske, *Biochem. Z.*, **46**, 7 (1912).

<sup>67</sup> R. B. Woodward and W. von E. Doering, *J. Am. Chem. Soc.*, **67**, 860 (1945).

The biochemical method of obtaining active compounds, as the method of mechanical separation (Sec. 4-4a) and the method of separation by crystallization of diastereoisomers (Sec. 4-4b), was discovered by Pasteur.<sup>68</sup> Pasteur noticed that when the ammonium salt of racemic tartaric acid was fermented by means of yeast or *Penicillium glaucum* (a mold), the salt of the natural (dextrorotatory) form was used up preferentially, and after the fermentation had proceeded for some time, the salt of pure (−)-tartaric acid could be isolated from the fermentation broth. This is evidently a case of asymmetric destruction: The penicillium metabolizes the naturally occurring enantiomer preferentially and leaves the unnatural (levorotatory) enantiomer behind. The later work on the synthesis of mandelonitrile in the presence of emulsin (page 76) showed definitely that no living organism or living cell is necessarily involved in this type of asymmetric synthesis but that the active agents are the enzymes (which may function either within or outside the organism).

The above examples of mandelonitrile and tartaric acid illustrate biochemical asymmetric synthesis and biochemical asymmetric destruction. A third and particularly useful method is biochemical kinetic resolution. This method has found widespread application in the preparation of optically active amino



**Fig. 4-48.** Enzymatic resolution of alanine.

acids. For example,<sup>69</sup> when an acylated racemic amino acid in aqueous solution is treated with hog-kidney acylase ("acylase I")† until about half the acyl groups are hydrolyzed, the residual acyl-amino acid is the derivative of the unnatural (so-called "D"; cf. Chap. 5) isomer, whereas the free amino acid obtained in the hydrolysis is the so-called "L" or natural isomer. The unchanged acyl derivative can readily be extracted with ethyl acetate and, in most cases, converted to the free amino acid by non-enzymatic (acid-catalyzed) hydrolysis, whereas the free natural amino acid may be recovered by an ion-exchange process. The method is exemplified in Fig. 4-48 for the case of alanine.

One of the drawbacks of using hog-kidney acylases for resolution is that these enzymes are not stable and must therefore be prepared freshly whenever they are to be used. Fortunately, for some amino acids resolution methods have been elaborated which employ commercially available enzyme preparations. For example,<sup>70</sup> the papain-catalyzed reaction of ( $\pm$ )-acetylphenyl-

<sup>†</sup>The enzyme seems to be effective for all common amino acids except aspartic acid for which another acylase ("acylase II"), also obtained from kidney, is used.

<sup>68</sup> L. Pasteur, *Compt. rend.*, **46**, 615 (1858).

<sup>69</sup> V. E. Price and J. P. Greenstein, *J. Biol. Chem.*, **175**, 969 (1948); see also Ref. 88.

<sup>70</sup> H. T. Huang and C. Niemann, *J. Am. Chem. Soc.*, **73**, 475 (1951).

alanine with *p*-toluidine gives the *p*-toluide of acetyl-L-phenylalanine and unchanged acetyl-D-phenylalanine which may be readily separated chemically and reconverted individually to D-(+)-phenylalanine and L-(-)-phenylalanine by hydrolysis.

Of particular interest are biochemical methods leading to optically active compounds of the type RR'CHD (cf. Chap. 3). Here may be mentioned the synthesis of (-)-ethanol-1-*d*, CH<sub>3</sub>CHDOH, by reduction of acetaldehyde-1-*d*, CH<sub>3</sub>CDO, with reduced diphosphopyridine nucleotide in the presence of yeast alcohol dehydrogenase<sup>70a</sup> and the synthesis of optically active tyramine-1-*d*, *p*-HOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>CHDNH<sub>2</sub>, by decarboxylation of (-)-tyrosine, *p*-HOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>CH(NH<sub>2</sub>)CO<sub>2</sub>H, in D<sub>2</sub>O solution by tyrosine decarboxylase.<sup>70b</sup> Whereas the latter example merely involves the stereospecific conversion of one optically active compound into another (a conversion, however, which it would be difficult to effect stereospecifically by conventional chemical means), the former example actually represents an asymmetric enzymatic synthesis.

While speaking of biochemical discrimination between enantiomers, it is pertinent to point out that such discrimination is also exercised by the human organism. Of the two enantiomeric asparagines, HO<sub>2</sub>CCH(NH<sub>2</sub>)CH<sub>2</sub>CONH<sub>2</sub>, only the unnatural dextrorotatory isomer is sweet to the taste, and of the monosodium glutamates, only the salt of the natural (+)-glutamic acid (Fig. 4-23) acts as a flavor-enhancing agent. Among drugs there are numerous instances where but one optical antipode of a compound is efficacious. An example is chloramphenicol, *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CHOHCH(NHCOCHCl<sub>2</sub>)CH<sub>2</sub>OH, of whose four stereoisomers only one acts as an antibiotic.<sup>99</sup>

**f. Absolute Asymmetric Synthesis.** Most of the methods for obtaining optically active compounds discussed so far require other optically active substances as auxiliary devices. These methods, especially the biochemical method, provide rational explanations as to how new dissymmetric molecules may be generated in the presence of the old. They do not, however, explain how optically active molecules originated in the first place.

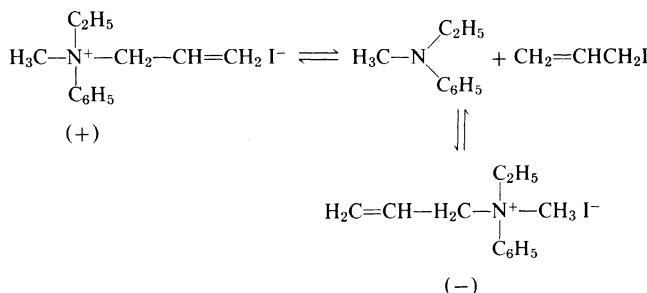
To some extent, the question of the ultimate origin of optical activity is a metaphysical one, entwined with the related questions of the ultimate origin of matter and of life. There are, however, some purely rational, experimentally demonstrable ways in which optically active substances may be formed in the absence of any other dissymmetric molecules. For example, optically active material may be obtained from a solution of the racemic modification by spontaneous crystallization (Sec. 4-4a). This is in no way a mysterious process. It has already been mentioned that all crystals of optically active substances are hemihedric, the crystals of one enantiomer being the mirror images of those of the other. If, in a solution of a racemic modification supersaturated with respect to the enantiomers, a nucleus of one of the enantiomeric crystals begins to form spontaneously and fortuitously, this nucleus is apt to grow by the addition of molecules of its own configuration, and it is quite

<sup>70a</sup> F. A. Loewus, F. H. Westheimer, and B. Vennesland, *J. Am. Chem. Soc.*, **75**, 5018 (1953); H. R. Levy, F. A. Loewus, and B. Vennesland, *ibid.*, **79**, 2949 (1957).

<sup>70b</sup> S. Mandelis, R. Koppelman, and M. E. Hanke, *J. Biol. Chem.*, **209**, 327 (1954); B. Belleau, M. Fang, J. Burba, and J. Moran, *J. Am. Chem. Soc.*, **82**, 5752 (1960).

possible that a macroscopic crystal of this particular enantiomer results before any of the other enantiomer crystallizes. If, through some accident, the mother liquor is at this point separated from the crystal, a partial resolution of the material as between the crystal and the mother liquor will have been effected.

A slight variant of this process has been observed<sup>18b</sup> in the crystallization of methylethylallylaminium iodide from chloroform solution in sealed glass tubes. The variant here is that the quaternary iodide (whose dissymmetry is due to the asymmetrically substituted nitrogen atom) is subject to spontaneous interconversion of the enantiomers, as shown in Fig. 4-49. Thus, even if one enantiomer crystallizes in preference to the other, due to spontaneous nucleation, the mother liquor will become racemic again after some time, because of the above equilibration process. The crystals isolated from the chloroform solutions after prolonged standing gave rise, in most cases, to optically active solutions when dissolved in water—sometimes dextrorotatory, sometimes levorotatory.



**Fig. 4-49.** Racemization of methylethylallylanilinium iodide

Another variant of the process is that crystallization of one enantiomer may be induced not by spontaneous nucleation but by seeding. The seed crystal must itself be hemihedric, but it may owe its hemihedrism to crystal dissymmetry rather than molecular dissymmetry. The resolution of solutions of asparagine by seeding with crystals of glycine (p. 48) may be of this type.

Compounds such as quartz and urea which are apt to crystallize in dissymmetric, optically active crystals without themselves possessing molecular dissymmetry may yet induce molecular dissymmetry in other molecules. Several cases, such as resolution by adsorption on active adsorbents (e.g., quartz powder), resolution via inclusion compounds (e.g., with urea), and asymmetric destruction by quartz-supported catalysts (as in the dehydration of 2-butanol) have already been mentioned.

In addition to these possibilities, two methods of so-called "absolute asymmetric synthesis"† have been recognized. These are syntheses of compounds in active form without the intervention of any dissymmetric chemicals. Some sort of physically dissymmetric influence is required in such syntheses, and it

<sup>†</sup> As distinct from the “partial asymmetric synthesis” discussed in Sec. 4-4d.

is necessary that the physical agent in question be essential to the synthesis, rather than accidental to it. For example, experiments<sup>71</sup> on the addition of bromine to methyl cinnamate,  $C_6H_5CH=CHCO_2CH_3$ , to give methyl 2,3-dibromo-3-phenylpropionate,  $C_6H_5CHBrCHBrCO_2CH_3$  (two asymmetric carbon atoms), under the influence of visible plane-polarized light passed through a magnetic field were doomed to failure; for although the physical influence is truly dissymmetric, it is not in any way involved in the chemical reaction of bromine addition. A successful absolute asymmetric synthesis<sup>72</sup> was, however, effected in the decomposition of the dimethylamide of  $\alpha$ -azido-

\* propionic acid,  $CH_3CHN_3CON(CH_3)_2$ , with circularly polarized light† of wavelength 2800 to 3100 Å. The azido compound has an adsorption band in the ultraviolet spectrum at 2900 Å. and is photochemically decomposed (with the evolution of nitrogen) by light of that wavelength. Using circularly polarized light of that wavelength introduces an asymmetric influence that is now essential to the reaction, and indeed it was found that the amide recovered after partial (40%) photochemical destruction was in one case levorotatory,  $\alpha_D - 1.04^\circ$ , and in another case dextrorotatory,  $\alpha_D + 0.78^\circ$ , depending on whether the light was levocircularly polarized or dextrocircularly polarized. (These rotations are observed rotations of the liquid in a 1-dm. tube.) This result is close to what had been predicted on theoretical grounds. Whereas this particular case is one of asymmetric *destruction*, cases of absolute asymmetric *synthesis* under the influence of circularly polarized light (e.g., in the photochemical addition of bromine to 2,4,6-trinitrostilbene) have also been recorded,<sup>73</sup> although the observed rotations of the product were very small (less than  $0.1^\circ$ ).

Since sunlight reflected by the sea possesses slight circular (or elliptical) polarization, asymmetric syntheses similar to the above could possibly have taken place on the surface of the earth.

Another approach to the problem of absolute asymmetric synthesis is to effect the synthesis under the influence of particulate (alpha or beta) radiation. Since this radiation is itself affected by a kind of handedness or dissymmetry (called "parity"), it might possibly induce dissymmetry in the molecule to be synthesized.<sup>74</sup>

The possibilities for spontaneous formation of optically active material discussed above do not by themselves explain, however, why most naturally occurring compounds, such as carbohydrates, amino acids, terpenes, steroids, alkaloids, antibiotics, etc., are found in nature in only one of the enantiomeric forms. This "configurational specificity" of natural products is very high; thus it appears that all the amino acids occurring in the higher forms of life

† Circularly polarized light is light whose plane of polarization rotates in corkscrew fashion along the line of propagation of the ray (cf. Chap. 14).

<sup>71</sup> P. A. Guye and G. Drouginine, *J. chim. phys.*, **7**, 96 (1909).

<sup>72</sup> W. Kuhn and E. Knopf, *Z. physik. Chem.*, **7B**, 292 (1930).

<sup>73</sup> T. L. Davis and R. Heggie, *J. Am. Chem. Soc.*, **57**, 377 (1935).

<sup>74</sup> F. Vester, T. L. V. Ulbricht, and H. Krauch, *Naturwiss.*, **46**, 68 (1959); cf. T. L. V. Ulbricht, *Quart. Revs. (London)*, **13**, 48 (1959).

in the form of proteins and polypeptides have the so-called "L configuration" (cf. Chap. 5), the arrangement of the atoms about the asymmetric carbon being that shown in Fig. 4-50. (Only a few amino acids occurring in bacteria and fungi have the opposite or "D configuration."<sup>74a</sup>) Propagation of the activity in nature involves enzyme systems made up, in part, of proteins as well as nucleic acids; since these proteins and nucleic acids are high-molecular-weight polymers made up of dissymmetric monomer units, they are highly dissymmetric molecules, and it is perhaps not surprising that the reactions that they catalyze lead almost exclusively to molecules of the same configuration. However, there are still a number of unanswered questions: how the enzymes came to be so stereospecific to begin with, what happens to molecules which are accidentally racemized and to the small but probably finite number of molecules which are synthesized in the wrong configuration, etc. Only speculations on this subject are possible at the present time.<sup>18, 75</sup>

**g. Asymmetric Syntheses Involving Symmetric Compounds.**<sup>90, 98</sup> In this section will be discussed some reactions of symmetric compounds of the type C<sub>x</sub>xyz with dissymmetric reagents in which the two identical substituents (x) behave in a different way, even though the products of the reaction are not, themselves, dissymmetric. Reactions of this type are of importance since

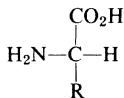


Fig. 4-50. Natural L-amino acid.

they show that even in a symmetric compound apparently identical groups may be operationally distinguishable.

In order to demonstrate that the two identical x groups do, in fact, behave differently it is necessary to label one of them. This has been done,<sup>76</sup> as shown in Fig. 4-51. The optically active lactone I was deuterated in the active methylene position by means of D<sub>2</sub>O and then decarboxylated by means of D<sub>2</sub>O<sub>2</sub> to citric acid. Because of the dissymmetry of the starting material, the  $\alpha,\alpha$ -dideuterocitric acid (II) was labeled exclusively in *one* of the two unequally placed acetic acid groupings. [As it happened, the acid II was also demonstrably optically active (cf. Sec. 3-1), but this is in no way essential to the argument.] The dideuterocitric acid was then degraded to  $\alpha$ -ketoglutaric acid (III), using an enzyme preparation made from pigeon-breast homogenate and arsenite. (The arsenite presumably serves to poison enzymes which would bring about further degradation.) Now when one of the antipodes of II (made from active I) was so degraded, all the deuterium was retained in the  $\alpha$ -ketoglutaric acid III, indicating that only the unlabeled methylene group

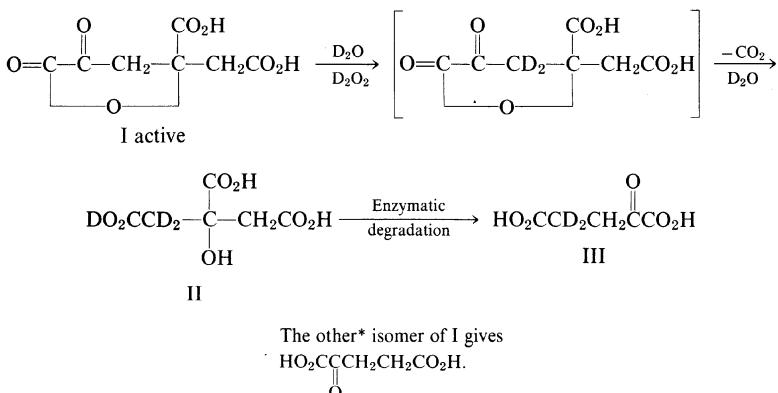
<sup>74a</sup> For example, C. M. Stevens, R. P. Gigger, and S. W. Bowne, *J. Biol. Chem.*, **212**, 461 (1955).

<sup>75</sup> W. Langenbeck, "Die Organischen Katalysatoren," 2d ed., Springer Verlag, Berlin, Vienna, 1949, pp. 99-103.

<sup>76</sup> C. Martius and G. Schorre, *Ann.*, **570**, 143 (1950); see also P. E. Wilcox, C. Heidelberger, and V. R. Potter, *J. Am. Chem. Soc.*, **72**, 5019 (1950).

was oxidized by the enzyme. This is not due to an isotope effect, for when the other antipode of II (made from the other antipode of I) was degraded, all the deuterium was lost in III. *Thus which of the methylene groups is oxidized in the enzymatic degradation of II depends on the relative position of these groups with respect to the rest of the molecule.*

It is important to realize that the above result is not dependent on the presence of the deuterium label (although in the absence of the label it would not have been detected). The essential point is that the methylene group in the ring in the enantiomer of lactone I shown in Fig. 4-51 is so located in the citric acid (II) that upon enzymatic degradation it ends up in the  $\alpha$ -ketoglutaric acid (III). If the other enantiomer of lactone I had served as starting



\* Assignment of configuration of I is arbitrary. The true configuration does not appear to be known.

Fig. 4-51. Asymmetric degradation of symmetric molecule.

material, its ring methylene group would have ended up in the opposite position in the citric acid (II) and would then have become so oriented on the enzyme that it would have been eliminated (as acetic acid?) rather than retained in the product III. The fact that, although citric acid is a symmetric intermediate in the sequence shown in Fig. 4-51, its methylene groups are not identical either as to origin or as to further fate is of considerable biochemical significance.

Several theories have been developed to explain (or predict) the experimental result discussed above, one of the most interesting being that of Ogston<sup>77</sup> which postulates a three-point contact between enzyme and substrate. It has been pointed out, however, by several investigators<sup>78, 79, 80</sup> that the above result can be predicted without any specific postulates as to the

<sup>77</sup> A. G. Ogston, *Nature*, **162**, 963 (1948).

<sup>78</sup> P. Schwartz and H. E. Carter, *Proc. Natl. Acad. Sci. U.S.A.*, **40**, 499 (1954).

<sup>79</sup> R. Altschul, P. Bernstein, and S. G. Cohen, *J. Am. Chem. Soc.*, **78**, 5091 (1956); S. G. Cohen and E. Khedouri, *Nature*, **186**, 75 (1960).

nature of the enzyme-substrate interaction. In a molecule C<sub>x</sub>xyz (or, for that matter, in any molecule which has two identical atoms or groups attached to the carbon skeleton *but which is devoid of a simple axis of symmetry*†) the two identical groups are not identically located with respect to the rest of the molecule, but the relationship of one group to the rest of the molecule is the mirror image of the relationship of the other group. As long as only symmetric reagents are considered, this is of no consequence, but toward a dissymmetric reagent (such as an enzyme) the two groups may behave differently and react at different rates. This is true even if the reagent or catalyst (enzyme) does not become incorporated in the product but only in the transition state or an intermediate (e.g., page 72), in fact, the product need not be dissymmetric at all (e.g., the case depicted in Fig. 4-51).‡

#### 4-5. Criteria of Optical Purity

By optical purity of a partially resolved material is meant the excess of one enantiomer in the material expressed as a percentage of the total. In a *dl* pair, there is no excess enantiomer and the optical purity is zero; in a completely resolved material, the excess enantiomer is equal in weight to the total material and the optical purity is 100%. It is often desirable to find out whether a given resolution has gone to completion, i.e., whether the enantiomer obtained is really 100% optically pure. Several simple criteria of optical purity have been developed, but none is completely reliable. For example, a crystalline enantiomer is often considered optically pure when its melting point and rotation are unchanged by further crystallization. Reference to Fig. 4-19 shows that such a criterion usually fails when the racemic modification forms a solid solution, since in that case even a *partially* resolved enantiomer may not change in either rotation or melting point by further recrystallization. A resolution is often deemed complete when the diastereoisomeric salt employed (Sec. 4-4b) does not change in rotation upon further crystallization. This criterion may also be foiled by certain special types of phase behavior. Finally, resolution is often deemed complete once *both* enantiomers are obtained in a state of equal purity (i.e., with equal and opposite specific rotation), the argument being that, since both were resolved in independent fashion, there is no reason why both should have equal rotations (of opposite signs) unless these rotations are maximal. This approach is not applicable when one of the enantiomers is not readily obtained pure; in that case one cannot tell whether the other one is pure either.

† The reader might note that we are speaking here of molecules devoid of a *simple axis* of symmetry, as distinct from Sec. 2-2 where criteria for optical activity were set up and it was found that molecules lacking an *alternating axis* of symmetry would show mirror-image forms.

‡ The explanation given here is a purely *thermodynamic* one (considering transition-state theory as an extension of thermodynamics); i.e., it says that the two methylene groups in citric acid *may* behave differently toward a dissymmetric reagent and that such behavior is entirely reasonable on the basis of energy differences between diastereoisomeric transition states. This does not mean that such differential behavior will necessarily be observed, i.e., that there is necessarily a *mechanistic* path to implement the potential difference. Ogston's explanation (Ref. 77) may still be useful in providing a picture for such a mechanistic path, thus rationalizing why what is thermodynamically permitted does actually occur.

There are three other ways known of determining optical purity (at least within specifiable experimental limits): an enzymatic method, an isotope dilution method, and a method of relating a compound of unknown optical purity to another one whose purity is known.

The enzymatic method depends on the fact that many enzymes are highly selective for one enantiomer of a *dl* pair.<sup>†</sup> If one incubates a supposedly pure preparation of the *other* enantiomer with such an enzyme, reaction (which must be detectable by suitable means) would indicate the presence of some of the wrong antipode, owing to incomplete resolution or racemization following complete resolution, whereas the absence of reaction would indicate purity.<sup>‡</sup> For example, an L-amino acid oxidase which is almost completely inert to D-amino acids can be isolated from rattlesnakes. A supposedly pure D-amino acid, when treated with this enzyme in a Warburg apparatus in the presence of oxygen, will take up none of this gas, but if L-amino acid is present as an impurity, gas consumption will be registered. The test is supposedly sensitive to 1 part in 1000 of the "wrong" antipode. This method is obviously limited in its application to optically active compounds that are subject to enzymatic reactions.

In the isotope dilution method, the supposedly pure [let us say (–)] enantiomer is mixed with some labeled (radioactively or otherwise) racemic material in solution, and the racemic material is then reisolated (usually by crystallization).<sup>||</sup> Since in solution the racemic material is split up into labeled (+) molecules and (–) molecules, the labeled (–) molecules get commingled with the molecules of the enantiomer whose optical purity is to be determined, but the (+) molecules do not (provided that the enantiomer was pure). One can thus calculate a dilution factor, knowing the weight of the original active material and the weight of the added labeled racemic material, and can thus predict how active the recovered labeled racemic material should be. The predicted activity is then compared with that experimentally found. If the experimental activity is less than that predicted, it indicates that there was some residual (unlabeled) racemic material in the supposedly pure enantiomer. For if one mixes labeled racemic material with unlabeled (–) material, only the (–) molecules in the recovered *dl* pair get diluted isotopically, but if one mixes it with unlabeled racemic material, then *all* molecules in the recovered *dl* pair will be diluted, i.e., the dilution factor will be greater. In fact, a relationship may be established<sup>80</sup>

$$C_{\pm} = aC_0 \frac{a + B}{(2B + a - R)(a + R)}$$

where  $C_0$  is the activity of the added racemic material,  $C_{\pm}$  is the activity of

<sup>†</sup> Not all enzymes are equally stereoselective, and the stereoselectivity of a given enzyme varies with the substrate.

<sup>‡</sup> It is assumed that the substrate is *chemically* pure, so that the only contaminant which could possibly be affected by the enzyme is the antipode of the desired compound.

<sup>||</sup> The method is dependent on the possibility of reisolating the racemate in pure form.

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<sup>80</sup> J. A. Benson and D. A. Ben-Efraim, *J. Am. Chem. Soc.*, **81**, 4083 (1959); cf. S. Graff, D. Rittenberg, and G. L. Foster, *J. Biol. Chem.*, **133**, 745 (1940).

the recovered racemic material,  $a$  is the weight of the added racemic material,  $B$  is the weight of the resolved material (whose purity is to be tested) admixed with  $a$ , and  $R$  is the weight of racemate (if any) in the amount  $B$ . By solving the above equation for  $R$ , knowing all the other quantities from experiment, one may calculate the amount of racemic contaminant and hence the optical purity which will be

$$100 \frac{B - R\%}{B}$$

The third method for determining optical purity is a correlative method. Suppose that the optical purity of a compound Cabde is known. The *minimum* purity of another compound Cabdf may be determined if Cabdf can be converted chemically to Cabde. Cabdf will be *at least* as pure optically as the Cabde prepared from it. (It may be *more* pure, for the reaction converting Cabdf to Cabde may have involved some racemization, and so the Cabde actually obtained may be less pure than the Cabdf starting material.) The following example will illustrate this method. The highest known rotation<sup>81</sup> of  $\alpha$ -phenethyl chloride,  $C_6H_5CHClCH_3$ , is  $\alpha_D^{25}$  (neat, 1 dm.)  $109^\circ$ .† When dextrorotatory material of this rotation is allowed to react with allylsodium and the resulting 4-phenyl-1-pentene,  $CH_2=CHCH_2CH(C_6H_5)CH_3$ , hydrogenated to 2-phenylpentane,  $CH_3CH_2CH_2CH(C_6H_5)CH_3$ , one obtains material of rotation  $\alpha_D^{25} - 12.96^\circ$  (neat, 1 dm.).‡ Since the known rotation of optically pure 2-phenylpentane, established in other ways, is  $\alpha_D^{25} 14.91^\circ$ , the optical purity of the hydrocarbon obtained from the chloride is  $12.96/14.91 \times 100$  or 86.9%. The *minimum* optical purity of chloride of  $\alpha_D^{25} 109^\circ$  is therefore also 86.9%, and it follows that the *maximum* possible rotation of  $\alpha$ -phenethyl chloride is  $109 \times 100/86.9$ , or  $125.4^\circ$ .

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† This rotation ( $109^\circ$ ) is obviously the *minimum* rotation of optically pure chloride.

‡ Actually, chloride of  $\alpha_D^{25} + 77.89^\circ$  gave 2-phenylpentane of  $\alpha_D^{25} - 9.26^\circ$ .