4

STEREOCHEMISTRY

In the previous chapters we discussed electron distribution in organic molecules. In this chapter we discuss the three-dimensional structure of organic compounds.[1] The structure may be such that *stereoisomerism*[2] is possible. Stereoisomers are compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable. These three-dimensional structures are called *configurations*.

OPTICAL ACTIVITY AND CHIRALITY

Any material that rotates the plane of polarized light is said to be *optically active*. If a pure compound is optically active, the molecule is nonsuperimposable on its mirror image. If a molecule is superimposable on its mirror image, the compound does not rotate the plane of polarized light; it is *optically inactive*. The property of nonsuperimposability of an object on its mirror image is called *chirality*. If a molecule is not superimposable on its mirror image, it is *chiral*. If it is superimposable on its mirror image, it is *achiral*. The relationship between optical activity and chirality is absolute. No exceptions are known, and many thousands of cases have been found in accord with it (however, see p. 98). The ultimate criterion, then, for optical activity is chirality (nonsuperimposability on the mirror image). This is both a necessary and a sufficient condition.[3] This fact has been used as evidence for the structure determination of many compounds, and historically the tetrahedral nature of carbon was deduced from the hypothesis that the relationship might be true.

If a molecule is nonsuperimposable on its mirror image, the mirror image must be a different molecule, since superimposability is the same as identity. In each case of optical activity of a pure compound there are two and only two isomers, called *enantiomers* (sometimes *enantiomorphs*), which differ in structure only in the left- and right-handedness of

[1]For books on this subject, see Sokolov *Introduction to Theoretical Stereochemistry*; Gordon and Breach: New York, 1991; Bassindale *The Third Dimension in Organic Chemistry*; Wiley: New York, 1984; Nógrádi. *Sterochemistry*; Pergamon: Elmsford, NY, 1981; Kagan *Organic Sterochemistry*; Wiley: New York, 1979; Testa *Principles of Organic Stereochemistry*; Marcel Dekker: New York, 1979; Izumi; Tai *Stereo-Differentiating Reactions;* Academic Press: New York, Kodansha Ltd.: Tokyo, 1977; Natta; Farina *Stereochemistry*; Harper and Row: New York, 1972; Eliel *Elements of Stereochemistry*; Wiley: New York, 1969; Mislow *Introduction to Stereochemistry*; W. A. Benjamin: New York, 1965. Three excellent treatments of stereochemistry that, though not recent, contain much that is valid and useful, are Eliel *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; Wheland *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1960, pp. 195-514; Shriner; Adams; Marvel, in Gilman *Advanced Organic Chemistry*; vol. 1, 2nd ed.; Wiley: New York, 1943, pp. 214-488. For a historical treatment, see Ramsay *Stereochemistry*; Heyden & Son, Ltd.: London, 1981.

[2]The IUPAC 1974 Recommendations, Section E, Fundamental Stereochemistry, give definitions for most of the terms used in this chapter, as well as rules for naming the various kinds of stereoisomers. They can be found in *Pure Appl. Chem.* **1976,** *45*, 13-30 and in *Nomenclature of Organic Chemistry*; Pergamon: Elmsford, NY, 1979 (the "Blue Book").

[3]For a discussion of the conditions for optical activity in liquids and crystals, see O'Loane *Chem. Rev.* **1980,** *80*, 41-61. For a discussion of chirality as applied to molecules, see Quack *Angew. Chem. Int. Ed. Engl.* **1989,** *28*, 571-586 [*Angew. Chem. 101*, 588-604].

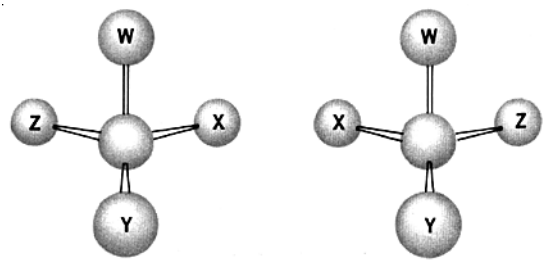


FIGURE 4.1 Enantiomers.

their orientations (Figure 4.1). Enantiomers have identical[4] physical and chemical properties except in two important respects:

1. They rotate the plane of polarized light in opposite directions, though in equal amounts. The isomer that rotates the plane to the left (counterclockwise) is called the *levo isomer* and is designated (−), while the one that rotates the plane to the right (clockwise) is called the *dextro isomer* and is designated (+). Because they differ in this property they are often called *optical antipodes*.

2. They react at different rates with other chiral compounds. These rates may be so close together that the distinction is practically useless, or they may be so far apart that one enantiomer undergoes the reaction at a convenient rate while the other does not react at all. This is the reason that many compounds are biologically active while their enantiomers are not. Enantiomers react at the same rate with achiral compounds.[4a]

In general, it may be said that enantiomers have identical properties in a symmetrical environment, but their properties may differ in an unsymmetrical environment.[5] Besides the important differences previously noted, enantiomers may react at different rates with achiral molecules if an optically active *catalyst* is present; they may have different solubilities in an optically active *solvent*; they may have different indexes of refraction or absorption spectra *when examined with circularly polarized light*, etc. In most cases these differences are too small to be useful and are often too small to be measured.

Although pure compounds are always optically active if they are composed of chiral molecules, mixtures of equal amounts of enantiomers are optically inactive since the equal and opposite rotations cancel. Such mixtures are called *racemic mixtures*[6] or *racemates*.[7] Their properties are not always the same as those of the individual enantiomers. The properties in the gaseous or liquid state or in solution usually are the same, since such a mixture is nearly ideal, but properties involving the solid state,[8] such as melting points, solubilities, and heats of fusion, are often different. Thus racemic tartaric acid has a melting point of 204-206°C and a solubility in water at 20°C of 206 g/liter, while for the (+) or the (−)

[4]Interactions between electrons, nucleons, and certain components of nucleons (e.g., bosons), called *weak interactions*, violate parity; that is, mirror image interactions do not have the same energy. It has been contended that interactions of this sort cause one of a pair of enantiomers to be (slightly) more stable than the other. See Tranter *J. Chem. Soc., Chem. Commun.* **1986,** 60, and references cited therein. See also Ref. 13.

[4a]For a reported exception, see Hata *Chem. Lett.* **1991,** 155.

[5]For a review of discriminating interactions between chiral molecules, see Craig; Mellor *Top. Curr. Chem.* **1976,** *63*, 1-48.

[6]Strictly speaking, the term *racemic mixture* applies only when the mixture of molecules is present as separate solid phases, but in this book we shall use this expression to refer to any equimolar mixture of enantiomeric molecules, liquid, solid, gaseous, or in solution.

[7]For a monograph on the properties of racemates and their resolution, see Jacques; Collet; Wilen *Enantiomers, Racemates, and Resolutions*; Wiley: New York, 1981.

[8]For a discussion, see Wynberg; Lorand *J. Org. Chem.* **1981,** *46*, 2538 and references cited therein.

enantiomer, the corresponding figures are 170°C and 1390 g/liter. The separation of a racemic mixture into its two optically active components is called *resolution*. The presence of optical activity always proves that a given compound is chiral, but its absence does not prove that the compound is achiral. A compound that is optically inactive may be achiral, or it may be a racemic mixture (see also p. 98).

Dependence of Rotation on Conditions of Measurement

The *amount* of rotation α is not a constant for a given enantiomer; it depends on the length of the sample vessel, the temperature, the solvent[9] and concentration (for solutions), the pressure (for gases), and the wavelength of light.[10] Of course, rotations determined for the same compound under the same conditions are identical. The length of the vessel and the concentration or pressure determine the number of molecules in the path of the beam and α is linear with this. Therefore, a number is defined, called the *specific rotation* $[\alpha]$, which is

$$[\alpha] = \frac{\alpha}{lc} \text{ for solutions} \qquad [\alpha] = \frac{\alpha}{ld} \text{ for pure compounds}$$

where α is the observed rotation, l is the cell length in decimeters, c is the concentration in grams per milliliter, and d is the density in the same units. The specific rotation is usually given along with the temperature and wavelength, in this manner: $[\alpha]^{25}_{546}$. These conditions must be duplicated for comparison of rotations, since there is no way to put them into a simple formula. The expression $[\alpha]_D$ means that the rotation was measured with sodium D light; i.e., $\lambda = 589$ nm. The molar rotation $[M]^t_\lambda$ is the specific rotation times the molecular weight divided by 100.

It must be emphasized that although the value of α changes with conditions, the molecular structure is unchanged. This is true even when the changes in conditions are sufficient to change not only the amount of rotation but even the direction. Thus one of the enantiomers of aspartic acid, when dissolved in water, has $[\alpha]_D$ equal to $+4.36°$ at 20°C and $-1.86°$ at 90°C, though the molecular structure is unchanged. A consequence of such cases is that there is a temperature at which there is *no* rotation (in this case 75°C). Of course, the other enantiomer exhibits opposite behavior. Other cases are known in which the direction of rotation is reversed by changes in wavelength, solvent, and even concentration.[11] In theory, there should be no change in $[\alpha]$ with concentration, since this is taken into account in the formula, but associations, dissociations, and solute–solvent interactions often cause nonlinear behavior. For example, $[\alpha]^{24}_D$ for (−)-2-ethyl-2-methylsuccinic acid in $CHCl_3$ is $-5.0°$ at $c = 16.5$, $-0.7°$ at $c = 10.6$, $+1.7°$ at $c = 8.5$, and $+18.9°$ at $c = 2.2$.[12]

What Kinds of Molecules Display Optical Activity?

Although the ultimate criterion is, of course, nonsuperimposability on the mirror image (chirality), other tests may be used that are simpler to apply but not always accurate. One such test is the presence of a *plane of symmetry*.[13] A plane of symmetry[14] (also called a

[9] A good example is found in Kumata; Furukawa; Fueno *Bull. Chem. Soc. Jpn.* **1970,** *43*, 3920.

[10] For a review of polarimetry, see Lyle; Lyle, in Morrison, Ref. 88, vol. 1, pp. 13-27.

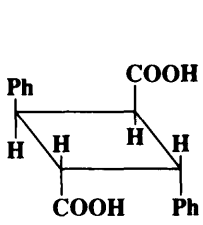
[11] For examples, see Shriner; Adams; Marvel, Ref. 1, pp. 291-301.

[12] Krow; Hill *Chem. Commun.* **1968,** 430.

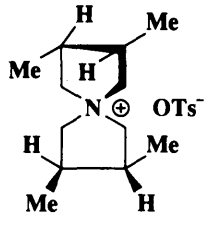
[13] For a theoretical discussion of the relationship between symmetry and chirality, including parity violation (Ref. 4), see Barron *Chem. Soc. Rev.* **1986,** *15*, 189-223.

[14] The definitions of plane, center, and alternating axis of symmetry are taken from Eliel *Elements of Stereochemistry*, Ref. 1, pp. 6,7. See also Lemière; Alderweireldt *J. Org. Chem.* **1980,** *45*, 4175.

mirror plane) is a plane passing through an object such that the part on one side of the plane is the exact reflection of the part on the other side (the plane acting as a mirror). *Compounds possessing such a plane are always optically inactive*, but there are a few cases known in which compounds lack a plane of symmetry and are nevertheless inactive. Such compounds possess a *center of symmetry*, such as in α-truxillic acid, or an *alternating axis of symmetry* as in **1**.[15] A center of symmetry[14] is a point within an object such that a straight



α-truxillic acid



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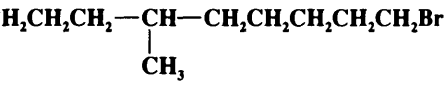
line drawn from any part or element of the object to the center and extended an equal distance on the other side encounters an equal part or element. An alternating axis of symmetry[14] of order *n* is an axis such that when an object containing such an axis is rotated by 360°/*n* about the axis and then reflection is effected across a plane at right angles to the axis, a new object is obtained that is indistinguishable from the original one. Compounds that lack an alternating axis of symmetry are always chiral.

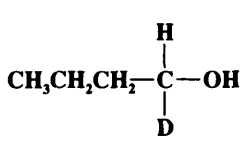
A molecule that contains just one *chiral carbon atom* (defined as a carbon atom connected to four different groups; also called an *asymmetric carbon atom*) is always chiral and hence optically active.[16] As seen in Figure 4.1, such a molecule cannot have a plane of symmetry, whatever the identity of W, X, Y, and Z, as long as they are all different. However, the presence of a chiral carbon is neither a necessary nor a sufficient condition for optical activity, since optical activity may be present in molecules with no chiral atom[17] and since some molecules with two or more chiral carbon atoms are superimposable on their mirror images and hence inactive. Examples of such compounds will be discussed subsequently.

Optically active compounds may be classified into several categories.

1. *Compounds with a chiral carbon atom.* If there is only one such atom, the molecule must be optically active. This is so no matter how slight the differences are among the four groups. For example, optical activity is present in



Optical activity has been detected even in cases[18] such as 1-butanol-1-*d*, where one group is hydrogen and another deuterium.[19]



[15]McCasland; Proskow *J. Am. Chem. Soc.* **1955**, *77*, 4688.

[16]For discussions of the relationship between a chiral carbon and chirality, see Mislow; Siegel *J. Am. Chem. Soc.* **1984**, *106*, 3319; Brand; Fisher *J. Chem. Educ.* **1987**, *64*, 1035.

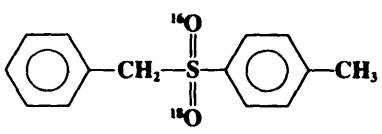
[17]For a review of such molecules, see Nakazaki *Top. Stereochem.* **1984**, *15*, 199-251.

[18]For reviews of compounds where chirality is due to the presence of deuterium or tritium, see Barth; Djerassi *Tetrahedron* **1981**, *24*, 4123-4142; Arigoni; Eliel *Top. Stereochem.* **1969**, *4*, 127-243; Verbit *Prog. Phys. Org. Chem.* **1970**, 7, 51-127. For a review of compounds containing chiral methyl groups, see Floss; Tsai; Woodard *Top. Stereochem.* **1984**, *15*, 253-321.

[19]Streitwieser; Schaeffer *J. Am. Chem. Soc.* **1956**, *78*, 5597.

However, the amount of rotation is greatly dependent on the nature of the four groups, in general increasing with increasing differences in polarizabilities among the groups. Alkyl groups have very similar polarizabilities[20] and the optical activity of 5-ethyl-5-propylundecane is too low to be measureable at any wavelength between 280 and 580 nm.[21]

2. *Compounds with other quadrivalent chiral atoms.*[22] Any molecule containing an atom that has four bonds pointing to the corners of a tetrahedron will be optically active if the four groups are different. Among atoms in this category are Si,[23] Ge, Sn,[24] and N (in quaternary salts or N-oxides).[25] In sulfones the sulfur bonds tetrahedrally, but since two of the groups are always oxygen, no chirality normally results. However, the preparation[26] of



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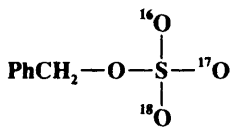

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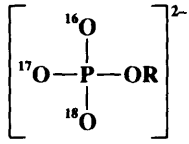

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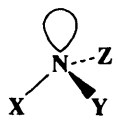
an optically active sulfone (**2**) in which one oxygen is ^{16}O and the other ^{18}O illustrates the point that slight differences in groups are all that is necessary. This has been taken even further with the preparation of the ester **3**, both enantiomers of which have been prepared.[27] Optically active chiral phosphates **4** have similarly been made.[28]

3. *Compounds with tervalent chiral atoms.* Atoms with pyramidal bonding[29] might be expected to give rise to optical activity if the atom is connected to three different groups, since the unshared pair of electrons is analogous to a fourth group, necessarily different from the others. For example, a secondary or tertiary amine where X, Y, and Z are different



would be expected to be chiral and thus resolvable. Many attempts have been made to resolve such compounds, but until 1968 all of them failed because of *pyramidal inversion*, which is a rapid oscillation of the unshared pair from one side of the XYZ plane to the other, thus converting the molecule into its enantiomer.[30] For ammonia there are 2×10^{11}

[20]For a discussion of optical activity in paraffins, see Brewster *Tetrahedron* **1974,** *30*, 1807.

[21]Wynberg; Hekkert; Houbiers; Bosch *J. Am. Chem. Soc.* **1965,** *87*, 2635; Wynberg and Hulshof *Tetrahedron* **1974,** *30*, 1775; Ten Hoeve; Wynberg *J. Org. Chem.* **1980,** *45*, 2754.

[22]For reviews of compounds with asymmetric atoms other than carbon, see Aylett *Prog. Stereochem.* **1969,** *4*, 213-217; Belloli *J. Chem. Educ.* **1969,** *46*, 640-644; Sokolov; Reutov *Russ. Chem. Rev.* **1965,** *34*, 1-12.

[23]For reviews of stereochemistry of silicon, see Corriu; Guérin; Moreau, in Patai; Rappoport *The Chemistry of Organic Silicon Compounds*; pt. 1: Wiley: New York, 1989, pp. 305-370, *Top. Stereochem.* **1984,** *15*, 43-198; Maryanoff; Maryanoff, in Morrison, Ref. 88, vol. 4, pp. 355-374.

[24]For reviews of the stereochemistry of Sn and Ge compounds, see Gielen *Top. Curr. Chem.* **1982,** *104*, 57-105; *Top. Stereochem.* **1981,** *12*, 217-251.

[25]For a review, see Davis; Jenkins, in Morrison, Ref. 88, vol. 4, pp. 313-353. The first resolution of a quaternary ammonium salt of this type was done by Pope; Peachey *J. Chem. Soc.* **1899,** *75*, 1127.

[26]Stirling *J. Chem. Soc.* **1963,** 5741; Sabol; Andersen *J. Am. Chem. Soc.* **1969,** *91*, 3603; Annunziata; Cinquini; Colonna *J. Chem. Soc., Perkin Trans. 1* **1972,** 2057.

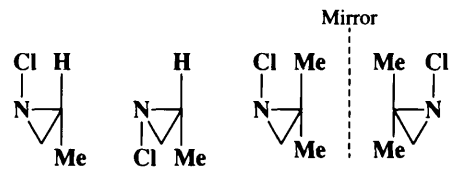
[27]Lowe; Salamone *J. Chem. Soc., Chem. Commun.* **1984,** 466; Lowe; Parratt *J. Chem. Soc., Chem. Commun.* **1985,** 1075.

[28]Abbott; Jones; Weinman; Knowles *J. Am. Chem. Soc.* **1978,** *100*, 2558; Cullis; Lowe *J. Chem. Soc., Chem. Commun.* **1978,** 512. For a review, see Lowe *Acc. Chem. Res.* **1983,** *16*, 244-251.

[29]For a review of the stereochemistry at trivalent nitrogen, see Raban and Greenblatt, in Patai *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley: New York, 1982, pp. 53-83.

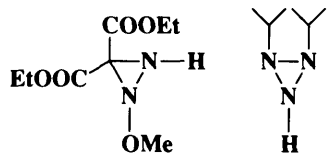
[30]For reviews of the mechanism of, and the effect of structure on, pyramidal inversion, see Lambert *Top. Stereochem.* **1971,** *6*, 19-105; Rauk; Allen; Mislow *Angew. Chem. Int. Ed. Engl.* **1970,** 9, 400-414 [*Angew. Chem. 82*, 453-468]; Lehn *Fortschr. Chem. Forsch.* **1970,** *15*, 311-377; Mislow *Pure Appl. Chem.* **1968,** *25*, 549-562.

inversions every second. The inversion is less rapid in substituted ammonias[31] (amines, amides, etc.). Two types of nitrogen atom invert particularly slowly, namely, a nitrogen atom in a three-membered ring and a nitrogen atom connected to another atom bearing an unshared pair. Even in such compounds, however, for many years pyramidal inversion proved too rapid to permit isolation of separate isomers. This goal was accomplished[25] only when compounds were synthesized in which both features are combined: a nitrogen atom in a three-membered ring connected to an atom containing an unshared pair. For example, the two isomers of 1-chloro-2-methylaziridine (**5** and **6**) were separated and do not interconvert at room temperature.[32] In suitable cases this barrier to inversion can result in compounds that are optically active solely because of a chiral tervalent nitrogen atom. For

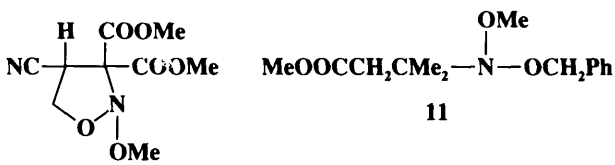


trans cis

5 **6** **7**



8 **9**



10 **11**

example, **7** has been resolved into its separate enantiomers.[32a] Note that in this case too, the nitrogen is connected to an atom with an unshared pair. Conformational stability has also been demonstrated for oxaziridines,[33] diaziridines, e.g., **8**,[34] triaziridines, e.g. **9**,[35] and

[31]For example, see Andose; Lehn; Mislow; Wagner *J. Am. Chem. Soc.* **1970,** *92*, 4050; Stackhouse; Baechler; Mislow *Tetrahedron Lett.* **1971,** 3437, 3441.

[32]Brois *J. Am. Chem. Soc.* **1968,** *90*, 506, 508. See also Shustov; Kadorkina; Kostyanovsky; Rauk *J. Am. Chem. Soc.* **1988,** *110*, 1719; Lehn; Wagner *Chem. Commun.* **1968,** 148; Felix; Eschenmoser *Angew. Chem. Int. Ed. Engl.* **1968,** *7*, 224 [*Angew. Chem. 80*, 197]; Kostyanovsky; Samoilova; Chervin *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1968,** 2705, *Tetrahedron Lett.* **1969,** 719. For a review, see Brois *Trans. N.Y. Acad. Sci.* **1969,** *31*, 931-951.

[32a]Schurig; Leyrer *Tetrahedron: Asymmetry* **1990,** *1*, 865.

[33]Boyd *Tetrahedron Lett.* **1968,** 4561; Boyd; Spratt; Jerina *J. Chem. Soc. C* **1969,** 2650; Montanari; Moretti; Torre *Chem. Commun.* **1968,** 1694, **1969,** 1086; Bucciarelli; Forni; Moretti; Torre; Prosyanik; Kostyanovsky *J. Chem. Soc., Chem. Commun.* **1985,** 998; Bucciarelli; Forni; Moretti; Torre; Brückner; Malpezzi *J. Chem. Soc., Perkin Trans. 2* **1988,** 1595. See also Mannschreck; Linss; Seitz *Liebigs Ann. Chem.* **1969,** *727*, 224; Forni; Moretti; Torre; Brückner; Malpezzi; Di Silvestro *J. Chem. Soc., Perkin Trans. 2* **1984,** 791. For a review of oxaziridines, see Schmitz *Adv. Heterocycl. Chem.* **1979,** *24*, 63-107.

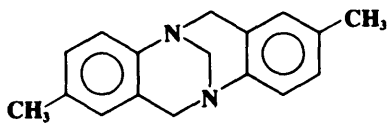
[34]Rudchenko; D'yachenko; Zolotoi; Atovmyan; Chervin; Kostyanovsky *Tetrahedron* **1982,** *38*, 961; Shustov; Denisenko; Chervin; Asfandiarov; Kostyanovsky *Tetrahedron* **1985,** *41*, 5719 and references cited in these papers. See also Mannschreck; Radeglia; Gründemann; Ohme *Chem. Ber.* **1967,** *100*, 1778.

[35]Hilpert; Hoesch; Dreiding *Helv. Chim. Acta* **1985,** *68*, 1691, **1987,** *70*, 381.

1,2-oxazolidines, e.g., **10**,[36] even though in this case the ring is five-membered. However, note that the nitrogen atom in **10** is connected to two oxygen atoms.

Another compound in which nitrogen is connected to two oxygens is **11**. In this case there is no ring at all, but it has been resolved into (+) and (−) enantiomers ($[\alpha]_D^{20} \approx \pm 3°$).[37] This compound and several similar ones reported in the same paper are the first examples of compounds whose optical activity is solely due to an acyclic tervalent chiral nitrogen atom. However, **11** is not optically stable and racemizes at 20°C with a half-life of 1.22 hr. A similar compound (**11**, with OCH_2Ph replaced by OEt) has a longer half-life—37.5 hr at 20°C.

In molecules in which the nitrogen atom is at a bridgehead, pyramidal inversion is of course prevented. Such molecules, if chiral, can be resolved even without the presence of the two structural features noted above. For example, optically active **12** (Tröger's base)



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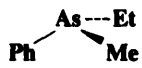
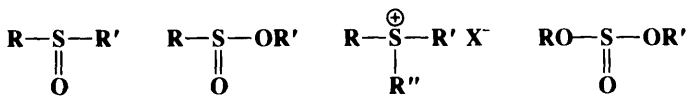


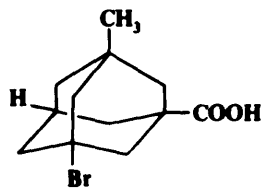
13

has been prepared.[38] Phosphorus inverts more slowly and arsenic still more slowly.[39] Non-bridgehead phosphorus,[40] arsenic, and antimony compounds have also been resolved, e.g., **13**.[41] Sulfur exhibits pyramidal bonding in sulfoxides, sulfinic esters, sulfonium salts, and sulfites. Examples of each of these have been resolved.[42] An interesting example is



(+)-$Ph^{12}CH_2SO^{13}CH_2Ph$, a sulfoxide in which the two alkyl groups differ only in ^{12}C versus ^{13}C but which has $[\alpha]_{280} = +0.71°$.[43]

4. *Suitably substituted adamantanes.* Adamantanes bearing four different substituents at the bridgehead positions are chiral and optically active and **14**, for example, has been



14

[36]Müller; Eschenmoser *Helv. Chim. Acta* **1969**, *52*, 1823; Dobler; Dunitz; Hawley *Helv. Chim. Acta* **1969**, *52*, 1831.

[37]Kostyanovsky; Rudchenko; Shtamburg; Chervin; Nasibov *Tetrahedron* **1981**, *37*, 4245; Kostyanovsky; Rudchenko *Doklad. Chem.* **1982**, *263*, 121. See also Rudchenko; Ignatov; Chervin; Kostyanovsky *Tetrahedron* **1988**, *44*, 2233.

[38]Prelog; Wieland *Helv. Chim. Acta* **1944**, *27*, 1127.

[39]For reviews, see Yambushev; Savin *Russ. Chem. Rev.* **1979**, *48*, 582-595; Gallagher; Jenkins *Top. Stereochem.* **1968**, *3*, 1-96; Kamai; Usacheva *Russ. Chem. Rev.* **1966**, *35*, 601-613.

[40]For a review of chiral phosphorus compounds, see Valentine, in Morrison, Ref. 88, vol. 4, pp. 263-312.

[41]Horner; Fuchs *Tetrahedron Lett.* **1962**, 203.

[42]For reviews of chiral organosulfur compounds, see Andersen, in Patai; Rappoport; Stirling *The Chemistry of Sulphones and Sulphoxides*; Wiley: New York, 1988, pp. 55-94; and in Stirling *The Chemistry of the Sulphonium Group*, pt. 1, Wiley: New York, 1981, pp. 229-312; Barbachyn; Johnson, in Morrison, Ref. 88, vol. 4, pp. 227-261; Cinquini; Cozzi; Montanari, in Bernardi; Csizmadia; Mangini *Organic Sulfur Chemistry*; Elsevier: New York, 1985, pp. 355-407; Mikołajczyk; Drabowicz *Top. Stereochem.* **1982**, *13*, 333-468.

[43]Andersen; Colonna; and Stirling, *J. Chem. Soc., Chem. Commun.* **1973**, 645.

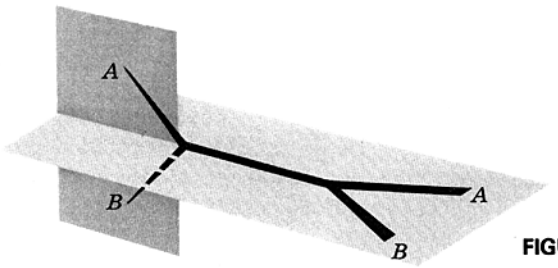
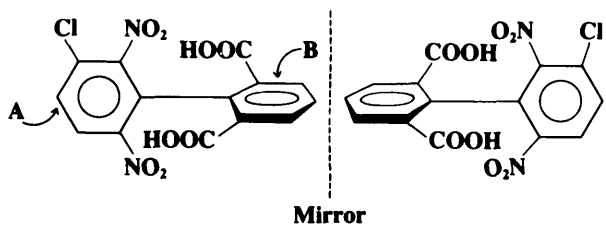


FIGURE 4.2 Perpendicular disymmetric planes.

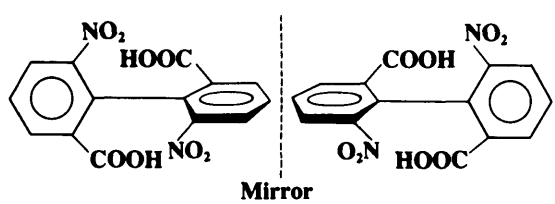
resolved.[44] This type of molecule is a kind of expanded tetrahedron and has the same symmetry properties as any other tetrahedron.

5. *Restricted rotation giving rise to perpendicular disymmetric planes.* Certain compounds that do not contain asymmetric atoms are nevertheless chiral because they contain a structure that can be schematically represented as in Figure 4.2. For these compounds we can draw two perpendicular planes neither of which can be bisected by a plane of symmetry. If either plane could be so bisected, the molecule would be superimposable on its mirror image, since such a plane would be a plane of symmetry. These points will be illustrated by examples.

Biphenyls containing four large groups in the ortho positions cannot freely rotate about the central bond because of steric hindrance.[45] In such compounds the two rings are in perpendicular planes. If either ring is symmetrically substituted, the molecule has a plane of symmetry. For example, consider:



Ring B is symmetrically substituted. A plane drawn perpendicular to ring B contains all the atoms and groups in ring A; hence it is a plane of symmetry and the compound is achiral. On the other hand, consider:



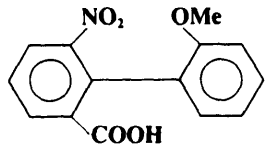
There is no plane of symmetry and the molecule is chiral; many such compounds have been resolved. Note that groups in the para position cannot cause lack of symmetry. Isomers that

[44]Hamill; McKervey *Chem. Commun.* **1969,** 864; Applequist; Rivers; Applequist *J. Am. Chem. Soc.* **1969,** *91,* 5705.

[45]When the two rings of a biphenyl are connected by a bridge, rotation is of course impossible. For a review of such compounds, see Hall *Prog. Stereochem.* **1969,** *4,* 1-42.

can be separated only because rotation about single bonds is prevented or greatly slowed are called *atropisomers*.[46]

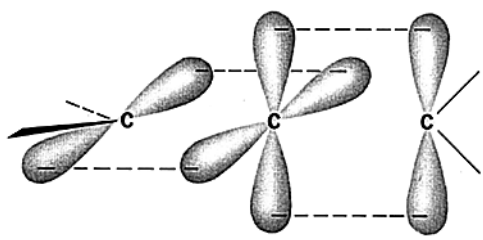
It is not always necessary for four large ortho groups to be present in order for rotation to be prevented. Compounds with three and even two groups, if large enough, can have hindered rotation and, if suitably substituted, can be resolved. An example is biphenyl-2,2'-bissulfonic acid.[47] In some cases, the groups may be large enough to slow rotation greatly but not to prevent it completely. In such cases, optically active compounds can be prepared that slowly racemize on standing. Thus, **15** loses its optical activity with a half-life



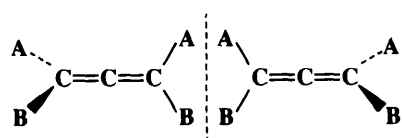
15

of 9.4 min in ethanol at 25°C.[48] Compounds with greater rotational stability can often be racemized if higher temperatures are used to supply the energy necessary to force the groups past each other.[49] Many analogous cases are known, where optical activity arises from hindered rotation of other types of aromatic ring, e.g., binaphthyls, bipyrryls, etc.

In allenes the central carbon is *sp*-bonded. The remaining two *p* orbitals are perpendicular to each other and each overlaps with the *p* orbital of one adjacent carbon atom, forcing the

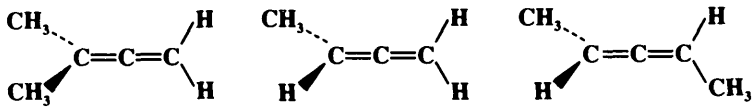


two remaining bonds of each carbon into perpendicular planes. Thus allenes fall into the category represented by Figure 4.2:



[46]For a review, see Ōki *Top. Stereochem.* **1983,** *14*, 1-81.
[47]Patterson; Adams *J. Am. Chem. Soc.* **1935,** *57*, 762.
[48]Stoughton; Adams *J. Am. Chem. Soc.* **1932,** *54*, 4426.
[49]For a monograph on the detection and measurement of restricted rotations, see Ōki *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH: New York, 1985.

Like biphenyls, allenes are chiral only if both sides are unsymmetrically substituted.[50] For example,

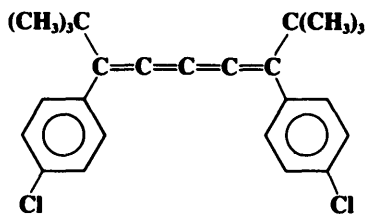


Inactive Inactive Active

These cases are completely different from the cis-trans isomerism of compounds with one double bond (p. 127). In the latter cases the four groups are all in one plane, the isomers are not enantiomers, and neither is chiral, while in allenes the groups are in two perpendicular planes and the isomers are a pair of optically active enantiomers.

When three, five, or any *odd* number of cumulative double bonds exist, orbital overlap causes the four groups to occupy one plane and cis–trans isomerism is observed. When four, six, or any *even* number of cumulative double bonds exist, the situation is analogous to that in the allenes and optical activity is possible. **16** has been resolved.[51]

Among other types of compounds that contain the system illustrated in Figure 4.2 and



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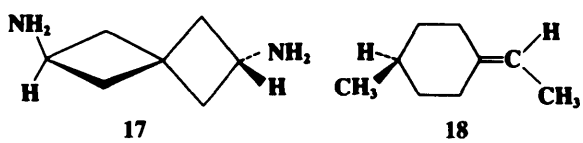


17 **18**

that are similarly chiral if both sides are dissymmetric are spiranes, e.g., **17**, and compounds with exocyclic double bonds, e.g., **18**.

6. *Chirality due to a helical shape.*[52] Several compounds have been prepared that are chiral because they have a shape that is actually helical and can therefore be left- or right-handed in orientation. The entire molecule is usually less than one full turn of the helix, but this does not alter the possibility of left- and right-handedness. An example is hexahelicene,[53] in which one side of the molecule must lie above the other because of

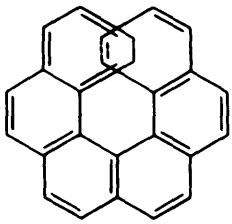
[50]For reviews of allene chirality, see Runge, in Landor *The Chemistry of the Allenes*, vol. 3; Academic Press: New York, 1982, pp. 579-678, and in Patai *The Chemistry of Ketenes, Allenes, and Related Compounds*, pt. 1; Wiley: New York, 1980, pp. 99-154; Rossi; Diversi *Synthesis* **1973**, 25-36.

[51]Nakagawa; Shingū; Naemura *Tetrahedron Lett.* **1961**, 802.

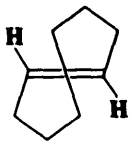
[52]For a review, see Meurer; Vögtle *Top. Curr. Chem.* **1985**, *127*, 1-76. See also Ref. 54.

[53]Newman; Lednicer *J. Am. Chem. Soc.* **1956**, *78*, 4765. Optically active heptahelicene has also been prepared, as have higher helicenes: Flammang-Barbieux; Nasielski; Martin *Tetrahedron Lett.* **1967**, 743; Martin; Baes *Tetrahedron* **1975**, *31*, 2135; Bernstein; Calvin; Buchardt, *J. Am. Chem. Soc.* **1972**, *94*, 494, **1973**, *95*, 527; Defay; Martin *Bull. Soc. Chim. Belg.* **1984**, *93*, 313. Even pentahelicene is crowded enough to be chiral: Goedicke; Stegemeyer *Tetrahedron Lett.* **1970**, 937; Bestmann; Roth *Chem. Ber.* **1974**, *107*, 2923.

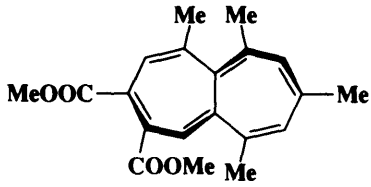
crowding.[54] Others are *trans*-cyclooctene (see also p. 128), in which the carbon chain must lie above the double bond on one side and below it on the other,[55] and suitably substituted



hexahelicene



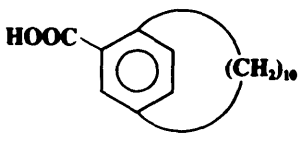
trans-cyclooctene



19

heptalenes. Heptalene itself is not planar (p. 49), and its twisted structure makes it chiral, but the enantiomers rapidly interconvert. However, bulky substituents can hinder the interconversion and several such compounds, including **19**, have been resolved.[56]

7. *Optical activity caused by restricted rotation of other types.* Substituted paracyclophanes may be optically active and **20**, for example, has been resolved.[57] In this case chirality



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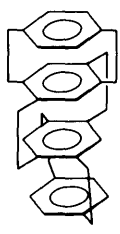

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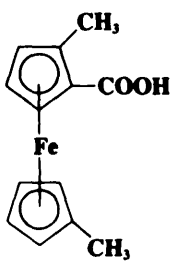

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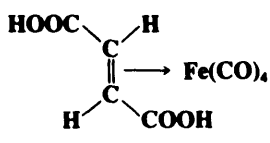

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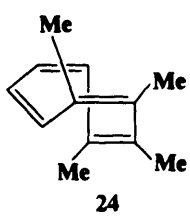


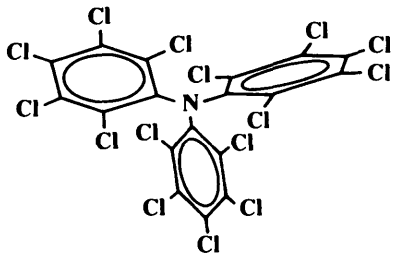
24

[54]For reviews of the helicenes, see Laarhoven; Prinsen *Top. Curr. Chem.* **1984,** *125*, 63-130; Martin *Angew. Chem. Int. Ed. Engl.* **1974,** *13*, 649-660 [*Angew. Chem. 86*, 727-738].

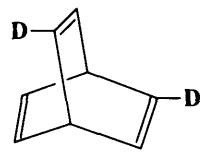
[55]Cope; Ganellin; Johnson; Van Auken; Winkler *J. Am. Chem. Soc.* **1963,** *85*, 3276. Also see Levin; Hoffmann *J. Am. Chem. Soc.* **1972,** *94*, 3446.

[56]Hafner; Knaup; Lindner; Flöter *Angew. Chem. Int. Ed. Engl.* **1985,** *24*, 212 [*Angew. Chem.* 97, 209]; Bernhard; Brügger; Daly; Schönholzer; Weber; Hansen *Helv. Chim. Acta* **1985,** *68*, 415.

[57]Blomquist; Stahl; Meinwald; Smith *J. Org. Chem.* **1961,** *26*, 1687. For a review of chiral cyclophanes and related molecules, see Schlögl *Top. Curr. Chem.* **1984,** *125*, 27-62.



perchlorotriphenylamine



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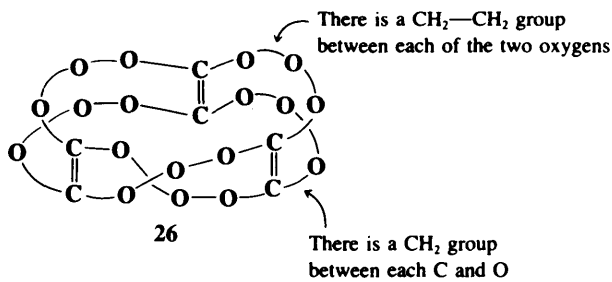
results because the benzene ring cannot rotate in such a way that the carboxyl group goes through the alicyclic ring. Many chiral layered cyclophanes, e.g. **21,** have been prepared.[58] Metallocenes substituted with at least two different groups on one ring are also chiral.[59] Several hundred such compounds have been resolved, one example being **22.** Chirality is also found in other metallic complexes of suitable geometry.[60] For example, fumaric acid–iron tetracarbonyl (**23**) has been resolved.[61] 1,2,3,4-Tetramethylcyclooctatetraene (**24**) is also chiral.[62] This molecule, which exists in the tub form (p. 57), has neither a plane nor an alternating axis of symmetry. Another compound that is chiral solely because of hindered rotation is the propellor-shaped perchlorotriphenylamine, which has been resolved.[63] The 2,5-dideuterio derivative (**25**) of barrelene is chiral, though the parent hydrocarbon and the monodeuterio derivative are not. **25** has been prepared in optically active form[64] and is another case where chirality is due to isotopic substitution.

The main molecular chain in compound **26** has the form of a Möbius strip (see Figure 15.8).[65] This molecule has no chiral carbons, nor does it have a rigid shape, but it too has



26

neither a plane nor an alternating axis of symmetry. **26** has been synthesized and has, in fact, been shown to be chiral.[66] Another interesting type of chirality has been proposed,

[58]Nakazaki; Yamamoto; Tanaka; Kametani *J. Org. Chem.* **1977,** *42*, 287.

[59]For reviews on the stereochemistry of metallocenes, see Schlögl *J. Organomet. Chem.* **1986,** *300*, 219-248, *Top. Stereochem.* **1967,** *1*, 39-91, *Pure Appl. Chem.* **1970,** *23*, 413-432.

[60]For reviews of such complexes, see Paiaro *Organomet. Chem. Rev., Sect. A* **1970,** *6*, 319-335.

[61]Paiaro; Palumbo; Musco; Panunzi *Tetrahedron Lett.* **1965,** 1067; also see Paiaro; Panunzi *J. Am. Chem. Soc.* **1964,** *86*, 5148.

[62]Paquette; Gardlik; Johnson; McCullough *J. Am. Chem. Soc.* **1980,** *102*, 5026.

[63]Hayes; Nagumo; Blount; Mislow *J. Am. Chem. Soc.* **1980,** *102*, 2773; Okamoto; Yashima; Hatada; Mislow *J. Org. Chem.* **1984,** *49*, 557.

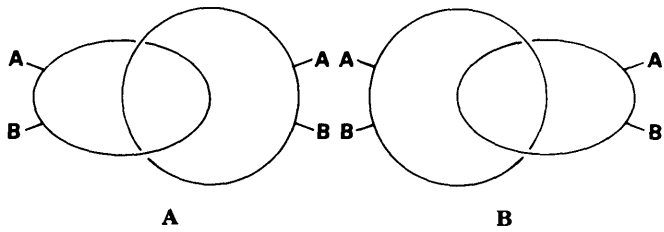
[64]Lightner; Paquette; Chayangkoon; Lin; Peterson *J. Org. Chem.* **1988,** *53*, 1969.

[65]For a review of chirality in Möbius-strip molecules catenanes, and knots, see Walba *Tetrahedron* **1985,** *41*, 3161-3212.

[66]Walba; Richards; Haltiwanger *J. Am. Chem. Soc.* **1982,** *104*, 3219.

though no example is yet known.[67] Rings containing 50 or more members should be able to exist as knots (**27**). Such a knot would be nonsuperimposable on its mirror image. A compound of this type has been synthesized (by the copper ion method discussed in **9-65**),

27



A **B**

though not yet resolved.[68] Catenanes and rotaxanes (see p. 91) can also be chiral if suitably substituted.[69] For example, **A** and **B** are nonsuperimposable mirror images.

Creation of a Chiral Center

Any structural feature of a molecule that gives rise to optical activity may be called a *chiral center*. In many reactions a new chiral center is created, e.g.,

$$CH_3CH_2COOH + Br_2 \xrightarrow{P} CH_3CHBrCOOH$$

If the reagents and reaction conditions are all symmetrical, the product must be a racemic mixture. No optically active material can be created if all starting materials and conditions are optically inactive.[70] This statement also holds when one begins with a racemic mixture. Thus racemic 2-butanol, treated with HBr, must give racemic 2-bromobutane.

The Fischer Projection

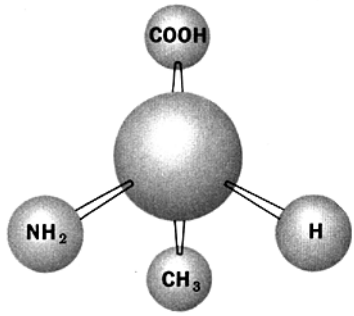
For a thorough understanding of stereochemistry it is useful to examine molecular models (like those depicted in Figure 4.1). However, this is not feasible when writing on paper or a blackboard. In 1891 Emil Fischer greatly served the interests of chemistry by inventing the Fischer projection, a method of representing tetrahedral carbons on paper. By this convention, the model is held so that the two bonds in front of the paper are horizontal and those behind the paper are vertical.

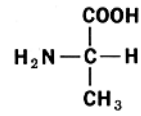
[67]Frisch; Wasserman *J. Am. Chem. Soc.* **1961,** *83*, 3789.

[68]Dietrich-Buchecker; Guilhem; Pascard; Sauvage *Angew. Chem. Int. Ed. Engl.* **1990,** *29*, 1154 [*Angew. Chem. 102*, 1202].

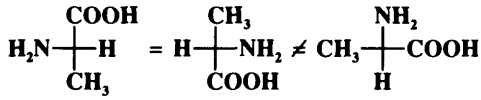
[69]For a discussion of the stereochemistry of these compounds, see Schill *Catenanes, Rotaxanes, and Knots*; Academic Press: New York, 1971, pp. 11-18.

[70]There is one exception to this statement. In a very few cases racemic mixtures may crystalize from solution in such a way that all the (+) molecules go into one crystal and the (−) molecules into another. If one of the crystals crystallizes before the other, a rapid filtration results in optically active material. For a discussion, see Pincock; Wilson *J. Chem. Educ.* **1973,** *50*, 455.

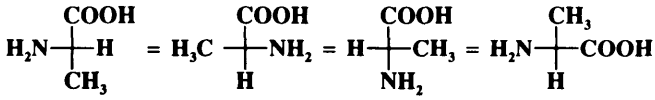


$\equiv$ 

In order to obtain proper results with these formulas, it should be remembered that they are projections and must be treated differently from the models in testing for superimposability. Every plane is superimposable on its mirror image; hence with these formulas there must be added the restriction that they may not be taken out of the plane of the blackboard or paper. Also they may not be rotated 90°, though 180° rotation is permissible:



It is also permissible to keep any one group fixed and to rotate the other three clockwise or counterclockwise (because this can be done with models):

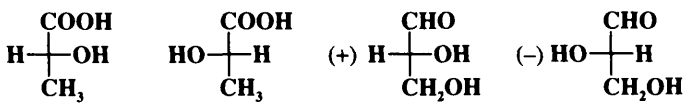


However, the *interchange* of any two groups results in the conversion of an enantiomer into its mirror image (this applies to models as well as to the Fischer projections).

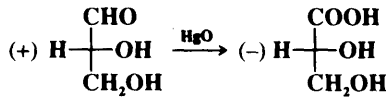
With these restrictions Fischer projections may be used instead of models to test whether a molecule containing asymmetric carbons is superimposable on its mirror image. However, there are no such conventions for molecules whose chirality arises from anything other than chiral atoms; when such molecules are examined on paper, three-dimensional pictures must be used. With models or three-dimensional pictures there are no restrictions about the plane of the paper.

Absolute Configuration

Suppose we have two test tubes, one containing (−)-lactic acid and the other the (+) enantiomer. One test tube contains **28** and the other **29**. How do we know which is which? Chemists in the early part of this century pondered this problem and decided that they could



not know—for lactic acid or any other compound. Therefore Rosanoff proposed that one compound be chosen as a standard and a configuration be arbitrarily assigned to it. The compound chosen was glyceraldehyde because of its relationship to the sugars. The (+) isomer was assigned the configuration shown in **30** and given the label D. The (−) isomer, designated to be **31,** was given the label L. Once a standard was chosen, other compounds could then be related to it. For example, (+)-glyceraldehyde, oxidized with mercuric oxide, gives (−)-glyceric acid:



Since it is highly improbable that the configuration at the central carbon changed, it can be concluded that (−)-glyceric acid has the same configuration as (+)-glyceraldehyde and therefore (−)-glyceric acid is also called D. This example emphasizes that molecules with the same configuration need not rotate the plane of polarized light in the same direction. This fact should not surprise us when we remember that the same compound can rotate the plane in opposite directions under different conditions.

Once the configuration of the glyceric acids was known (in relation to the glyceraldehydes), it was then possible to relate other compounds to either of these, and each time a new compound was related, others could be related to *it*. In this way many thousands of compounds were related, indirectly, to D- or L-glyceraldehyde, and it was determined that **28,** which has the D configuration, is the isomer that rotates the plane of polarized light to the left. Even compounds without asymmetric atoms, such as biphenyls and allenes, have been placed in the D or L series.[71] When a compound has been placed in the D or L series, its *absolute configuration* is said to be known.[72]

In 1951 it became possible to determine whether Rosanoff's guess was right. Ordinary x-ray crystallography cannot distinguish between a D and a L isomer, but by use of a special technique, Bijvoet was able to examine sodium rubidium tartrate and found that Rosanoff had made the correct choice.[73] It was perhaps historically fitting that the first true absolute configuration should have been determined on a salt of tartaric acid, since Pasteur made his great discoveries on another salt of this acid.

In spite of the former widespread use of D and L to denote absolute configuration, the method is not without faults. The designation of a particular enantiomer as D or L can depend on the compounds to which it is related. Examples are known where an enantiomer can, by five or six steps, be related to a known D compound, and by five or six other steps, be related to the L enantiomer of the same compound. In a case of this sort, an arbitrary choice of D or L must be used. Because of this and other flaws, the DL system is no longer used, except for certain groups of compounds such as carbohydrates and amino acids.

[71]The use of small *d* and *l* is now discouraged, since some authors used it for rotation, and some for configuration. However, a racemic mixture is still a *dl* mixture, since there is no ambiguity here.

[72]For lists of absolute configurations of thousands of compounds, with references, mostly expressed as (*R*) or (*S*) rather than D or L, see Klyne; Buckingham *Atlas of Stereochemistry*, 2nd ed., 2 vols.; Oxford University Press: Oxford, 1978; Jacques; Gros; Bourcier; Brienne; Toullec *Absolute Configurations* (vol. 4 of Kagan *Stereochemistry*), Georg Thieme Publishers: Stuttgart, 1977.

[73]Bijvoet; Peerdeman; van Bommel *Nature* **1951,** *168*, 271. For a list of organic structures whose absolute configurations have been determined by this method, see Allen; Rogers *Chem. Commun.* **1966,** 838; Allen; Neidle; Rogers *Chem. Commun.* **1968,** 308, **1969,** 452; Neidle; Rogers; Allen *J. Chem. Soc. C* **1970,** 2340.

The Cahn–Ingold–Prelog System

The system that has replaced the DL system is the *Cahn–Ingold–Prelog* system, in which the four groups on an asymmetric carbon are ranked according to a set of sequence rules.[74] For our purposes we confine ourselves to only a few of these rules, which are sufficient to deal with the vast majority of chiral compounds.

1. Substituents are listed in order of decreasing atomic number of the atom directly joined to the carbon.

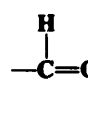
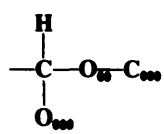
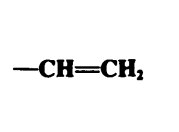
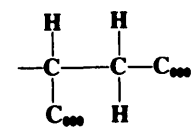
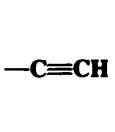
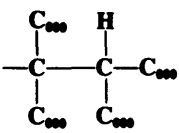
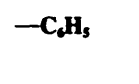
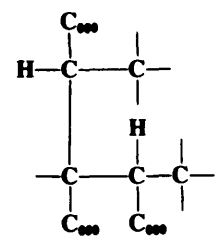
2. Where two or more of the atoms connected to the asymmetric carbon are the same, the atomic number of the second atom determines the order. For example, in the molecule $Me_2CH—CHBr—CH_2OH$, the CH_2OH group takes precedence over the Me_2CH group because oxygen has a higher atomic number than carbon. Note that this is so even though there are two carbons in Me_2CH and only one oxygen in CH_2OH. If two or more atoms connected to the second atom are the same, the third atom determines the precedence, etc.

3. All atoms except hydrogen are formally given a valence of 4. Where the actual valence is less (as in nitrogen, oxygen, or a carbanion), phantom atoms (designated by a subscript $_0$) are used to bring the valence up to four. These phantom atoms are assigned an atomic number of zero and necessarily rank lowest. Thus the ligand $—\overset{\oplus}{N}HMe_2$ ranks higher than $—NMe_2$.

4. A tritium atom takes precedence over deuterium, which in turn takes precedence over ordinary hydrogen. Similarly, any higher isotope (such as ^{14}C) takes precedence over any lower one.

5. Double and triple bonds are counted as if they were split into two or three single bonds, respectively, as in the examples in Table 4.1 (note the treatment of the phenyl group).

TABLE 4.1 How four common groups are treated in the Cahn–Ingold–Prelog system

Group	Treated as if it were	Group	Treated as if it were
			
			

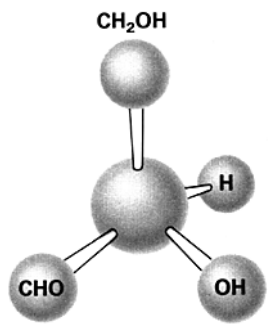
[74]For descriptions of the system and sets of sequence rules, see Ref. 2; Cahn; Ingold; Prelog *Angew. Chem. Int. Ed. Engl.* **1966,** *5,* 385-415 [*Angew. Chem. 78,* 413-447]; Cahn *J. Chem. Educ.* **1964,** *41,* 116; Fernelius; Loening; Adams *J. Chem. Educ.* **1974,** *51,* 735. See also Prelog and Helmchen *Angew. Chem., Int. Ed. Engl.* **1982,** *21,* 567-583 [*Angew. Chem. 94,* 614-631].

Note that in a C=C double bond, the two carbon atoms are *each* regarded as being connected to two carbon atoms and that one of the latter is counted as having three phantom substituents.

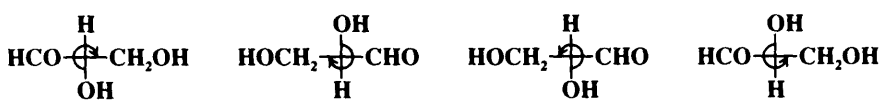
As an exercise, we shall compare the four groups in Table 4.1. The first atoms are connected, respectively, to (H, O, O), (H, C, C), (C, C, C), and (C, C, C). That is enough to establish that —CHO ranks first and —CH=CH_2 last, since even one oxygen outranks three carbons and three carbons outrank two carbons and a hydrogen. To classify the remaining two groups we must proceed further along the chains. We note that —C_6H_5 has two of its (C, C, C) carbons connected to (C, C, H), while the third is $(_{000})$ and is thus preferred to —C≡CH, which has only one (C, C, H) and two $(_{000})$s.

By application of the above rules, some groups in descending order of precedence are COOH, COPh, COMe, CHO, $CH(OH)_2$, *o*-tolyl, *m*-tolyl, *p*-tolyl, phenyl, C≡CH, *t*-butyl, cyclohexyl, vinyl, isopropyl, benzyl, neopentyl, allyl, *n*-pentyl, ethyl, methyl, deuterium, and hydrogen. Thus the four groups of glyceraldehyde are arranged in the sequence: OH, CHO, CH_2OH, H.

Once the order is determined, the molecule is held so that the lowest group in the sequence is pointed away from the viewer. Then if the other groups, in the order listed, are oriented clockwise, the molecule is designated *R*, and if counterclockwise, *S*. For glyceraldehyde, the (+) enantiomer is *R*:



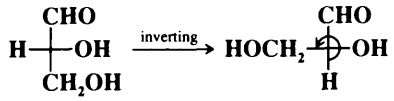
Note that when a compound is written in the Fischer projection, the configuration can easily be determined without constructing the model.[75] If the lowest-ranking group is either at the top or the bottom (because these are the two positions pointing away from the viewer), the *R* configuration is present if the other three groups in descending order are clockwise, e.g.,



(*R*)-Glyceraldehyde (*S*)-Glyceraldehyde

[75]For a discussion of how to determine *R* or *S* from other types of formula, see Eliel *J. Chem. Educ.* **1985**, *62*, 223.

If the lowest-ranking group is not at the top or bottom, one can simply interchange it with the top or bottom group, bearing in mind that in so doing, one is inverting the configuration, e.g.:



(*S*)-Glyceraldehyde

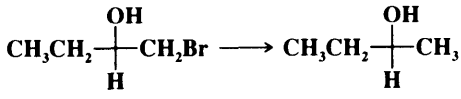
Therefore the original compound was (*R*)-glyceraldehyde.

The Cahn–Ingold–Prelog system is unambiguous and easily applicable in most cases. Whether to call an enantiomer *R* or *S* does not depend on correlations, but the configuration must be known before the system can be applied and this does depend on correlations. The Cahn–Ingold–Prelog system has also been extended to chiral compounds that do not contain chiral atoms.[76]

Methods of Determining Configuration[77]

In all the methods,[78] it is necessary to relate the compound of unknown configuration to another whose configuration is known. The most important methods of doing this are:

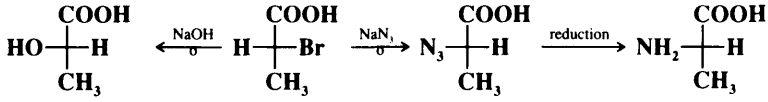
1. Conversion of the unknown to, or formation of the unknown from, a compound of known configuration without disturbing the chiral center. See the glyceraldehyde–glyceric acid example above (p. 108). Since the chiral center was not disturbed, the unknown obviously has the same configuration as the known. This does not necessarily mean that if the known is *R*, the unknown is also *R*. This will be so if the sequence is not disturbed but not otherwise. For example, when (*R*)-1-bromo-2-butanol is reduced to 2-butanol without dis-



R *S*

turbing the chiral center, the product is the *S* isomer, even though the configuration is unchanged, because CH_3CH_2 ranks lower than $BrCH_2$ but higher than CH_3.

2. Conversion at the chiral center if the mechanism is known. Thus, the SN2 mechanism proceeds with inversion of configuration at an asymmetric carbon (see p. 294). It was by a series of such transformations that lactic acid was related to alanine:



(*S*)-(+)-Lactic acid *R* *S* (*S*)-(+)-Alanine

See also the discussion on p. 295.

[76]For a discussion of these rules, as well as for a review of methods for establishing configurations of chiral compounds not containing chiral atoms, see Krow *Top. Stereochem.* **1970,** *5*, 31-68.

[77]For a monograph, see Kagan *Determination of Configuration by Chemical Methods* (vol. 3 of Kagan *Stereochemistry*); Georg Thieme Publishers: Stuttgart, 1977. For reviews, see Brewster, in Bentley; Kirby *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (vol. 4 of Weissberger *Techniques of Chemistry*), pt. 3; Wiley: New York, 1972, pp. 1-249; Klyne; Scopes *Prog. Stereochem.* **1969,** *4*, 97-166; Schlenk *Angew. Chem. Int. Ed. Engl.* **1965,** *4*, 139-145 [*Angew. Chem. 77*, 161-168]. For a review of absolute configuration of molecules in the crystalline state, see Addadi; Berkovitch-Yellin; Weissbuch; Lahav; Leiserowitz *Top. Stereochem.* **1986,** *16*, 1-85.

[78]Except the x-ray method of Bijvoet.

3. Biochemical methods. In a series of similar compounds, such as amino acids or certain types of steroids, a given enzyme will usually attack only molecules with one kind of configuration. If the enzyme attacks only the L form of eight amino acids, say, then attack on the unknown ninth amino acid will also be on the L form.

4. Optical comparison. It is sometimes possible to use the sign and extent of rotation to determine which isomer has which configuration. In a homologous series, the rotation usually changes gradually and in one direction. If the configurations of enough members of the series are known, the configurations of the missing ones can be determined by extrapolation. Also certain groups contribute more or less fixed amounts to the rotation of the parent molecule, especially when the parent is a rigid system such as a steroid.

5. The special x-ray method of Bijvoet gives direct answers and has been used in a number of cases.[73]

Other methods have also been used, including optical rotatory dispersion,[79] circular dichroism,[79] nmr, and asymmetric synthesis (see p. 118).

The Cause of Optical Activity

The question may be asked: Just why does a chiral molecule rotate the plane of polarized light? Theoretically, the answer to this question is known and in a greatly simplified form may be explained as follows.[80]

Whenever any light hits any molecule in a transparent material, the light is slowed because of interaction with the molecule. This phenomenon on a gross scale is responsible for the refraction of light and the decrease in velocity is proportional to the refractive index of the material. The extent of interaction depends on the polarizability of the molecule. Plane-polarized light may be regarded as being made up of two kinds of circularly polarized light. Circularly polarized light has the appearance (or would have, if one could see the wave) of a helix propagating around the axis of light motion, and one kind is a left-handed and the other a right-handed helix. As long as the plane-polarized light is passing through a symmetrical region, the two circularly polarized components travel at the same speed. However, a chiral molecule has a different polarizability depending on whether it is approached from the left or the right. One circularly polarized component approaches the molecule, so to speak, from the left and sees a different polarizability (hence on a gross scale, a different refractive index) than the other and is slowed to a different extent. This would seem to mean that the left- and right-handed circularly polarized components travel at different velocities, since each has been slowed to a different extent. However, it is not possible for two components of the same light to be traveling at different velocities. What actually takes place, therefore, is that the faster component "pulls" the other towards it, resulting in rotation of the plane. Empirical methods for the prediction of the sign and amount of rotation based on bond refractions and polarizabilities of groups in a molecule have been devised,[81] and have given fairly good results in many cases.

In liquids and gases the molecules are randomly oriented. A molecule that is optically inactive because it has a plane of symmetry will very seldom be oriented so that the plane

[79]See Ref. 191 for books and reviews on optical rotatory dispersion.

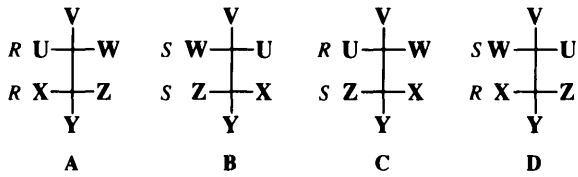
[80]For longer, nontheoretical discussions, see Eliel, *Stereochemistry of Carbon Compounds*, Ref. 1, pp. 398-412; Wheland, Ref. 1, pp. 204-211. For theoretical discussions, see Caldwell; Eyring *The Theory of Optical Activity* Wiley: New York, 1971; Buckingham; Stiles *Acc. Chem. Res.* **1974,** *7*, 258-264; Mason *Q. Rev., Chem. Soc.* **1963,** *17*, 20-66.

[81]Brewster *Top. Stereochem.* **1967,** *2*, 1-72, *J. Am. Chem. Soc.* **1959,** *81*, 5475, 5483, 5493; Davis; Jensen *J. Org. Chem.* **1970,** *35*, 3410; Jullien; Requin; Stahl-Larivière *Nouv. J. Chim.* **1979,** *3*, 91; Sathyanarayana; Stevens *J. Org. Chem.* **1987,** *52*, 3170; Wroblewski; Applequist; Takaya; Honzatko; Kim; Jacobson; Reitsma; Yeung; Verkade *J. Am. Chem. Soc.* **1988,** *110*, 4144.

of the polarized light coincides with the plane of symmetry. When it is so oriented, that particular molecule does not rotate the plane but all others not oriented in that manner do rotate the plane, even though the molecules are achiral. There is no net rotation because, the molecules being present in large number and randomly oriented, there will always be another molecule later on in the path of the light that is oriented exactly opposite and will rotate the plane back again. Even though nearly all molecules rotate the plane individually, the total rotation is zero. For chiral molecules, however (if there is no racemic mixture), no opposite orientation is present and there is a net rotation.

Molecules with More than One Chiral Center

When a molecule has two chiral centers, each has its own configuration and can be classified *R* or *S* by the Cahn–Ingold–Prelog method. There are a total of four isomers, since the first center may be *R* or *S* and so may the second. Since a molecule can have only one mirror image, only one of the other three can be the enantiomer of **A**. This is **B** (the mirror image

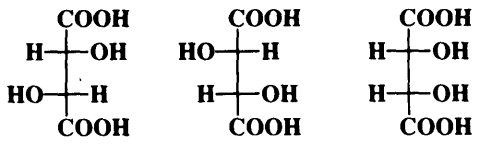


of an *R* center is *always* an *S* center). **C** and **D** are a second pair of enantiomers and the relationship of **C** and **D** to **A** and **B** is designated by the term *diastereomer*. Diastereomers may be defined as *stereoisomers that are not enantiomers*. **C** and **D** being enantiomers, must have identical properties, except as noted on p. 95; the same is true for **A** and **B**. However, the properties of **A** and **B** are not identical with those of **C** and **D.** They have different melting points, boiling points, solubilities, reactivity, and all other physical, chemical, and spectral properties. The properties are usually *similar* but not *identical*. In particular, diastereomers have different specific rotations; indeed one diastereomer may be chiral and rotate the plane of polarized light while another may be achiral and not rotate at all (an example is presented below).

It is now possible to see why, as mentioned on p. 95, enantiomers react at different rates with other chiral molecules but at the same rate with achiral molecules. In the latter case, the activated complex formed from the *R* enantiomer and the other molecule is the mirror image of the activated complex formed from the *S* enantiomer and the other molecule. Since the two activated complexes are enantiomeric, their energies are the same and the rates of the reactions in which they are formed must be the same (see Chapter 6). However, when an *R* enantiomer reacts with a chiral molecule that has, say, the *R* configuration, the activated complex has two chiral centers with configurations *R* and *R*, while the activated complex formed from the *S* enantiomer has the configurations *S* and *R*. The two activated complexes are diastereomeric, do not have the same energies, and consequently are formed at different rates.

Although four is the maximum possible number of isomers when the compound has two chiral centers (chiral compounds without a chiral carbon, or with one chiral carbon and another type of chiral center, also follow the rules described here), some compounds have fewer. When the three groups on one chiral atom are the same as those on the other, one of the isomers (called a *meso* form) has a plane of symmetry and hence is optically inactive,

even though it has two chiral carbons. Tartaric acid is a typical case. There are only three isomers of tartaric acid: a pair of enantiomers and an inactive meso form. For compounds

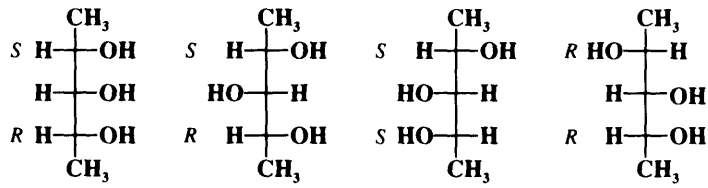


dl pair meso

the three stereoisomers of tartaric acid

that have two chiral atoms, meso forms are found only where the four groups on one of the chiral atoms are the same as those on the other chiral atom.

In most cases with more than two chiral centers, the number of isomers can be calculated from the formula 2^n, where n is the number of chiral centers, although in some cases the actual number is less than this, owing to meso forms.[82] An interesting case is that of 2,3,4-pentanetriol (or any similar molecule). The middle carbon is not asymmetric when the 2- and 4-carbons are both *R* (or both *S*) but is asymmetric when one of them is *R* and the



meso meso *dl* pair

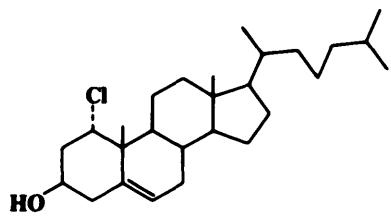
other *S*. Such a carbon is called a *pseudoasymmetric* carbon. In these cases there are four isomers: two meso forms and one *dl* pair. The student should satisfy himself or herself, remembering the rules governing the use of the Fischer projections, that these isomers are different, that the meso forms are superimposable on their mirror images, and that there are no other stereoisomers. Two diastereomers that have a different configuration at only one chiral center are called *epimers*.

In compounds with two or more chiral centers, the absolute configuration must be separately determined for each center. The usual procedure is to determine the configuration at one center by the methods discussed on pp. 111–112 and then to relate the configuration at that center to the others in the molecule. One method is x-ray crystallography, which, as previously noted, cannot be used to determine the absolute configuration at any chiral center but which does give relative configurations of all the chiral centers in a molecule and hence the absolute configurations of all once the first is independently determined. Other physical and chemical methods have also been used for this purpose.

The problem arises how to name the different stereoisomers of a compound when there are more than two.[2] Enantiomers are virtually always called by the same name, being distinguished by *R* and *S* or D and L or (+) and (−). In the early days of organic chemistry, it was customary to give each pair of enantiomers a different name or at least a different prefix (such as *epi-*, *peri-*, etc.). Thus the aldehexoses are called glucose, mannose, idose,

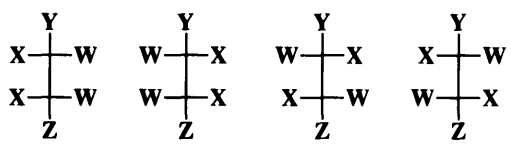
[82]For a method of generating all stereoisomers consistent with a given empirical formula, suitable for computer use, see Nourse; Carhart; Smith; Djerassi *J. Am. Chem. Soc.* **1979**, *101*, 1216; **1980**, *102*, 6289.

etc., although they are all 2,3,4,5,6-pentahydroxyhexanal (in their open-chain forms). This practice was partially due to lack of knowledge about which isomers had which configurations. Today it is customary to describe *each chiral position* separately as either *R* or *S* or, in special fields, to use other symbols. Thus, in the case of steroids, groups above the "plane" of the ring system are designated β, and those below it α. Solid lines are often used to depict β groups and dashed lines for α groups. An example is



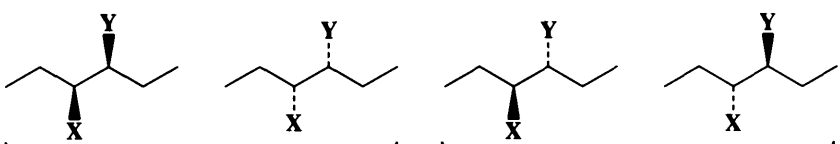
1α-Chloro-5-cholesten-3β-ol

For many open-chain compounds prefixes are used that are derived from the names of the corresponding sugars and that describe the whole system rather than each chiral center separately. Two such common prefixes are *erythro-* and *threo-*, which are applied to systems



Erythro *dl* pair Threo *dl* pair

containing two asymmetric carbons when two of the groups are the same and the third is different.[83] The erythro pair has the identical groups on the same side when drawn in the Fischer convention, and if Y were changed to Z, it would be meso. The threo pair has them on opposite sides, and if Y were changed to Z, it would still be a *dl* pair. Another system[84] for designating stereoisomers[85] uses the terms *syn* and *anti*. The "main chain" of the molecule is drawn in the common zig-zag manner. Then if two nonhydrogen substituents are on the same side of the plane defined by the main chain, the designation is syn; otherwise anti.



syn *dl* pair anti *dl* pair

[83]For more general methods of designating diastereomers, see Carey; Kuehne *J. Org. Chem.* **1982,** *47*, 3811; Boguslavskaya *J. Org. Chem. USSR* **1986,** *22*, 1412; Seebach; Prelog *Angew. Chem. Int. Ed. Engl.* **1982,** *21*, 654-660 [*Angew. Chem. 94*, 696-702]; Brewster *J. Org. Chem.* **1986,** *51*, 4751. See also Tavernier *J. Chem. Educ.* **1986,** *63*, 511; Brook *J. Chem. Educ.* **1987,** *64*, 218.

[84]For still another system, see Seebach; Prelog, Ref. 83.

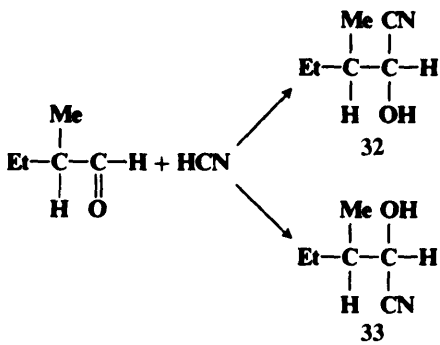
[85]Masamune; Kaiho; Garvey *J. Am. Chem. Soc.* **1982,** *104*, 5521.

Asymmetric Synthesis

Organic chemists often wish to synthesize a chiral compound in the form of a single enantiomer or diastereomer, rather than as a mixture of stereoisomers. There are two basic ways in which this can be done.[86] The first way, which is more common, is to begin with a single stereoisomer, and to use a synthesis that does not affect the chiral center (or centers), as in the glyceraldehyde–glyceric acid example on p. 108. The optically active starting compound can be obtained by a previous synthesis, or by resolution of a racemic mixture (p. 120), but it is often more convenient to obtain it from nature, since many compounds, such as amino acids, sugars, and steroids are present in nature in the form of a single enantiomer or diastereomer. These compounds are regarded as a *chiral pool*; that is, readily available compounds that can be used as starting materials.[87]

The other basic method is called *asymmetric synthesis*,[88] or *stereoselective synthesis*. As was mentioned before, optically active materials cannot be created from inactive starting materials and conditions; hence true asymmetric synthesis is impossible, except in the manner previously noted.[70] However, when a new chiral center is created, the two possible configurations need not be formed in equal amounts if anything is present that is not symmetric. We discuss asymmetric synthesis under four headings:

1. *Active substrate.* If a new chiral center is created in a molecule that is already optically active, the two diastereomers are not (except fortuitously) formed in equal amounts. The reason is that the direction of attack by the reagent is determined by the groups already there. For certain additions to the carbon–oxygen double bond of ketones containing an

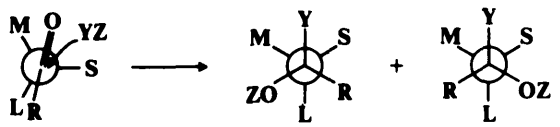


[86]For a monograph that covers both ways, including a list of commercially available optically active starting compounds, see Morrison; Scott *Asymmetric Synthesis*, vol. 4; Academic Press: New York, 1984. For a monograph covering a more limited area, see Williams *Synthesis of Optically Active α-Amino Acids*; Pergamon: Elmsford, NY, 1989. For reviews on both ways, see Crosby *Tetrahedron* **1991**, *47*, 4789-4846; Mori *Tetrahedron* **1989**, *45*, 3233-3298.

[87]For books on the synthesis of optically active compounds starting from natural products, see Coppola; Schuster *Asymmetric Synthesis*; Wiley: New York, 1987 (amino acids as starting compounds); Hanessian *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: Elmsford, NY, 1983 (mostly carbohydrates as starting compounds). For reviews, see Jurczak; Pikul; Bauer *Tetrahedron* **1986**, *42*, 447-488; Hanessian *Aldrichimica Acta* **1989**, *22*, 3-15; Jurczak; Gotębiowski *Chem. Rev.* **1989**, *89*, 149-164.

[88]For a treatise on this subject, see Morrison *Asymmetric Synthesis*, 5 vols. [vol. 4 co-edited by Scott]; Academic Press: New York, 1983-1985. For books, see Nógrádi *Stereoselective Synthesis*; VCH: New York, 1986; Eliel; Otsuka *Asymmetric Reactions and Processes in Chemistry*; American Chemical Society: Washington, 1982; Morrison; Mosher *Asymmetric Organic Reactions*; Prentice-Hall: Englewood Cliffs, NJ, 1971, paperback reprint, American Chemical Society: Washington, 1976; Izumi; Tai, Ref. 1. For reviews, see Ward *Chem. Soc. Rev.* **1990**, *19*, 1-19; Whitesell *Chem. Rev.* **1989**, *89*, 1581-1590; Fujita; Nagao *Adv. Heterocycl. Chem.* **1989**, *45*, 1-36; Kochetkov; Belikov *Russ. Chem. Rev.* **1987**, *56*, 1045-1067; Oppolzer *Tetrahedron* **1987**, *43*, 1969-2004; Seebach; Imwinkelried; Weber *Mod. Synth. Methods* **1986**, *4*, 125-259; ApSimon; Collier *Tetrahedron* **1986**, *42*, 5157-5254; Mukaiyama; Asami *Top. Curr. Chem.* **1985**, *127*, 133-167; Martens *Top. Curr. Chem.* **1984**, *125*, 165-246; Duhamel; Duhamel; Launay; Plaquevent *Bull. Soc.Chim. Fr.* **1984**, II-421-II-430; Mosher; Morrison *Science* **1983**, *221*, 1013-1019; Schöllkopf *Top. Curr. Chem.*

asymmetric α carbon, *Cram's rule* predicts which diastereomer will predominate.[89] If the molecule is observed along its axis, it may be represented as in **34** (see p. 139), where S, M, and L stand for small, medium, and large, respectively. The oxygen of the carbonyl

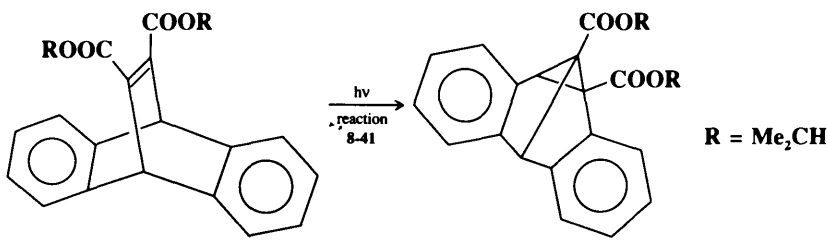


34 **Major product** **Minor product**

orients itself between the small- and the medium-sized groups. The rule is that the incoming group preferentially attacks on the side of the plane containing the small group. By this rule, it can be predicted that **33** will be formed in larger amounts than **32.**

Many reactions of this type are known, in some of which the extent of favoritism approaches 100% (for an example see **2-11**).[90] The farther away the reaction site is from the chiral center, the less influence the latter has and the more equal the amounts of diastereomers formed.

In a special case of this type of asymmetric synthesis, a compound (**35**) with achiral molecules, but whose crystals are chiral, was converted by ultraviolet light to a single enantiomer of a chiral product (**36**).[91]



35 not chiral **36** optically active

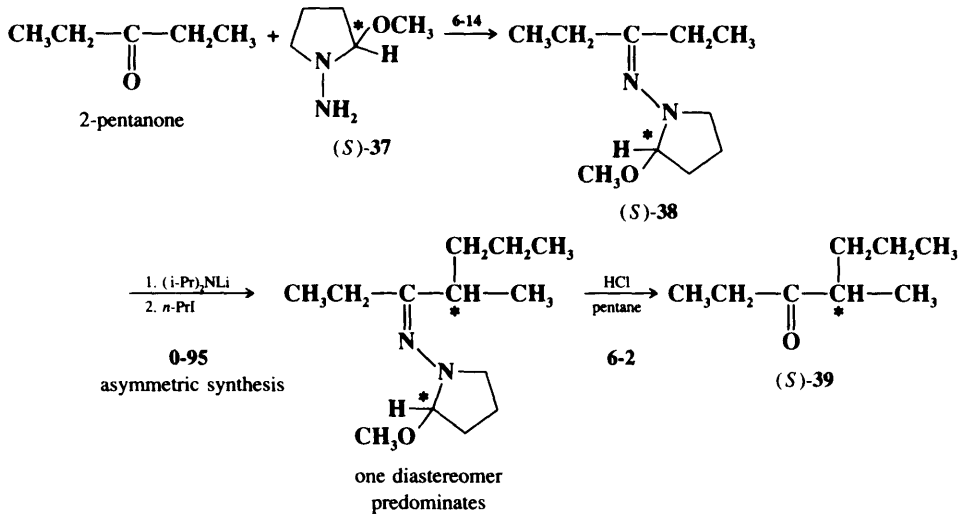
1983, *109*, 65-84; Quinkert; Stark *Angew. Chem. Int. Ed. Engl.* **1983,** *22*, 637-655 [*Angew. Chem. 95*, 651-669]; Tramontini *Synthesis* **1982,** 605-644; Drauz; Kleeman; Martens *Angew. Chem. Int. Ed. Engl.* **1982,** *21*, 584-608 [*Angew. Chem. 94*, 590-613]; Wynberg *Recl. Trav. Chim. Pays-Bas* **1981,** *100*, 393-399; Bartlett *Tetrahedron* **1980,** *36*, 2-72; ApSimon; Seguin *Tetrahedron* **1979,** *35*, 2797-2842; Valentine; Scott *Synthesis* **1978,** 329-356; Scott; Valentine *Science* **1974,** *184*, 943-952; Kagan; Fiaud *Top. Stereochem.* **1978,** *10*, 175-285; ApSimon, in Bentley; Kirby, Ref. 77, pp. 251-408; Boyd; McKervey *Q. Rev., Chem. Soc* **1968,** *22*, 95-122; Goldberg *Sel. Org. Transform.* **1970,** *1*, 363-394; Klabunovskii; Levitina *Russ. Chem. Rev.* **1970,** *39*, 1035-1049; Inch *Synthesis* **1970,** 466-473; Mathieu; Weill-Raynal *Bull. Soc. Chim. Fr.* **1968,** 1211-1244; Amariglio; Amariglio; Duval *Ann. Chim. (Paris)* [14] **1968,** *3*, 5-25; Pracejus *Fortschr. Chem. Forsch.* **1967,** *8*, 493-553; Velluz; Valls; Mathieu *Angew. Chem. Int. Ed. Engl.* **1967,** *6*, 778-789 [*Angew. Chem. 79*, 774-785].

[89]Cram; Elhafez *J. Am. Chem. Soc.* **1952,** *74*, 5828; Cram; Kopecky *J. Am. Chem. Soc.* **1959,** *81*, 2748; Leitereg; Cram *J. Am. Chem. Soc.* **1968,** *90*, 4019. For reviews, see Ref. 5 in Chapter 16. For discussions, see Salem *J. Am. Chem. Soc.* **1973,** *95*, 94; Anh *Top. Curr. Chem* **1980,** *88*, 145-162, pp. 151-161; Eliel, in Morrison, Ref. 88, vol. 2, pp. 125-155.

[90]For other examples and references to earlier work, see Eliel, Ref. 89; Eliel; Koskimies; Lohri *J. Am. Chem. Soc.* **1978,** *100*, 1614; Still; McDonald *Tetrahedron Lett.* **1980,** *21*, 1031; Still; Schneider *Tetrahedron Lett.* **1980,** *21*, 1035.

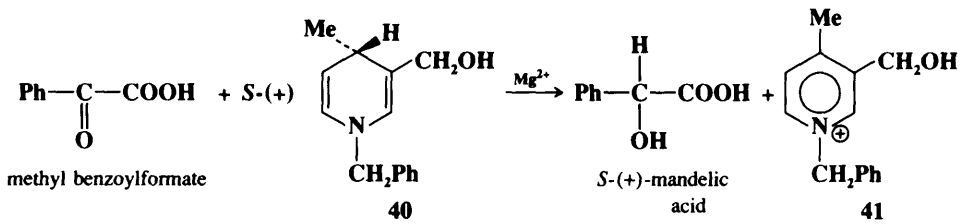
[91]Evans; Garcia-Garibay; Omkaram; Scheffer; Trotter; Wireko *J. Am. Chem. Soc.* **1986,** *108*, 5648; Garcia-Garibay; Scheffer; Trotter; Wireko *Tetrahedron Lett.* **1987,** *28*, 4789. For an earlier example, see Penzien; Schmidt *Angew. Chem. Int. Ed. Engl.* **1969,** *8*, 608 [*Angew. Chem. 81*, 628].

It is often possible to convert an achiral compound to a chiral compound by (1) addition of a chiral group; (2) running an asymmetric synthesis, and (3) cleavage of the original chiral group. An example is conversion of the achiral 2-pentanone to the chiral 4-methyl-3-heptanone **39**.[92] In this case more than 99% of the product was the (*S*) enantiomer.



The compound **37** is called a *chiral auxiliary* because it is used to induce asymmetry and then removed.

2. *Active reagent.* A pair of enantiomers can be separated by an active reagent that reacts faster with one of them than it does with the other (this is also a method of resolution). If the absolute configuration of the reagent is known, the configuration of the enantiomers can often be determined by a knowledge of the mechanism and by seeing which diastereomer is preferentially formed.[93] Creation of a new chiral center in an inactive molecule can also be accomplished with an active reagent, though it is rare for 100% selectivity to be observed. An example[94] is the reduction of methyl benzoylformate with optically active N-benzyl-3-(hydroxymethyl)-4-methyl-1,4-dihydropyridine (**40**) to produce mandelic acid that contained about 97.5% of the *S*-(+) isomer and 2.5% of the *R*-(−) isomer (for another

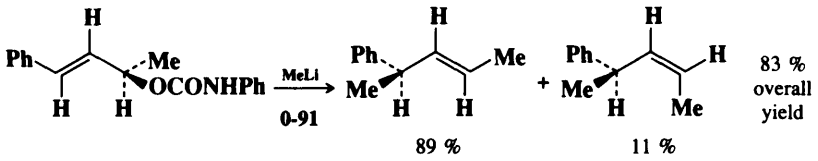


[92]Enders; Eichenauer; Baus; Schubert; Kremer *Tetrahedron* **1984,** *40*, 1345.

[93]See, for example, Horeau *Tetrahedron Lett.* **1961,** 506; Marquet; Horeau *Bull. Soc. Chim. Fr.* **1967,** 124; Brockmann; Risch *Angew. Chem. Int. Ed. Engl.* **1974,** *13*, 664 [*Angew. Chem. 86*, 707]; Potapov; Gracheva; Okulova *J. Org. Chem. USSR* **1989,** *25*, 311.

[94]Meyers; Oppenlaender *J. Am. Chem. Soc.* **1986,** *108*, 1989. For reviews of asymmetric reduction, see Morrison *Surv. Prog. Chem.* **1966,** *3*, 147-182; Yamada; Koga *Sel. Org. Transform.* **1970,** *1*, 1-33; Ref. 232 in Chapter 15. See also Morrison, Ref. 88, vol. 2.

example, see p. 786). Note that the other product, **41**, is not chiral. Reactions like this, in which one reagent (in this case **40**) gives up its chirality to another, are called *self-immolative*. In this intramolecular example:

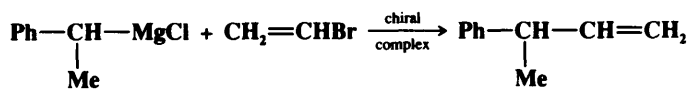


chirality is transferred from one atom to another in the same molecule.[95]

A reaction in which an inactive substrate is converted selectively to one of two enantiomers is called an *enantioselective* reaction, and the process is called *asymmetric induction*. These terms apply to reactions in this category and in categories 3 and 4.

When an optically active substrate reacts with an optically active reagent to form two new chiral centers, it is possible for both centers to be created in the desired sense. This type of process is called *double asymmetric synthesis*[96] (for an example, see p. 942).

3. *Active catalyst or solvent.*[97] Many such examples are present in the literature, among them reduction of ketones and substituted alkenes to optically active (though not optically pure) secondary alcohols and substituted alkanes by treatment with hydrogen and a chiral homogeneous hydrogenation catalyst (reactions **6-25** and **5-9**),[98] the treatment of aldehydes or ketones with organometallic compounds in the presence of a chiral catalyst (see **6-29**), and the conversion of alkenes to optically active epoxides by treatment with a hydroperoxide and a chiral catalyst (see **5-36**). In some instances, notably in the homogeneous catalytic hydrogenation of alkenes (**5-9**), the ratio of enantiomers prepared in this way is as high as 98:2.[99] Other examples of the use of a chiral catalyst or solvent are the reaction between secondary alkyl Grignard reagents and vinylic halides (**0-87**) in the presence of chiral transition-metal complexes:[100]



the conversion of chlorofumaric acid (in the form of its diion) to the (−)-*threo* isomer of the diion of chloromalic acid by treatment with H_2O and the enzyme fumarase,[101]

[95]Goering; Kantner; Tseng *J. Org. Chem.* **1983,** *48*, 715.

[96]For a review, see Masamune; Choy; Petersen; Sita *Angew. Chem. Int. Ed. Engl.* **1985,** *24*, 1-30 [*Angew. Chem.* *97*, 1-31].

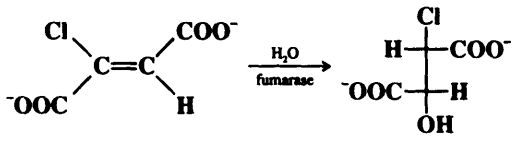
[97]For a monograph, see Morrison *Asymmetric Synthesis*, vol. 5; Academic Press: New York, 1985. For reviews, see Tomioka *Synthesis* **1990,** 541-549; Consiglio; Waymouth *Chem. Rev.* **1989,** *89*, 257-276; Brunner, in Hartley *The Chemistry of the Metal-Carbon Bond*, vol. 5; Wiley: New York, 1989, pp. 109-146; Noyori; Kitamura *Mod. Synth. Methods* **1989,** *5*, 115-198; Pfaltz *Mod. Synth. Methods* **1989,** *5*, 199-248; Kagan *Bull. Soc. Chim. Fr.* **1988,** 846-853; Brunner *Synthesis* **1988,** 645-654; Wynberg *Top. Stereochem.* **1986,** *16*, 87-129. See also papers in *Tetrahedron: Asymmetry* **1991,** *2*, 481-732.

[98]For reviews of these and related topics, see Zief; Crane *Chromatographic Separations*; Marcel Dekker: New York, 1988; Brunner *J. Organomet. Chem.* **1986,** *300*, 39-56; Bosnich; Fryzuk *Top. Stereochem.* **1981,** *12*, 119-154.

[99]See Vineyard; Knowles; Sabacky; Bachman; Weinkauff *J. Am. Chem. Soc.* **1977,** *99*, 5946; Fryzuk; Bosnich *J. Am. Chem. Soc.* **1978,** *100*, 5491.

[100]For reviews of chiral transition metal complex catalysts, see Brunner *Top. Stereochem.* **1988,** *18*, 129-247; Hayashi; Kumada *Acc. Chem. Res.* **1982,** *15*, 395-401.

[101]Findeis; Whitesides *J. Org. Chem.* **1987,** *52*, 2838. For a monograph on enzymes as chiral catalysts, see Rétey; Robinson *Stereospecificity in Organic Chemistry and Enzymology*; Verlag Chemie: Deerfield Beach, FL, 1982. For reviews, see Klibanov *Acc. Chem. Res.* **1990,** *23*, 114-120; Jones *Tetrahedron* **1986,** *42*, 3351-3403; Jones, in Morrison, Ref. 88, vol. 5, pp. 309-344; Švedas; Galaev *Russ. Chem. Rev.* **1983,** *52*, 1184-1202. See also Simon; Bader; Günther; Neumann; Thanos *Angew. Chem. Int. Ed. Engl.* **1985,** *24*, 539-553 [*Angew. Chem.* 97, 541-555].



(–)-threo isomer

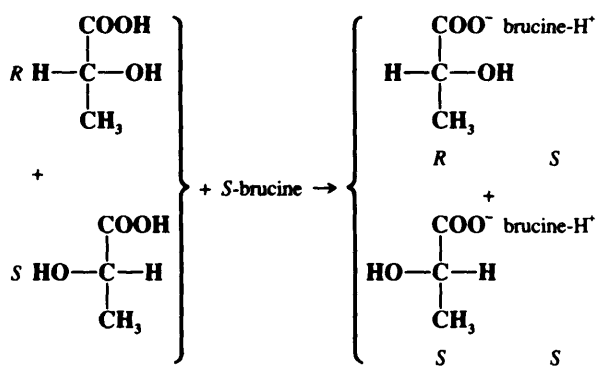
and the preparation of optically active alcohols by the treatment of Grignard reagents with aldehydes in optically active ether solvents.[102]

4. *Reactions in the presence of circularly polarized light.*[103] If the light used to initiate a photochemical reaction (Chapter 7) of achiral reagents is circularly polarized, then, in theory, a chiral product richer in one enantiomer might be obtained. However, such experiments have not proved fruitful. In certain instances, the use of left and right circularly polarized light *has* given products with opposite rotations[104] (showing that the principle is valid), but up to now the extent of favoritism has always been less than 1%.

Methods of Resolution[105]

A pair of enantiomers can be separated in several ways, of which conversion to diastereomers and separation of these by fractional crystallization is the most often used. In this method and in some of the others, both isomers can be recovered, but in some methods it is necessary to destroy one.

1. *Conversion to diastereomers.* If the racemic mixture to be resolved contains a carboxyl group (and no strongly basic group), it is possible to form a salt with an optically active base. Since the base used is, say, the *S* form, there will be a mixture of two salts



[102]See, for example, Blomberg; Coops *Recl. Trav. Chim. Pays-Bas* **1964,** *83,* 1083; Inch; Lewis; Sainsbury; Sellers *Tetrahedron Lett.* **1969,** 3657; Jalander; Strandberg *Acta Chem. Scand., Ser. B* **1983,** *37,* 15. See also Seebach; Kalinowski; Langer; Crass; Wilka *Org. Synth. VII,* 41.

[103]For a review, See Buchardt *Angew. Chem. Int. Ed. Engl.* **1974,** *13,* 179-185 [*Angew. Chem. 86,* 222]. For a discussion, see Barron *J. Am. Chem. Soc.* **1986,** *108,* 5539.

[104]See, for example, Moradopour; Nicoud; Balavoine; Kagan; Tsoucaris *J. Am. Chem. Soc.* **1971,** *93,* 2353; Bernstein; Calvin; Buchardt *J. Am. Chem. Soc.* **1972,** *94,* 494, **1973,** *95,* 527, *Tetrahedron Lett.* **1972,** 2195; Nicoud; Kagan *Isr. J. Chem.* **1977,** *15,* 78. See also Zandomeneghi; Cavazza; Pietra *J. Am. Chem. Soc.* **1984,** *106,* 7261.

[105]For a monograph, see Ref. 7. For reviews, see Wilen; Collet; Jacques *Tetrahedron* **1977,** *33,* 2725-2736; Wilen *Top. Stereochem.* **1971,** *6,* 107-176; Boyle *Q. Rev., Chem. Soc.* **1971,** *25,* 323-341; Buss; Vermeulen *Ind. Eng. Chem.* **1968,** *60* (8), 12-28.

produced having the configurations *SS* and *RS*. Although the acids are enantiomers, the salts are diastereomers and have different properties. The property most often used for separation is differential solubility. The mixture of diastereomeric salts is allowed to crystallize from a suitable solvent. Since the solubilities are different, the initial crystals formed will be richer in one diastereomer. Filtration at this point will already have achieved a partial resolution. Unfortunately, the difference in solubilities is rarely if ever great enough to effect total separation with one crystallization. Usually fractional crystallizations must be used and the process is long and tedious. Fortunately, naturally occurring optically active bases (mostly alkaloids) are readily available. Among the most commonly used are brucine, ephedrine, strychnine, and morphine. Once the two diastereomers have been separated, it is easy to convert the salts back to the free acids and the recovered base can be used again.

Most resolution is done on carboxylic acids and often, when a molecule does not contain a carboxyl group, it is converted to a carboxylic acid before resolution is attempted. However, the principle of conversion to diastereomers is not confined to carboxylic acids, and other groups[106] may serve as handles to be coupled to an optically active reagent.[107] Racemic bases can be converted to diastereomeric salts with active acids. Alcohols[108] can be converted to diastereomeric esters, aldehydes to diastereomeric hydrazones, etc. Even hydrocarbons can be converted to diastereomeric inclusion compounds,[109] with urea. Urea is not chiral, but the cage structure is.[110] Chiral crown ethers have been used to separate mixtures of enantiomeric alkyl- and arylammonium ions, by the formation of diastereomeric complexes[111] (see also category 3, below). *trans*-Cyclooctene (p. 104) was resolved by conversion to a platinum complex containing an optically active amine.[112]

Although fractional crystallization has always been the most common method for the separation of diastereomers, its tediousness and the fact that it is limited to solids prompted a search for other methods. Fractional distillation has given only limited separation, but gas chromatography[113] and preparative liquid chromatography[114] have proved more useful and, in many cases, have supplanted fractional crystallization, especially where the quantities to be resolved are small.[115]

[106]For summaries of methods used to resolve particular types of compounds, see Boyle, Ref. 105; Eliel *Stereochemistry of Carbon Compounds*, Ref. 1, pp. 49-63.

[107]For an extensive list of reagents that have been used for this purpose and of compounds resolved, see Wilen *Tables of Resolving Agents and Optical Resolutions*; University of Notre Dame Press: Notre Dame, IN, 1972.

[108]For a review of resolution of alcohols, see Klyashchitskii; Shvets *Russ. Chem. Rev.* **1972,** *41*, 592-602.

[109]For reviews of chiral inclusion compounds, including their use for resolution, see Prelog; Kovačević; Egli *Angew. Chem. Int. Ed. Engl.* **1989,** *28*, 1147-1152 [*Angew. Chem. 101*, 1173-1178]; Worsch; Vögtle *Top. Curr. Chem.* **1987,** *140*, 21-41; Toda *Top. Curr. Chem.* **1987,** *140*, 43-69; Stoddart *Top. Stereochem.* **1987,** *17*, 207-288; Sirlin *Bull. Soc. Chim. Fr.* **1984,** II-5-II-40; Arad-Yellin; Green; Knossow; Tsoucaris, in Atwood; Davies; MacNicol *Inclusion Compounds*, vol. 3; Academic Press: New York, 1984, pp. 263-295; Stoddart *Prog. Macrocyclic Chem.* **1981,** *2*, 173-250; Cram et al., Pure Appl. Chem. **1975,** *43*, 327-349; Cram; Cram *Science* **1974,** *183*, 803-809.

[110]See Schlenk, *Liebigs Ann. Chem.* **1973,** 1145, 1156, 1179, 1195. Inclusion complexes of tri-*o*-thymotide can be used in a similar manner: see Arad-Yellin; Green; Knossow; Tsoucaris *J. Am. Chem. Soc.* **1983,** *105*, 4561.

[111]See, for example, Kyba; Koga; Sousa; Siegel; Cram *J. Am. Chem. Soc.* **1973,** *95*, 2692; Sogah; Cram *J. Am. Chem. Soc.* **1979,** *101*, 3035; Lingenfelter; Helgeson; Cram *J. Org. Chem.* **1981,** *46*, 393; Pearson; Leigh; Sutherland *J. Chem. Soc., Perkin Trans. 1* **1979,** 3113; Bussman; Lehn; Oesch; Plumeré; Simon *Helv. Chim. Acta* **1981,** *64*, 657; Davidson; Bradshaw; Jones; Dalley; Christensen; Izatt; Morin; Grant *J. Org. Chem.* **1984,** *49*, 353. See also Toda; Tanaka; Omata; Nakamura; Ōshima *J. Am. Chem. Soc.* **1983,** *105*, 5151.

[112]Ref. 55. For a review, see Tsuji *Adv. Org. Chem.* **1969,** *6*, 109-255, pp. 220-227.

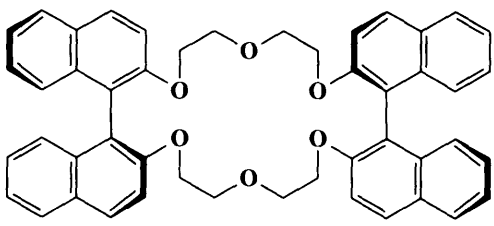
[113]See, for example, Casanova; Corey *Chem. Ind. (London)* **1961,** 1664; Gil-Av; Nurok *Proc. Chem. Soc.* **1962,** 146; Gault; Felkin *Bull. Soc. Chim. Fr.* **1965,** 742; Vitt; Saporovskaya; Gudkova; Belikov *Tetrahedron Lett.* **1965,** 2575; Westley; Halpern; Karger *Anal. Chem.* **1968,** *40*, 2046; Kawa; Yamaguchi; Ishikawa *Chem. Lett.* **1982,** 745.

[114]For example, See Pirkle; Hoekstra *J. Org. Chem.* **1974,** *39*, 3904; Pirkle; Hauske *J. Org. Chem.* **1977,** *42*, 1839; Helmchen; Nill *Angew. Chem. Int. Ed. Engl.* **1979,** *18*, 65 [*Angew. Chem. 91*, 66]; Meyers; Slade; Smith; Mihelich; Hershenson; Liang *J. Org. Chem.* **1979,** *44*, 2247; Goldman; Kustanovich; Weinstein; Tishbee; Gil-Av *J. Am. Chem. Soc.* **1982,** *104*, 1093.

[115]For monographs on the use of liquid chromatography to effect resolutions, see Lough *Chiral Liquid Chromatography*; Blackie and Sons: London, 1989; Krstulović *Chiral Separations by HPLC*; Ellis Horwood: Chichester, 1989; Zief; Crane, Ref. 98. For a review, see Karger *Anal. Chem.* **1967,** *39* (8), 24A-50A.

2. *Differential absorption.* When a racemic mixture is placed on a chromatographic column, if the column consists of chiral substances, then in principle the enantiomers should move along the column at different rates and should be separable without having to be converted to diastereomers.[115] This has been successfully accomplished with paper, column, thin-layer,[116] and gas and liquid chromatography.[117] For example, racemic mandelic acid has been almost completely resolved by column chromatography on starch.[118] Many workers have achieved separations with gas and liquid chromatography by the use of columns packed with chiral absorbents.[119] Columns packed with chiral materials are now commercially available and are capable of separating the enantiomers of certain types of compounds.[120]

3. *Chiral recognition.* The use of chiral hosts to form diastereomeric inclusion compounds was mentioned above. But in some cases it is possible for a host to form an inclusion compound with one enantiomer of a racemic guest, but not the other. This is called *chiral recognition.* One enantiomer fits into the chiral host cavity, the other does not. More often, both diastereomers are formed, but one forms more rapidly than the other, so that if the guest is removed it is already partially resolved (this is a form of kinetic resolution, see category 6). An example is use of the chiral crown ether **42** partially to resolve the racemic amine salt **43.**[121] When an aqueous solution of **43** was mixed with a solution of optically active **42** in chloroform, and the layers separated, the chloroform layer contained about



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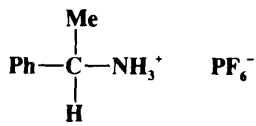


43

twice as much of the complex between **42** and (*R*)-**43** as of the diastereomeric complex. Many other chiral crown ethers and cryptands have been used, as have been cyclodextrins,[122]

[116]Weinstein *Tetrahedron Lett.* **1984,** *25,* 985.

[117]For monographs, see Allenmark *Chromatographic Enantioseparation*; Ellis Horwood: Chichester, 1988; König *The Practice of Enantiomer Separation by Capillary Gas Chromatography*; Hüthig: Heidelberg, 1987. For reviews, see Schurig; Nowotny *Angew. Chem. Int. Ed. Engl.* **1990,** *29,* 939-957 [*Angew. Chem. 102,* 969-986]; Pirkle; Pochapsky *Chem. Rev.* **1989,** *89,* 347-362, *Adv. Chromatogr.* **1987,** *27,* 73-127; Okamoto *CHEMTECH* **1987,** 176-181; Schurig *Angew. Chem. Int. Ed. Engl.* **1984,** *23,* 747-765 [*Angew. Chem. 96,* 733-752]; Blaschke *Angew. Chem. Int. Ed. Engl.* **1980,** *19,* 13-24 [*Angew. Chem. 92,* 14-25]; Rogozhin; Davankov *Russ. Chem. Rev.* **1968,** *37,* 565-575. See also many articles in the journal *Chirality.*

[118]Ohara; Fujita; Kwan *Bull. Chem. Soc. Jpn.* **1962,** *35,* 2049; Ohara; Ohta; Kwan *Bull. Chem. Soc. Jpn.* **1964,** *37,* 76. See also Blaschke; Donow *Chem. Ber.* **1975,** *108,* 2792; Hess; Burger; Musso *Angew. Chem. Int. Ed. Engl.* **1978,** *17,* 612 [*Angew. Chem. 90,* 645].

[119]See, for example, Gil-Av; Feibush; Charles-Sigler *Tetrahedron Lett.* **1966,** 1009; Gil-Av; Tishbee; Hare *J. Am. Chem. Soc.* **1980,** *102,* 5115; Hesse; Hagel *Liebigs Ann. Chem.* **1976,** 996; Schlögl; Widhalm *Chem. Ber.* **1982,** *115,* 3042; Koppenhoefer; Allmendinger; Nicholson *Angew. Chem. Int. Ed. Engl.* **1985,** *24,* 48 [*Angew. Chem. 97,* 46]; Dobashi; Hara *J. Am. Chem. Soc.* **1985,** *107,* 3406, *Tetrahedron Lett.* **1985,** *26,* 4217, *J. Org. Chem.* **1987,** *52,* 2490; Konrad; Musso *Liebigs Ann. Chem.* **1986,** 1956; Pirkle; Pochapsky; Mahler; Corey; Reno; Alessi *J. Org. Chem.* **1986,** *51,* 4991; Okamoto; Aburatani; Kaida; Hatada *Chem. Lett.* **1988,** 1125; Ehlers; König; Lutz; Wenz; tom Dieck *Angew. Chem. Int. Ed. Engl.* **1988,** *27,* 1556 [*Angew. Chem. 100,* 1614]; Hyun; Park; Baik *Tetrahedron Lett.* **1988,** *29,* 4735; Schurig; Nowotny; Schmalzing *Angew. Chem. Int. Ed. Engl.* **1989,** *28,* 736 [*Angew. Chem. 101,* 785]; Ôi; Shijo; Miyano *Chem. Lett.* **1990,** 59; Erlandsson; Marle; Hansson; Isaksson; Pettersson; Pettersson *J. Am. Chem. Soc.* **1990,** *112,* 4573.

[120]See, for example, Pirkle and Welch *J. Org. Chem.* **1984,** *49,* 138.

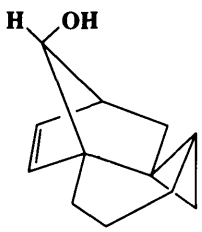
[121]Cram; Cram, Ref. 109. See also Yamamoto; Fukushima; Okamoto; Hatada; Nakazaki *J. Chem. Soc., Chem. Commun.* **1984,** 1111; Kanoh; Hongoh; Katoh; Motoi; Suda *J. Chem. Soc., Chem. Commun.* **1988,** 405; Bradshaw; Huszthy; McDaniel; Zhu; Dalley; Izatt; Lifson *J. Org. Chem.* **1990,** *55,* 3129.

[122]See, for example, Hamilton; Chen *J. Am. Chem. Soc.* **1988,** *110,* 5833.

cholic acid,[123] and other kinds of hosts.[109] Of course, enzymes are generally very good at chiral recognition, and much of the work in this area has been an attempt to mimic the action of enzymes.

4. *Biochemical processes.*[124] The chiral compound that reacts at different rates with the two enantiomers may be present in a living organism. For instance, a certain bacterium may digest one enantiomer but not the other. This method is limited, since it is necessary to find the proper organism and since one of the enantiomers is destroyed in the process. However, when the proper organism is found, the method leads to a high extent of resolution since biological processes are usually very stereoselective.

5. *Mechanical separation.*[125] This is the method by which Pasteur proved that racemic acid was actually a mixture of (+)- and (−)-tartaric acids.[126] In the case of racemic sodium ammonium tartrate the enantiomers crystallize separately—all the (+) molecules going into one crystal and all the (−) into another. Since the crystals too are nonsuperimposable, their appearance is not identical and a trained crystallographer can separate them with tweezers.[127] However, this is seldom a practical method, since few compounds crystallize in this manner. Even sodium ammonium tartrate does so only when it is crystallized below 27°C. A more useful variation of the method, though still not very common, is the seeding of a racemic solution with something that will cause only one enantiomer to crystallize.[128] An interesting example of the mechanical separation technique was reported in the isolation of heptahelicene (p. 103). One enantiomer of this compound, which incidentally has the extremely high rotation of $[\alpha]_D^{20} = +6200°$, spontaneously crystallizes from benzene.[129] In the case of 1,1′-binaphthyl, optically active crystals can be formed simply by heating polycrystalline racemic samples of the compound at 76–150°. A phase change from one crystal form to another takes place.[130] It may be noted that 1,1′-binaphthyl is one of the few compounds that can be resolved by the Pasteur tweezer method. In some cases resolution can be achieved by enantioselective crystallization in the presence of a chiral additive.[131] Spontaneous resolution has also been achieved by sublimation. In the case of the norborneol derivative **44,**



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[123]See Miyata; Shibakana; Takemoto *J. Chem. Soc., Chem. Commun.* **1988,** 655.

[124]For a review, see Sih; Wu *Top. Stereochem.* **1989,** *19,* 63-125.

[125]For reviews, see Collet; Brienne; Jacques *Chem. Rev.* **1980,** *80,* 215-230; *Bull. Soc. Chim. Fr.* **1972,** 127-142, **1977,** 494-498. For a discussion, see Curtin; Paul *Chem. Rev.* **1981,** *81,* 525-541, pp. 535-536.

[126]Besides discovering this method of resolution, Pasteur also discovered the method of conversion to diastereomers and separation by fractional crystallization and the method of biochemical separation (and, by extension, kinetic resolution).

[127]This is a case of optically active materials arising from inactive materials. However, it may be argued that an optically active investigator is required to use the tweezers. Perhaps a hypothetical human being constructed entirely of inactive molecules would be unable to tell the difference between left- and right-handed crystals.

[128]For a review of the seeding method, see Secor *Chem. Rev.* **1963,** *63,* 297.

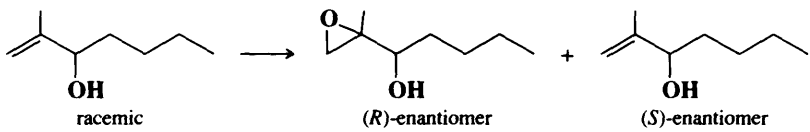
[129]Martin et al., Ref. 53. See also Wynberg; Groen *J. Am. Chem. Soc.* **1968,** *90,* 5339. For a discussion of other cases, see McBride; Carter *Angew. Chem. Int. Ed. Engl.* **1991,** *30,* 293 [*Angew. Chem. 103,* 298].

[130]Wilson; Pincock *J. Am. Chem. Soc.* **1975,** *97,* 1474; Kress; Duesler; Etter; Paul; Curtin *J. Am. Chem. Soc.* **1980,** *102,* 7709. See also Lu; Pincock *J. Org. Chem.* **1978,** *43,* 601; Gottarelli; Spada *J. Org. Chem.* **1991,** *56,* 2096. For a discussion and other examples, see Agranat; Perlmutter-Hayman; Tapuhi *Nouv. J. Chem.* **1978,** *2,* 183.

[131]Addadi; Weinstein; Gati; Weissbuch; Lahav *J. Am. Chem. Soc.* **1982,** *104,* 4610. See also Weissbuch; Addadi; Berkovitch-Yellin; Gati; Weinstein; Lahav; Leiserowitz *J. Am. Chem. Soc.* **1983,** *105,* 6615.

when the racemic solid is subjected to sublimation, the (+) molecules condense into one crystal and the (−) molecules into another.[132] In this case the crystals are superimposable, unlike the situation with sodium ammonium tartrate, but the investigators were able to remove a single crystal, which proved optically active.

6. *Kinetic resolution.*[133] Since enantiomers react with chiral compounds at different rates, it is sometimes possible to effect a partial separation by stopping the reaction before completion. This method is very similar to the asymmetric syntheses discussed on p. 102. An important application of this method is the resolution of racemic alkenes by treatment with optically active diisopinocampheylborane,[134] since alkenes do not easily lend themselves to conversion to diastereomers if no other functional groups are present. Another example is the resolution of allylic alcohols such as **45** with one enantiomer of a chiral epoxidizing agent (see **5-36**).[135] In the case of **45** the discrimination was extreme. One enantiomer was converted to the epoxide and the other was not, the rate ratio (hence the selectivity factor)



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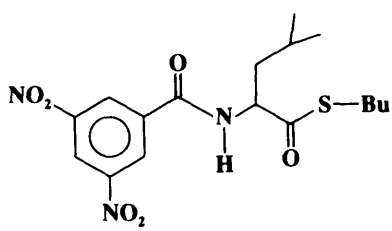
being more than 100. Of course, in this method only one of the enantiomers of the original racemic mixture is obtained, but there are at least two possible ways of getting the other: (1) use of the other enantiomer of the chiral reagent; (2) conversion of the product to the starting compound by a reaction that preserves the stereochemistry.

Reactions catalyzed by enzymes can be utilized for this kind of resolution.[136]

7. *Deracemization.* In this type of process, one enantiomer is converted to the other, so that a racemic mixture is converted to a pure enantiomer, or to a mixture enriched in one enantiomer. This is not quite the same as the methods of resolution previously mentioned, though an outside optically active substance is required. For example, the racemic thioester **46** was placed in contact with a certain optically active amide. After 28 days the solution contained 89% of one enantiomer and 11% of the other.[137] To effect the deracem-



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[132]Paquette; Lau *J. Org. Chem.* **1987,** *52*, 1634.

[133]For reviews, see Kagan; Fiaud *Top. Stereochem.* **1988,** *18*, 249-330; Brown *Chem. Ind. (London)* **1988,** 612-617.

[134]Brown; Ayyangar; Zweifel *J. Am. Chem. Soc.* **1964,** *86*, 397.

[135]Martin; Woodard; Katsuki; Yamada; Ikeda; Sharpless *J. Am. Chem. Soc.* **1981,** *103*, 6237. See also Kobayashi; Kusakabe; Kitano; Sato *J. Org. Chem.* **1988,** *53*, 1586; Kitano; Matsumoto; Sato *Tetrahedron* **1988,** *44*, 4073; Carlier; Mungall; Schröder; Sharpless *J. Am. Chem. Soc.* **1988,** *110*, 2978; Discordia; Dittmer *J. Org. Chem.* **1990,** *55*, 1414. For other examples, see Miyano; Lu; Viti; Sharpless *J. Org. Chem.* **1985,** *50*, 4350; Paquette; DeRussy; Cottrell *J. Am. Chem. Soc.* **1988,** *110*, 890; Weidert; Geyer; Horner *Liebigs Ann. Chem.* **1989,** 533; Katamura; Ohkuma; Tokunaga; Noyori *Tetrahedron: Assymetry* **1990,** *1*, 1; Hayashi; Miwata; Oguni *J. Chem. Soc., Perkin Trans. 1* **1991,** 1167.

[136]For example, see Schwartz; Madan; Whitesell; Lawrence *Org. Synth. 69*, 1; Guibé-Jampel; Rousseau; Salaün *J. Chem. Soc., Chem. Commun.* **1987,** 1080; Francalanci; Cesti; Cabri; Bianchi; Martinengo; Foá *J. Org. Chem.* **1987,** *52*, 5079; Mohr; Rösslein; Tamm *Tetrahedron Lett.* **1989,** *30*, 2513; Kazlauskas *J. Am. Chem. Soc.* **1989,** *111*, 4953.

[137]Pirkle; Reno *J. Am. Chem. Soc.* **1987,** *109*, 7189. For another example, see Reider; Davis; Hughes; Grabowski *J. Org. Chem.* **1987,** *52*, 955.

ization two conditions are necessary: (1) the enantiomers must complex differently with the optically active substance; (2) they must interconvert under the conditions of the experiment. In this case the presence of a base (Et_3N) was necessary for the interconversion to take place.

Optical Purity[138]

Suppose we have just attempted to resolve a racemic mixture by one of the methods described in the previous section. How do we know that the two enantiomers we have obtained are pure? For example, how do we know that the (+) isomer is not contaminated by, say, 20% of the (−) isomer and vice versa? If we knew the value of [α] for the pure material ($[\alpha]_{max}$), we could easily determine the purity of our sample by measuring its rotation. For example, if $[\alpha]_{max}$ is +80° and our (+) enantiomer contains 20% of the (−) isomer, [α] for the sample will be +48°.[139] We define *optical purity* as

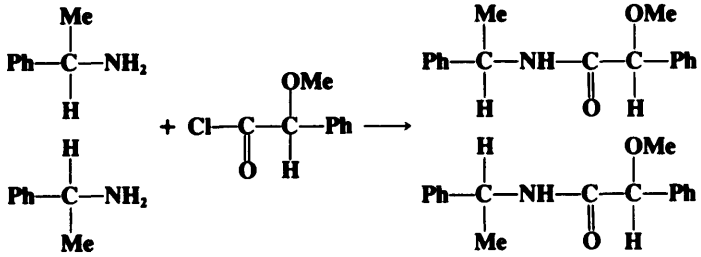
$$\text{Percent optical purity} = \frac{[\alpha]_{obs}}{[\alpha]_{max}} \times 100$$

Assuming a linear relationship between [α] and concentration, which is true for most cases, the optical purity is equal to the percent excess of one enantiomer over the other:

$$\text{Optical purity} = \text{percent enantiomeric excess} = \frac{[R] - [S]}{[R] + [S]} \times 100 = \%\ R - \%\ S$$

But how do we determine the value of $[\alpha]_{max}$? It is plain that we have two related problems here; namely, what are the optical purities of our two samples and what is the value of $[\alpha]_{max}$. If we solve one, the other is also solved. Several methods for solving these problems are known.

One of these methods involves the use of nmr.[140] Suppose we have a nonracemic mixture of two enantiomers and wish to know the proportions. We convert the mixture into a mixture of diastereomers with an optically pure reagent and look at the nmr spectrum of the resulting mixture, e.g.,



If we examined the nmr spectrum of the starting mixture, we would find only one peak (split into a doublet by the C—H) for the Me protons, since enantiomers give identical nmr

[138]For a review, see Raban; Mislow *Top. Stereochem.* **1967,** *2*, 199-230.

[139]If a sample contains 80% (+) and 20% (−) isomer, the (−) isomer cancels an equal amount of (+) isomer and the mixture behaves as if 60% of it were (+) and the other 40% inactive. Therefore the rotation is 60% of 80° or 48°. This type of calculation, however, is not valid for cases in which [α] is dependent on concentration (p. 96); see Horeau *Tetrahedron Lett.* **1969,** 3121.

[140]Raban; Mislow *Tetrahedron Lett.* **1965,** 4249, **1966,** 3961; Jacobus; Raban *J. Chem. Educ.* **1969,** *46*, 351; Tokles; Snyder *Tetrahedron Lett.* **1988,** *29*, 6063. For a review, see Yamaguchi, in Morrison, Ref. 88, vol. 1, pp. 125-152. See also Ref. 138.

spectra.[141] But the two amides are not enantiomers and each Me gives its own doublet. From the intensity of the two peaks, the relative proportions of the two diastereomers (and hence of the original enantiomers) can be determined. Alternatively, the unsplit OMe peaks could have been used. This method was satisfactorily used to determine the optical purity of a sample of 1-phenylethylamine (the case shown above),[142] as well as other cases, but it is obvious that sometimes corresponding groups in diastereomeric molecules will give nmr signals that are too close together for resolution. In such cases one may resort to the use of a different optically pure reagent. ^{13}C nmr can be used in a similar manner.[143] It is also possible to use these spectra to determine the absolute configuration of the original enantiomers by comparing the spectra of the diastereomers with those of the original enantiomers.[144] From a series of experiments with related compounds of known configurations it can be determined in which direction one or more of the ^{1}H or ^{13}C nmr peaks are shifted by formation of the diastereomer. It is then assumed that the peaks of the enantiomers of unknown configuration will be shifted the same way.

A closely related method does not require conversion of enantiomers to diastereomers but relies on the fact that (in principle, at least) enantiomers have different nmr spectra *in a chiral solvent*, or when mixed with a chiral molecule (in which case transient diastereomeric species may form). In such cases the peaks may be separated enough to permit the proportions of enantiomers to be determined from their intensities.[145] Another variation, which gives better results in many cases, is to use an achiral solvent but with the addition of a *chiral lanthanide shift reagent* such as tris[3-trifluoroacetyl-*d*-camphorato]europium-(III).[146] Lanthanide shift reagents have the property of spreading nmr peaks of compounds with which they can form coordination compounds, e.g., alcohols, carbonyl compounds, amines, etc. Chiral lanthanide shift reagents shift the peaks of the two enantiomers of many such compounds to different extents.

Another method, involving gas chromatography,[147] is similar in principle to the nmr method. A mixture of enantiomers whose purity is to be determined is converted by means of an optically pure reagent into a mixture of two diastereomers. These diastereomers are then separated by gas chromatography (p. 121) and the ratios determined from the peak areas. Once again, the ratio of diastereomers is the same as that of the original enantiomers. High-pressure liquid chromatography has been used in a similar manner and has wider applicability.[148] The direct separation of enantiomers by gas or liquid chromatography on a chiral column has also been used to determine optical purity.[149]

[141]Though enantiomers give identical nmr spectra, the spectrum of a single enantiomer may be different from that of the racemic mixture, even in solution. See Williams; Pitcher; Bommer; Gutzwiller; Uskoković *J. Am. Chem. Soc.* **1969,** *91*, 1871.

[142]Ref. 138, pp. 216-218.

[143]For a method that relies on diastereomer formation without a chiral reagent, see Feringa; Smaardijk; Wynberg *J. Am. Chem. Soc.* **1985,** *107*, 4798; Feringa; Strijtveen; Kellogg *J. Org. Chem.* **1986,** *51*, 5484. See also Pasquier; Marty *Angew. Chem. Int. Ed. Engl.* **1985,** *24*, 315 [*Angew. Chem.* 97, 328]; Luchinat; Roelens *J. Am. Chem. Soc.* **1986,** *108*, 4873.

[144]See Dale; Mosher *J. Am. Chem. Soc.* **1973,** *95*, 512; Rinaldi *Prog. NMR Spectrosc.* **1982,** *15*, 291-352; Faghih; Fontaine; Horibe; Imamura; Lukacs; Olesker; Seo *J. Org. Chem.* **1985,** *50*, 4918; Trost et al. *J. Org. Chem.* **1986,** *51*, 2370.

[145]For reviews of nmr chiral solvating agents, see Weisman, in Morrison, Ref. 88, vol. 1, pp. 153-171; Pirkle; Hoover *Top. Stereochem.* **1982,** *13*, 263-331. For literature references, see Sweeting; Anet *Org. Magn. Reson.* **1984,** *22*, 539. See also Pirkle; Tsipouras *Tetrahedron Lett.* **1985,** *26*, 2989; Parker; Taylor *Tetrahedron* **1987,** *43*, 5451.

[146]Whitesides; Lewis *J. Am. Chem. Soc.* **1970,** *92*, 6979, **1971,** *93*, 5914; Sweeting; Crans; Whitesides *J. Org. Chem.* **1987,** *52*, 2273. For a monograph on chiral lanthanide shift reagents, see Morrill *Lanthanide Shift Reagents in Stereochemical Analysis*; VCH: New York, 1986. For reviews, see Fraser, in Morrison, Ref. 88, vol. 1, pp. 173-196; Sullivan *Top. Stereochem.* **1978,** *10*, 287-329.

[147]Charles; Fischer; Gil-Av *Isr. J. Chem.* **1963,** *1*, 234; Halpern; Westley *Chem. Commun.* **1965,** 246; Vitt; Saporovskaya; Gudkova; Belikov *Tetrahedron Lett.* **1965,** 2575; Guetté; Horeau *Tetrahedron Lett.* **1965,** 3049; Westley; Halpern *J. Org. Chem.* **1968,** *33*, 3978.

[148]For a review, see Pirkle; Finn, in Morrison, Ref. 88, vol. 1, pp. 87-124.

[149]For reviews, see in Morrison, Ref. 88, vol. 1, the articles by Schurig, pp. 59-86 and Pirkle; Finn, pp. 87-124.

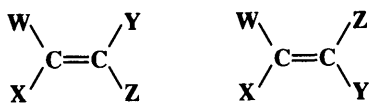
Other methods[150] involve isotopic dilution,[151] kinetic resolution,[152] ^{13}C nmr relaxation rates of diastereomeric complexes,[153] and circular polarization of luminescence.[154]

CIS–TRANS ISOMERISM

Compounds in which rotation is restricted may exhibit cis–trans isomerism.[155] These compounds do not rotate the plane of polarized light (unless they also happen to be chiral), and the properties of the isomers are not identical. The two most important types are isomerism resulting from double bonds and that resulting from rings.

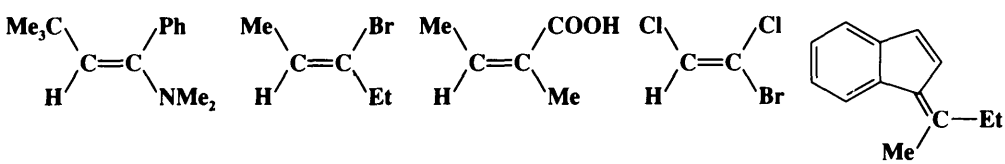
Cis–Trans Isomerism Resulting from Double Bonds

It has been mentioned (p. 9) that the two carbon atoms of a C=C double bond and the four atoms directly attached to them are all in the same plane and that rotation around the double bond is prevented. This means that in the case of a molecule WXC=CYZ, stereoisomerism exists when W ≠ X and Y ≠ Z. There are two and only two isomers (**E** and **F**), each superimposable on its mirror image unless one of the groups happens to carry a



E **F**

chiral center. Note that **E** and **F** are diastereomers, by the definition given on p. 113. There are two ways to name such isomers. In the older method, one isomer is called *cis* and the other *trans*. When W = Y, **E** is the cis and **F** the trans isomer. Unfortunately, there is no easy way to apply this method when the four groups are different. The newer method, which can be applied to all cases, is based on the Cahn–Ingold–Prelog system (p. 109). The two groups at each carbon are ranked by the sequence rules. Then that isomer with the two higher ranking groups on the same side of the double bond is called *Z* (for the German word *zusammen* meaning *together*); the other is *E* (for *entgegen* meaning *opposite*).[156] A few examples are shown. Note that the *Z* isomer is not necessarily the one that would be called cis under the older system (e.g., **47, 48**). Like cis and trans, *E* and *Z* are used as prefixes; e.g., **48** is called (*E*)-1-bromo-1,2-dichloroethene.



E *Z* *Z* *E* *E*

47 **48**

[150]See also Leitich *Tetrahedron Lett.* **1978,** 3589; Hill; Zens; Jacobus *J. Am. Chem. Soc.* **1979,** *101*, 7090; Matsumoto; Yajima; Endo *Bull. Chem. Soc. Jpn.* **1987,** *60*, 4139.

[151]Berson; Ben-Efraim *J. Am. Chem. Soc.* **1959,** *81*, 4083. For a review, see Andersen; Gash; Robertson, in Morrison, Ref. 88, vol. 1, pp. 45-57.

[152]Horeau *J. Am. Chem. Soc.* **1964,** *86*, 3171, *Bull. Soc. Chim. Fr.* **1964,** 2673; Horeau; Guetté; Weidmann *Bull. Soc. Chim. Fr.* **1966,** 3513. For a review, see Schoofs; Guetté, in Morrison, Ref. 88, vol. 1, pp. 29-44.

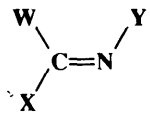
[153]Hofer; Keuper *Tetrahedron Lett.* **1984,** *25*, 5631.

[154]Eaton, *Chem. Phys. Lett.* **1971,** *8*, 251; Schippers; Dekkers *Tetrahedron* **1982,** *38*, 2089.

[155]Cis-trans isomerism was formerly called *geometrical isomerism*.

[156]For a complete description of the system, see Ref. 2.

This type of isomerism is also possible with other double bonds, such as C=N,[157] N=N, or even C=S,[158] though in these cases only two or three groups are connected to the double-bond atoms. In the case of imines, oximes, and other C=N compounds, if W = Y **49** may be called syn and **50** anti, though *E* and *Z* are often used here too. In azo compounds there is no ambiguity. **51** is always syn or *Z* regardless of the nature of W and Y.



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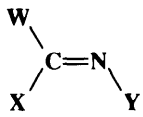

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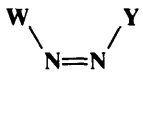
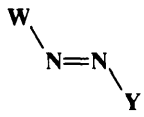


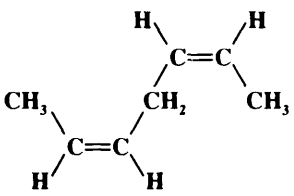
Z



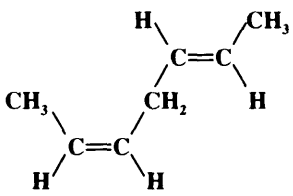
E

51

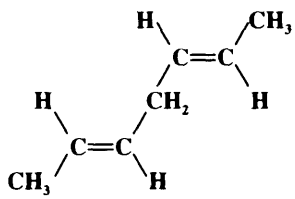
If there is more than one double bond[159] in a molecule and if W ≠ X and Y ≠ Z for each, the number of isomers in the most general case is 2^n, although this number may be decreased if some of the substituents are the same, as in



cis-cis or
Z, Z

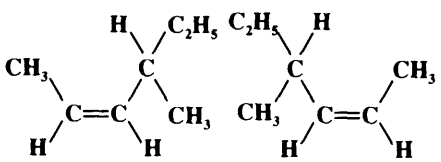


cis-trans or
Z, E

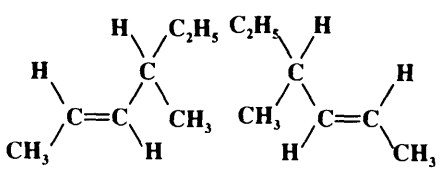


trans-trans or
E, E

When a molecule contains a double bond and an asymmetric carbon, there are four isomers, a cis pair of enantiomers and a trans pair:



Z or cis *dl* pair



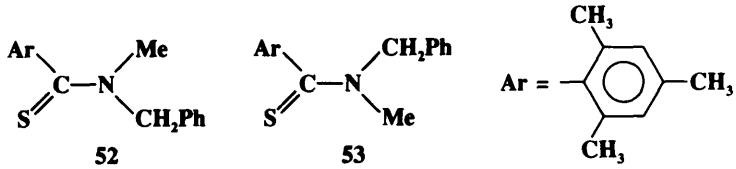
E or trans *dl* pair

Double bonds in small rings are so constrained that they must be cis. From cyclopropene (a known system) to cycloheptene, double bonds in a stable ring cannot be trans. However, the cyclooctene ring is large enough to permit trans double bonds to exist (see p. 104), and for rings larger than 10- or 11-membered, trans isomers are more stable[160] (see also p. 158).

In a few cases, single-bond rotation is so slowed that cis and trans isomers can be isolated even where no double bond exists[161] (see also p. 162). One example is

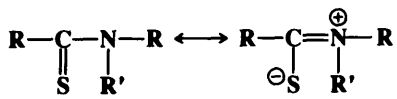
[157]For reviews of isomerizations about C=N bonds, see, in Patai *The Chemistry of the Carbon-Nitrogen Double Bond*; Wiley: New York, 1970, the articles by McCarty, 363-464 (pp. 364-408), and Wettermark, 565-596 (pp. 574-582).
[158]King; Durst *Can. J. Chem.* **1966**, *44*, 819.
[159]This rule does not apply to allenes, which do not show cis-trans isomerism at all (see p. 103).
[160]Cope; Moore; Moore *J. Am. Chem. Soc.* **1959**, *81*, 3153.
[161]For a review, see Ref. 49, pp. 41-71.

N-methyl-N-benzylthiomesitylide (**52** and **53**),[162] the isomers of which are stable in the crystalline state but interconvert with a half-life of about 25 hr in $CDCl_3$ at 50°C.[163] This

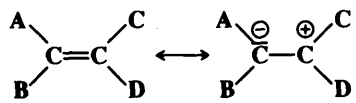


52 **53**

type of isomerism is rare; it is found chiefly in certain amides and thioamides, because resonance gives the single bond some double-bond character and slows rotation.[46] (For other examples of restricted rotation about single bonds, see pp. 161–163).



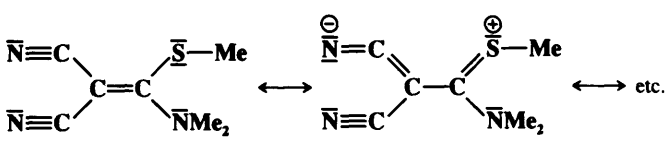
Conversely, there are compounds in which nearly free rotation is possible around what are formally C=C double bonds. These compounds, called *push–pull* or *captodative* ethylenes, have two electron-withdrawing groups on one carbon and two electron-donating groups on the other (**54**).[164] The contribution of diionic canonical forms such as the one



54

A, B = electron-withdrawing
C, D = electron-donating

shown decreases the double-bond character and allows easier rotation. For example, the compound **55** has a barrier to rotation of 13 kcal/mol (55 kJ/mol)[165], compared to a typical value of about 62-65 kcal/mol (260-270 kJ/mol) for simple alkenes.



55

Since they are diastereomers, cis–trans isomers always differ in properties; the differences may range from very slight to considerable. The properties of maleic acid are so different from those of fumaric acid (Table 4.2) that it is not surprising that they have different names.

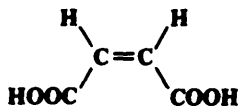
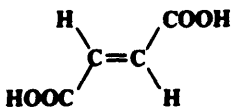
[162]Mannschreck *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 985 [*Angew. Chem.* 77, 1032]. See also Toldy; Radics *Tetrahedron Lett.* **1966**, 4753; Völter; Helmchen *Tetrahedron Lett.* **1978**, 1251; Walter; Hühnerfuss *Tetrahedron Lett.* **1981**, *22*, 2147.

[163]This is another example of atropisomerism (p. 102).

[164]For reviews, see Sandström *Top. Stereochem.* **1983**, *14*, 83-181; Ref. 49, pp. 111-125.

[165]Sandström; Wennerbeck *Acta Chem. Scand., Ser. B* **1978**, *32*, 421.

TABLE 4.2 Some properties of maleic and fumaric acids

Property	 Maleic acid	 Fumaric acid
Melting point, °C	130	286
Solubility in water at 25°C, g/liter	788	7
K_1 (at 25°C)	1.5×10^{-2}	1×10^{-3}
K_2 (at 25°C)	2.6×10^{-7}	3×10^{-5}

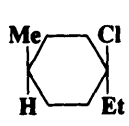
Since they generally have more symmetry than cis isomers, trans isomers in most cases have higher melting points and lower solubilities in inert solvents. The cis isomer usually has a higher heat of combustion, which indicates a lower thermochemical stability. Other noticeably different properties are densities, acid strengths, boiling points, and various types of spectra, but the differences are too involved to be discussed here.

Cis–Trans Isomerism of Monocyclic Compounds

Although rings of four carbons and larger are not generally planar (see p. 148), they will be treated as such in this section, since the correct number of isomers can be determined when this is done[166] and the principles are easier to visualize (see p. 145).

The presence of a ring, like that of a double bond, prevents rotation. Cis and trans isomers are possible whenever there are two carbons on a ring, each of which is substituted by two different groups. The two carbons need not be adjacent. Examples are

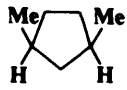
As with double bonds, W may equal Y and X may equal Z, but W may not equal X and Y may not equal Z if cis and trans isomers are to be possible. There is an important difference from the double-bond case: The substituted carbons are chiral carbons. This means that there are not *only* two isomers. In the most general case, where W, X, Y, and Z are all different, there are four isomers since neither the cis nor the trans isomer is superimposable on its mirror image. This is true regardless of ring size or which carbons are involved, except that in rings of even-numbered size when W, X, Y, and Z are at opposite corners, no chirality is present, e.g., **56**. In this case the substituted carbons are *not* chiral carbons. Note also that



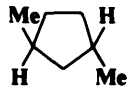
56

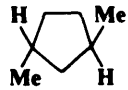
[166]For a discussion of why this is so, see Leonard; Hammond; Simmons *J. Am. Chem. Soc.* **1975**, *97*, 5052.

a plane of symmetry exists in such compounds. When W = Y and X = Z, the cis isomer is always superimposable on its mirror image and hence is a meso compound, while the trans isomer consists of a *dl* pair, except in the case noted above. Again, the cis isomer has a plane of symmetry while the trans does not.



cis meso



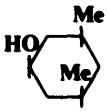


trans *dl* pair

Rings with more than two differently substituted carbons can be dealt with on similar principles. In some cases it is not easy to tell the number of isomers by inspection.[82] The best method for the student is to count the number n of differently substituted carbons (these will usually be asymmetric, but not always, e.g., in **56**) and then to draw 2^n structures, crossing out those that can be superimposed on others (usually the easiest method is to look for a plane of symmetry). By this means it can be determined that for 1,2,3-cyclohexanetriol there are two meso compounds and a *dl* pair; and for 1,2,3,4,5,6-hexachlorocyclohexane there are seven meso compounds and a *dl* pair. The drawing of these structures is left as an exercise for the student.

Similar principles apply to heterocyclic rings as long as there are carbons (or other ring atoms) containing two different groups.

Cyclic stereoisomers containing only two differently substituted carbons are named either cis or trans, as previously indicated. The *Z*, *E* system is not used for cyclic compounds. However, cis–trans nomenclature will not suffice for compounds with more than two differently substituted atoms. For these compounds, a system is used in which the configuration of each group is given with respect to a reference group, which is chosen as the group attached to the lowest-numbered ring member bearing a substituent giving rise to cis–trans isomerism. The reference group is indicated by the symbol *r*. Three stereoisomers named according to this system are *c*-3,*c*-5-dimethylcyclohexan-*r*-1-ol (**57**), *t*-3,*t*-5-dimethylcyclohexan-*r*-1-ol (**58**), and *c*-3,*t*-5-dimethylcyclohexan-*r*-1-ol (**59**). The last



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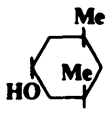

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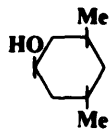

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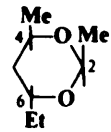


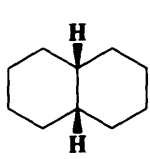
60

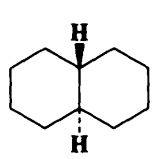
example demonstrates the rule that when there are two otherwise equivalent ways of going around the ring, one chooses the path that gives the cis designation to the first substituent after the reference. Another example is *r*-2,*c*-4-dimethyl-*t*-6-ethyl-1,3-dioxane (**60**).

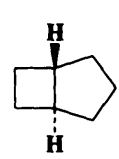
Cis–Trans Isomerism of Fused and Bridged Ring Systems

Fused bicyclic systems are those in which two rings share two and only two atoms. In such systems there is no new principle. The fusion may be cis or trans, as illustrated by *cis*- and *trans*-decalin. However, when the rings are small enough, the trans configuration is impossible and the junction must be cis. The smallest trans junction that has been prepared when

one ring is four-membered is a four-five junction; *trans*-bicyclo[3.2.0]heptane (**61**) is known.[167] For the bicyclo[2.2.0] system (a four-four fusion), only cis compounds have been


cis-Decalin


trans-Decalin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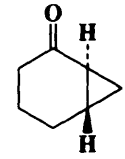
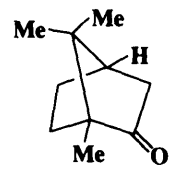
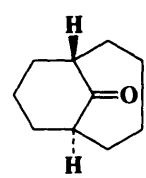

62

made. The smallest known trans junction when one ring is three-membered is a six-three junction (a bicyclo[4.1.0] system). An example is **62.**[168] When one ring is three-membered and the other eight-membered (an eight-three junction), the trans-fused isomer is more stable than the corresponding cis-fused isomer.[169]

In *bridged* bicyclic ring systems, two rings share more than two atoms. In these cases there may be fewer than 2^n isomers because of the structure of the system. For example, there are only two isomers of camphor (a pair of enantiomers), although it has two chiral


camphor

carbons. In both isomers the methyl and hydrogen are cis. The trans pair of enantiomers is impossible in this case, since the bridge *must* be cis. The smallest bridged system so far prepared in which the bridge is trans is the [4.3.1] system; the trans ketone **63** has been

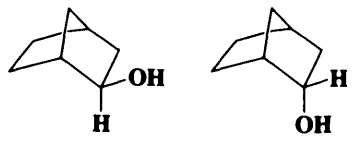

63

prepared.[170] In this case there are four isomers, since both the trans and the cis (which has also been prepared) are pairs of enantiomers.

When one of the bridges contains a substituent, the question arises as to how to name the isomers involved. When the two bridges that do *not* contain the substituent are of unequal length, the rule generally followed is that the prefix *endo-* is used when the substituent is

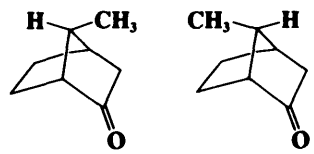
[167]Meinwald; Tufariello; Hurst *J. Org. Chem.* **1964,** *29,* 2914.
[168]Paukstelis; Kao *J. Am. Chem. Soc.* **1972,** *94,* 4783. For references to other examples, see Gassman; Bonser *J. Am. Chem. Soc.* **1983,** *105,* 667; Dixon; Gassman *J. Am. Chem. Soc.* **1988,** *110,* 2309.
[169]Corbally; Perkins; Carson; Laye; Steele *J. Chem. Soc., Chem. Commun.* **1978,** 778.
[170]Winkler; Hey; Williard *Tetrahedron Lett.* **1988,** *29,* 4691.

closer to the longer of the two unsubstituted bridges; the prefix *exo-* is used when the substituent is closer to the shorter bridge; e.g.,



exo-2-Norborneol *endo*-2-Norborneol

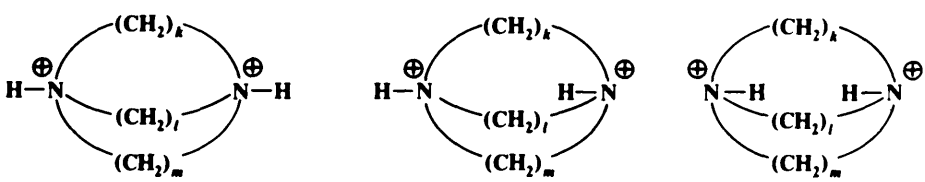
When the two bridges not containing the substituent are of equal length, this convention cannot be applied, but in some cases a decision can still be made; e.g., if one of the two bridges contains a functional group, the endo isomer is the one in which the substituent is closer to the functional group:



endo-7-Methyl-2-norcamphor *exo*-7-Methyl-2-norcamphor

Out–In Isomerism

Another type of stereoisomerism, called *out–in isomerism*,[171] is found in salts of tricyclic diamines with nitrogen at the bridgeheads. In cases where k, l, and $m > 6$, the N—H bonds can be inside the molecular cavity or outside, giving rise to three isomers, as shown. Simmons and Park[172] isolated several such isomers with k, l, and m varying from 6 to 10. In the 9,9,9



out-out isomer out-in isomer in-in isomer

compound, the cavity of the in–in isomer is large enough to encapsulate a chloride ion that is hydrogen bonded to the two N—H groups. The species thus formed is a cryptate, but differs from the cryptates discussed at p. 83 in that there is a negative rather than a positive ion enclosed.[173] Even smaller ones (e.g., the 4,4,4 compound) have been shown to form

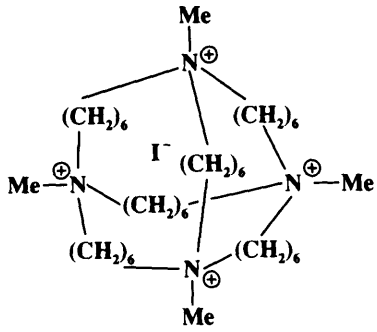
[171]For reviews, see Alder *Tetrahedron* **1990,** *46*, 683-713, *Acc. Chem. Res.* **1983,** *16*, 321-327.

[172]Simmons; Park *J. Am. Chem. Soc.* **1968,** *90*, 2428; Park; Simmons *J. Am. Chem. Soc.* **1968,** *90*, 2429, 2431; Simmons; Park; Uyeda; Habibi *Trans. N.Y. Acad. Sci.* **1970,** *32*, 521. See also Dietrich; Lehn; Sauvage *Tetrahedron Lett.* **1969,** 2885, 2889, *Tetrahedron* **1973,** *29*, 1647; Dietrich; Lehn; Sauvage; Blanzat *Tetrahedron* **1973,** *29*, 1629.

[173]For reviews, see Schmidtchen; Gleich; Schummer *Pure. Appl. Chem.* **1989,** *61*, 1535-1546; Pierre; Baret *Bull. Soc. Chim. Fr.* **1983,** II-367-II-380. See also Hosseini; Lehn *Helv. Chim. Acta* **1988,** *71*, 749.

mono-inside-protonated ions.[174] Out–in and in–in isomers have also been prepared in analogous all-carbon tricyclic systems.[175]

In the compound **64**, which has four quaternary nitrogens, a halide ion has been encapsulated without a hydrogen being present on a nitrogen.[176] This ion does not display out–in isomerism.



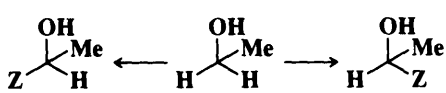
64

Enantiotopic and Diastereotopic Atoms, Groups, and Faces[177]

Many molecules contain atoms or groups which appear to be equivalent but which a close inspection will show to be actually different. We can test whether two atoms are equivalent by replacing each of them in turn with some other atom or group. If the new molecules created by this process are identical, the original atoms are equivalent; otherwise not. We can distinguish three cases.

1. In the case of malonic acid $CH_2(COOH)_2$, propane CH_2Me_2, or any other molecule of the form CH_2Y_2,[178] if we replace either of the CH_2 hydrogens by a group Z, the identical compound results. The two hydrogens are thus equivalent. Equivalent atoms and groups need not, of course, be located on the same carbon atom. For example, all the chlorine atoms of hexachlorobenzene are equivalent as are the two bromine atoms of 1,3-dibromopropane.

2. In the case of ethanol CH_2MeOH, if we replace one of the CH_2 hydrogens by a group Z, we get one enantiomer of the compound ZCHMeOH (**65**), while replacement of the other hydrogen gives the *other* enantiomer (**66**). Since the two compounds that result upon



65 **66**

[174]Alder; Moss; Sessions *J. Chem. Soc., Chem. Commun.* **1983,** 997, 1000; Alder; Orpen; Sessions *J. Chem. Soc., Chem. Commun.* **1983,** 999; Dietrich; Lehn; Guilhem; Pascard *Tetrahedron Lett.* **1989,** *30*, 4125; Wallon; Peter-Katalinić; Werner; Müller; Vögtle *Chem. Ber.* **1990,** *123*, 375.

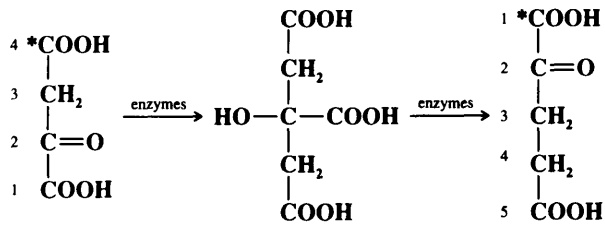
[175]Park; Simmons *J. Am. Chem. Soc.* **1972,** *94*, 7184; Gassman; Thummel *J. Am. Chem. Soc.* **1972,** *94*, 7183; Gassman; Hoye *J. Am. Chem. Soc.* **1981,** *103*, 215; McMurry; Hodge *J. Am. Chem. Soc.* **1984,** *106*, 6450; Winkler; Hey; Williard *J. Am. Chem. Soc.* **1986,** *108*, 6425.

[176]Schmidtchen; Müller *J. Chem. Soc., Chem. Commun.* **1984,** 1115. See also Schmidtchen *J. Am. Chem. Soc.* **1986,** *108*, 8249, *Top. Curr. Chem.* **1986,** *132*, 101-133.

[177]These terms were coined by Mislow. For lengthy discussions of this subject, see Eliel *Top. Curr. Chem.* **1982,** *105*, 1-76, *J. Chem. Educ.* **1980,** *57*, 52; Mislow; Raban *Top. Stereochem.* **1967,** *1*, 1-38. See also Ault *J. Chem. Educ.* **1974,** *51*, 729; Kaloustian; Kaloustian *J. Chem. Educ.* **1975,** *52*, 56; Jennings *Chem. Rev.* **1975,** *75*, 307-322.

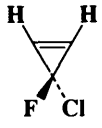
[178]In the case where Y is itself a chiral group, this statement is only true when the two Y groups have the same configuration.

replacement of H by Z (**65** and **66**) are not identical but enantiomeric, the hydrogens are *not* equivalent. We define as *enantiotopic* two atoms or groups that upon replacement with a third group give enantiomers. In any symmetrical environment the two hydrogens behave as equivalent, but in a dissymmetrical environment they may behave differently. For example, in a reaction with a chiral reagent they may be attacked at different rates. This has its most important consequences in enzymatic reactions,[179] since enzymes are capable of much greater discrimination than ordinary chiral reagents. An example is found in the Krebs cycle, in biological organisms, where oxaloacetic acid (**67**) is converted to α-oxoglutaric acid (**69**) by a sequence that includes citric acid (**68**) as an intermediate. When **67** is labeled with ^{14}C at the 4 position, the label is found only at C-1 of **69**, despite the fact that **68** is not



67 **68** **69**

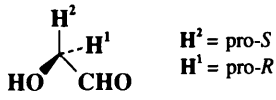
chiral. The two CH_2COOH groups of **68** are enantiotopic and the enzyme easily discriminates between them.[180] Note that the X atoms or groups of any molecule of the form CX_2WY are always enantiotopic if neither W nor Y is chiral, though enantiotopic atoms and groups may also be found in other molecules, e.g., the hydrogen atoms in 3-fluoro-3-chlorocyclopropene (**70**). In this case, substitution of an H by a group Z makes the C-3



70

atom asymmetric and substitution at C-1 gives the opposite enantiomer from substitution at C-2.

The term *prochiral*[181] is used for a compound or group that has two enantiotopic atoms or groups, e.g., CX_2WY. That atom or group X that would lead to an R compound if preferred to the other is called *pro*-R. The other is *pro*-S; e.g.,

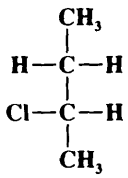


[179]For a review, see Benner; Glasfeld; Piccirilli *Top. Stereochem.* **1989,** *19*, 127-207. For a nonenzymatic example, see Job; Bruice *J. Am. Chem. Soc.* **1974,** *96*, 809.

[180]The experiments were carried out by Evans; Slotin *J. Biol. Chem.* **1941,** *141*, 439; Wood; Werkman; Hemingway; Nier *J. Biol. Chem.* **1942,** *142*, 31. The correct interpretation was given by Ogston *Nature* **1948,** *162*, 963. For discussion, see Hirschmann, in Florkin; Stotz *Comprehensive Biochemistry*, vol. 12, pp. 236-260, Elsevier: New York, 1964; Cornforth *Tetrahedron* **1974,** *30*, 1515; Vennesland *Top. Curr. Chem.* **1974,** *48*, 39-65; Eliel *Top. Curr. Chem.*, Ref. 177, pp. 5-7, 45-70.

[181]Hanson *J. Am. Chem. Soc.* **1966,** *88*, 2731; Hirschmann; Hanson *Tetrahedron* **1974,** *30*, 3649.

3. Where two atoms or groups in a molecule are in such positions that replacing each of them in turn by a group Z gives rise to diastereomers, the atoms or groups are called *diastereotopic*. Some examples are the CH_2 groups of 2-chlorobutane (**71**), vinyl chloride (**72**), and chlorocyclopropane (**73**) and the two olefinic hydrogens of **74.** Diastereotopic atoms and groups are different in any environment, chiral or achiral. These hydrogens react



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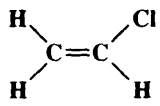

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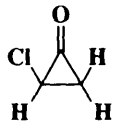

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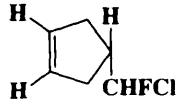
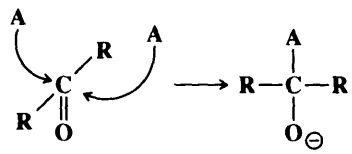


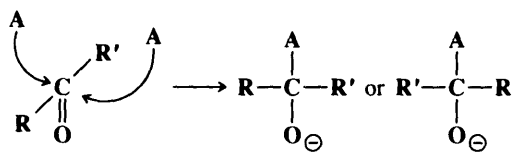
74

at different rates with achiral reagents, but an even more important consequence is that in nmr spectra, diastereotopic hydrogens theoretically give different peaks and split each other. This is in sharp contrast to equivalent or enantiotopic hydrogens, which are indistinguishable in the nmr, except when chiral solvents are used, in which case enantiotopic (but not equivalent) protons give different peaks.[182] The term *isochronous* is used for hydrogens that are indistinguishable in the nmr.[183] In practice, the nmr signals from diastereotopic protons are often found to be indistinguishable, but this is merely because they are very close together. Theoretically they are distinct, and they have been resolved in many cases. When they appear together, it is sometimes possible to resolve them by the use of lanthanide shift reagents (p. 126) or by changing the solvent or concentration. Note that X atoms or groups CX_2WY are diastereotopic if either W or Y is chiral.

Just as there are enantiotopic and diastereotopic atoms and groups, so we may distinguish *enantiotopic and diastereotopic faces* in trigonal molecules. Again we have three cases: (1) In formaldehyde or acetone (**G**), attack by an achiral reagent A from either face of the molecule gives rise to the same transition state and product; the two faces are thus equivalent. (2) In butanone or acetaldehyde (**H**), attack by an achiral A at one face gives a transition



G

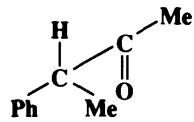


H

[182]Pirkle *J. Am. Chem. Soc.* **1966,** *88*, 1837; Burlingame; Pirkle *J. Am. Chem. Soc.* **1966,** *88*, 4294; Pirkle; Burlingame *Tetrahedron Lett.* **1967,** 4039.

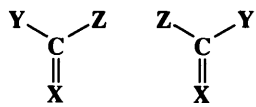
[183]For a review of isochronous and nonisochronous nuclei in the nmr, see van Gorkom; Hall *Q. Rev., Chem. Soc.* **1968,** *22*, 14-29. For a discussion, see Silverstein; LaLonde *J. Chem. Educ.* **1980,** *57*, 343.

state and product that are the enantiomers of those arising from attack at the other face. Such faces are enantiotopic. As we have already seen (p. 106), a racemic mixture must result in this situation. However, attack at an enantiotopic face by a chiral reagent gives diastereomers, which are not formed in equal amounts. (3) In a case like **75**, the two faces are



75

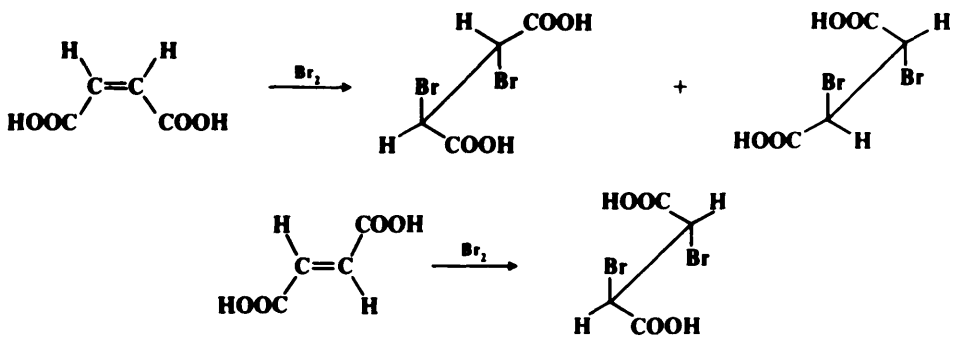
obviously not equivalent and are called diastereotopic. Enantiotopic and diastereotopic faces can be named by an extension of the Cahn–Ingold–Prelog system.[181] If the three groups as arranged by the sequence rules have the order X > Y > Z, that face in which the groups in this sequence are clockwise (as in **J**) is the *Re* face (from Latin *rectus*) whereas **K** shows the *Si* face (from Latin *sinister*).



J **K**

Stereospecific and Stereoselective Syntheses

Any reaction in which only one of a set of stereoisomers is formed exclusively or predominantly is called a *stereoselective* synthesis.[184] The same term is used when a mixture of two or more stereoisomers is exclusively or predominantly formed at the expense of other stereoisomers. In a *stereospecific* reaction, a given isomer leads to one product while another stereoisomer leads to the opposite product. All stereospecific reactions are necessarily stereoselective, but the converse is not true. These terms are best illustrated by examples. Thus, if maleic acid treated with bromine gives the *dl* pair of 2,3-dibromosuccinic acid while fumaric acid gives the meso isomer (this is the case), the reaction is stereospecific as well as stereoselective because two opposite isomers give two opposite isomers:



[184]For a further discussion of these terms and of stereoselective reactions in general, see Eliel *Stereochemisty of Carbon Compounds*, Ref. 1, pp. 434-446. For a review of how certain reactions can be run with stereocontrol, see Bartlett *Tetrahedron* **1980**, *36*, 2-72.

However, if both maleic and fumaric acid gave the *dl* pair or a mixture in which the *dl* pair predominated, the reaction would be stereoselective but not stereospecific. If more or less equal amounts of *dl* and meso forms were produced in each case, the reaction would be nonstereoselective. A consequence of these definitions is that if a reaction is carried out on a compound that has no stereoisomers, it cannot be stereospecific, but at most stereoselective. For example, addition of bromine to methylacetylene could (and does) result in preferential formation of *trans*-1,2-dibromopropene, but this can be only a stereoselective, not a stereospecific reaction.

CONFORMATIONAL ANALYSIS

If two different three-dimensional arrangements in space of the atoms in a molecule are interconvertible merely by free rotation about bonds, they are called *conformations*; if not, *configurations*.[185] Configurations represent *isomers* that can be separated, as previously discussed in this chapter. Conformations represent *conformers*, which are rapidly interconvertible and thus nonseparable. The terms "conformational isomer" and "rotamer" are sometimes used instead of "conformer." A number of methods have been used to determine conformations.[186] These include x-ray and electron diffraction, ir, Raman, uv, nmr,[187] and microwave spectra,[188] photoelectron spectroscopy,[189] supersonic molecular jet spectroscopy,[190] and optical rotatory dispersion and circular dichroism measurements.[191] Some of these methods are useful only for solids. It must be kept in mind that the conformation of a molecule in the solid state is not necessarily the same as in solution.[192] Conformations can be *calculated* by a method called molecular mechanics (p. 149).

[185]For books on conformational analysis, see Dale *Stereochemistry and Conformational Analysis*; Verlag Chemie: Deerfield Beach, FL, 1978; Chiurdoglu *Conformational Analysis*; Academic Press: New York, 1971; Eliel; Allinger; Angyal; Morrison *Conformational Analysis;* Wiley: New York, 1965; Hanack *Conformation Theory*; Academic Press: New York, 1965. For reviews, see Dale *Top. Stereochem.* **1976,** *9*, 199-270; Truax; Wieser *Chem. Soc. Rev.* **1976,** *5*, 411-429; Eliel *J. Chem. Educ.* **1975,** *52*, 762-767; Bastiansen; Seip; Boggs *Perspect. Struct. Chem.* **1971,** *4*, 60-165; Bushweller; Gianni, in Patai *The Chemistry of Functional Groups, Supplement E*; Wiley: New York, 1980, pp. 215-278.

[186]For a review, see Eliel; Allinger; Angyal; Morrison, Ref. 185, pp. 129-188.

[187]For monographs on the use of nmr to study conformational questions, see Ōki, Ref. 49; Marshall *Carbon–Carbon and Carbon–Proton NMR Couplings*; VCH: New York, 1983. For reviews, see Anet; Anet, in Nachod; Zuckerman *Determination of Organic Structures by Physical Methods*, vol. 3; Academic Press: New York, 1971, pp. 343-420; Kessler *Angew. Chem. Int. Ed. Engl.* **1970,** *9*, 219-235 [*Angew. Chem. 82*, 237-253]; Ivanova; Kugatova-Shemyakina *Russ. Chem. Rev.* **1970,** *39*, 510-528; Anderson *Q. Rev. Chem. Soc.* **1965,** *19*, 426-439; Franklin; Feltkamp *Angew. Chem. Int. Ed. Engl.* **1965,** *4*, 774-783 [*Angew. Chem. 77*, 798-807]; Johnson *Adv. Magn. Reson.* **1965,** *1*, 33-102. See also Whitesell; Minton *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*; Chapman and Hall: New York, 1987.

[188]For a review see Wilson *Chem. Soc. Rev.* **1972,** *1*, 293-318.

[189]For a review, see Klessinger; Rademacher *Angew. Chem. Int. Ed. Engl.* **1979,** *18*, 826-837 [*Angew. Chem. 91*, 885-896].

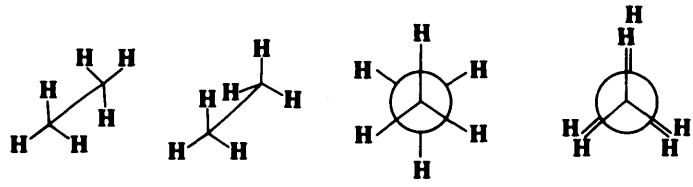
[190]Breen; Warren; Bernstein; Seeman *J. Am. Chem. Soc.* **1987,** *109*, 3453.

[191]For monographs, see Kagan *Determination of Configurations by Dipole Moments, CD, or ORD* (vol. 2 of Kagan, *Stereochemistry*); Georg Thieme Publishers: Stuttgart, 1977; Crabbé *ORD and CD in Chemistry and Biochemistry*; Academic Press: New York, 1972, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*; Holden-Day: San Francisco, 1965; Snatzke *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*; Sadtler Research Laboratories: Philadelphia, 1967; Velluz; Legrand; Grosjean *Optical Circular Dichroism*; Academic Press: New York, 1965. For reviews, see Smith, *Chem. Rev.* **1983,** *83*, 359-377; Håkansson, in Patai *The Chemistry of Acid Derivatives*, pt. 1; Wiley: New York, 1979, pp. 67-120; Hudec; Kirk *Tetrahedron* **1976,** *32*, 2475-2506; Schellman *Chem. Rev.* **1975,** *75*, 323-331; Velluz; Legrand *Bull. Soc. Chim. Fr.* **1970,** 1785-1795; Barrett, in Bentley; Kirby, Ref. 77, pt. 1, 1972, pp. 515-610; Snatzke *Angew. Chem. Int. Ed. Engl.* **1968,** *7*, 14-25 [*Angew. Chem. 18*, 15-26]; Crabbé in Nachod; Zuckerman, Ref. 187, vol. 3, pp. 133-205; Crabbé; Klyne *Tetrahedron* **1967,** *23*, 3449; Crabbé *Top. Stereochem.* **1967,** *1*, 93-198; Eyring; Liu; Caldwell *Chem. Rev.* **1968,** *68*, 525-540.

[192]See Kessler; Zimmermann; Förster; Engel; Oepen; Sheldrick *Angew. Chem. Int. Ed. Engl.* **1981,** *20*, 1053 [*Angew. Chem. 93*, 1085].

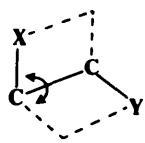
Conformation in Open-Chain Systems[193]

For any open-chain single bond that connects two sp^3 carbon atoms, an infinite number of conformations are possible, each of which has a certain energy associated with it. For ethane there are two extremes, a conformation of highest and one of lowest potential energy, depicted in two ways as:



In *Newman projection formulas* (the two figures on the right) the observer looks at the C—C bond head on. The three lines emanating from the center of the circle represent the bonds coming from the front carbon, with respect to the observer.

The staggered conformation is the conformation of lowest potential energy for ethane. As the bond rotates, the energy gradually increases until the eclipsed conformation is reached, when the energy is at a maximum. Further rotation decreases the energy again. Figure 4.3 illustrates this. The *angle of torsion*, which is a dihedral angle, is the angle between the XCC and the CCY planes, as shown:



For ethane the difference in energy is about 2.9 kcal/mol (12 kJ/mol).[194] This difference is called the *energy barrier*, since in free rotation about a single bond there must be enough rotational energy present to cross the barrier every time two hydrogen atoms are opposite each other. There has been much speculation about the cause of the barriers and many explanations have been suggested.[195] It has been concluded from molecular-orbital calculations that the barrier is caused by repulsion between overlapping filled molecular orbitals.[196] That is, the ethane molecule has its lowest energy in the staggered conformation because in this conformation the orbitals of the C—H bonds have the least amount of overlap with the C—H orbitals of the adjacent carbon.

At ordinary temperatures enough rotational energy is present for the ethane molecule rapidly to rotate, though it still spends most of its time at or near the energy minimum. Groups larger than hydrogen cause larger barriers. When the barriers are large enough, as

[193]For a review, see Berg; Sandström *Adv. Phys. Org. Chem.* **1989**, *25*, 1-97.

[194]Lide *J. Chem. Phys.* **1958**, *29*, 1426; Weiss; Leroi *J. Chem. Phys.* **1968**, *48*, 962; Hirota; Saito; Endo *J. Chem. Phys.* **1979**, *71*, 1183.

[195]For a review of methods of measuring barriers, of attempts to explain barriers, and of values of barriers, see Lowe *Prog. Phys. Org. Chem.* **1968**, *6*, 1-80. For other reviews of this subject, see Oosterhoff *Pure Appl. Chem.* **1971**, *25*, 563-571; Wyn-Jones; Pethrick *Top. Stereochem.* **1970**, *5*, 205-274; Pethrick; Wyn-Jones *Q. Rev., Chem. Soc.* **1969**, *23*, 301-324; Brier *J. Mol. Struct.* **1970**, *6*, 23-36; Lowe *Science* **1973**, *179*, 527-533.

[196]See Pitzer *Acc. Chem. Res.* **1983**, *16*, 207-210. See, however, Bader, Cheeseman; Laidig; Wiberg; Breneman *J. Am. Chem. Soc.* **1990**, *112*, 6350.

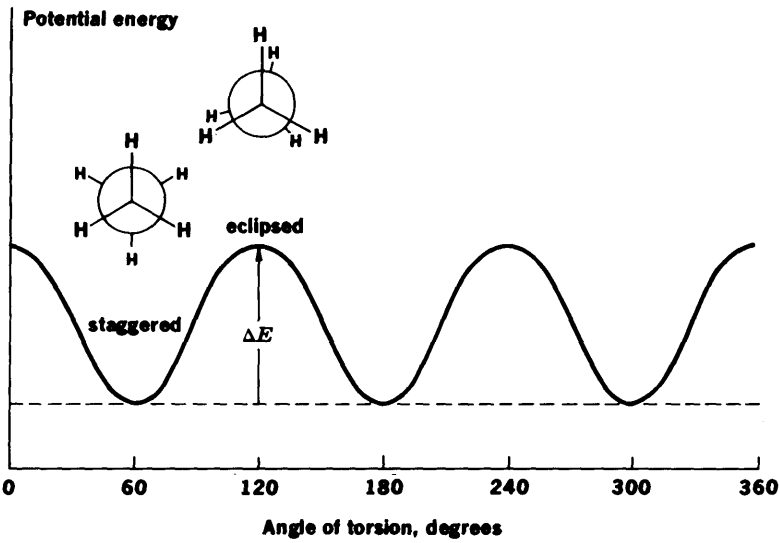
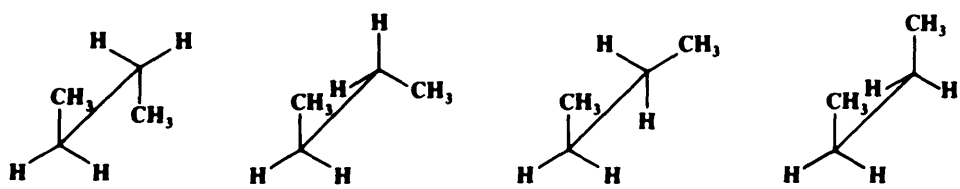


FIGURE 4.3 Conformational energy diagram for ethane.

in the case of suitably substituted biphenyls (p. 101) or the diadamantyl compound mentioned on p. 142, rotation at room temperature is completely prevented and we speak of configurations, not conformations. Even for compounds with small barriers, cooling to low temperatures may remove enough rotational energy for what would otherwise be conformational isomers to become configurational isomers.

A slightly more complicated case than ethane is that of a 1,2-disubstituted ethane (YCH_2—CH_2Y or YCH_2—CH_2X),[197] such as *n*-butane, for which there are four extremes: a fully staggered conformation, called *anti*, *trans*, or *antiperiplanar*; another staggered con-



anti, trans, or antiperiplanar | anticlinal | gauche or synclinal L | synperiplanar

formation, called *gauche* or *synclinal*; and two types of eclipsed conformations, called *synperiplanar* and *anticlinal*. An energy diagram for this system is given in Figure 4.4. Although there is constant rotation about the central bond, it is possible to estimate what percentage of the molecules are in each conformation at a given time. For example, it was concluded from a consideration of dipole moment and polarizability measurements that for 1,2-dichloroethane in CCl_4 solution at 25°C about 70% of the molecules are in the anti and

[197]For discussions of the conformational analysis of such systems, see Kingsbury *J. Chem. Educ.* **1979**, *56*, 431-437; Wiberg; Murcko *J. Am. Chem. Soc.* **1988**, *110*, 8029; Allinger; Grev; Yates; Schaefer **1990**, *112*, 114.

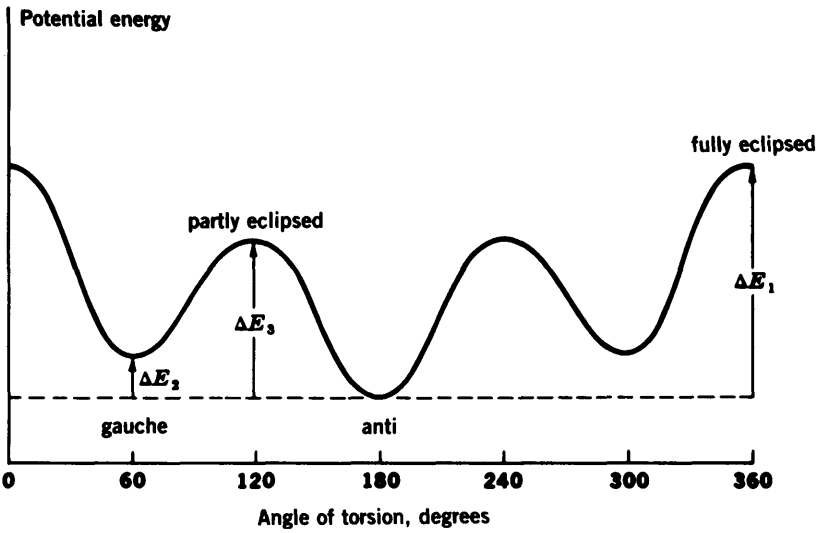


FIGURE 4.4 Conformational energy for $YCH_2—CH_2Y$ or $YCH_2—CH_2X$. For *n*-butane, ΔE_1 = 4 to 6, ΔE_2 = 0.9, and ΔE_3 = 3.4 kcal/mol (17–25, 3.8, 14 kJ/mol, respectively).

about 30% in the gauche conformation.[198] The corresponding figures for 1,2-dibromoethane are 89% anti and 11% gauche.[199] The eclipsed conformations are unpopulated and serve only as pathways from one staggered conformation to another. Solids normally consist of a single conformer.

It may be observed that the gauche conformation of butane (**L**) or any other similar molecule is chiral. The lack of optical activity in such compounds arises from the fact that **L** and its mirror image are always present in equal amounts and interconvert too rapidly for separation.

For butane and for most other molecules of the forms $YCH_2—CH_2Y$ and $YCH_2—CH_2X$, the anti conformer is the most stable, but exceptions are known. One group of exceptions consists of molecules containing small electronegative atoms, especially fluorine and oxygen. Thus 2-fluoroethanol,[200] 1,2-difluoroethane,[201] and 2-fluoroethyl trichloroacetate ($FCH_2CH_2OCOCCl_3$)[202] exist predominantly in the gauche form and compounds such as 2-chloroethanol and 2-bromoethanol[200] also prefer the gauche form. There is as yet no generally accepted explanation for this behavior.[203] It was believed that the favorable gauche conformation of 2-fluoroethanol was the result of intramolecular hydrogen bonding,

[198]Aroney; Izsak; Le Fèvre *J. Chem. Soc.* **1962,** 1407; Le Fèvre; Orr *Aust. J. Chem.* **1964,** *17*, 1098.

[199]The anti form of butane itself is also more stable than the gauche form: Schrumpf *Angew. Chem. Int. Ed. Engl.* **1982,** *21*, 146 [*Angew. Chem. 94*, 152].

[200]Wyn-Jones; Orville-Thomas *J. Mol. Struct.* **1967,** *1*, 79; Buckley; Giguère; Yamamoto *Can. J. Chem.* **1968,** *46*, 2917; Davenport; Schwartz *J. Mol. Struct.* **1978,** *50*, 259; Huang; Hedberg *J. Am. Chem. Soc.* **1989,** *111*, 6909.

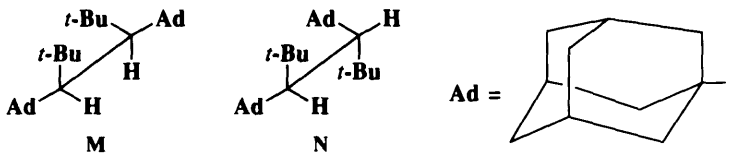
[201]Klaboe; Nielsen *J. Chem. Phys.* **1960,** *33*, 1764; Abraham; Kemp *J. Chem. Soc. B* **1971,** 1240; Bulthuis; van den Berg; Maclean *J. Mol. Struct.* **1973,** *16*, 11; van Schaick; Geise; Mijlhoff; Renes *J. Mol. Struct.* **1973,** *16*, 23; Friesen; Hedberg *J. Am. Chem. Soc.* **1980,** *102*, 3987; Fernholt; Kveseth *Acta Chem. Scand., Ser. A* **1980,** *34*, 163.

[202]Abraham; Monasterios *Org. Magn. Reson.* **1973,** *5*, 305.

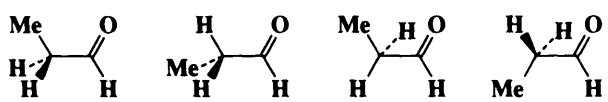
[203]It has been proposed that the preference for the gauche conformation in these molecules is an example of a more general phoenomenon, known as the *gauche effect*, i.e., a tendency to adopt that structure that has the maximum number of gauche interactions between adjacent electron pairs or polar bonds. This effect is ascribed to nuclear electron attactive forces between the groups or unshared pairs: Wolfe; Rauk; Tel; Csizmadia *J. Chem. Soc. B* **1971,** 136; Wolfe *Acc. Chem. Res.* **1972,** *5*, 102-111. See also Phillips; Wray *J. Chem. Soc., Chem. Commun.* **1973,** 90; Radom; Hehre; Pople *J. Am. Chem. Soc.* **1972,** *94*, 2371; Zefirov *J. Org. Chem. USSR* **1974,** *10*, 1147; Juaristi *J. Chem. Educ.* **1979,** *56*, 438.

but this explanation does not do for molecules like 2-fluoroethyl trichloroacetate and has in fact been ruled out for 2-fluoroethanol as well.[204] Other exceptions are known, where small electronegative atoms are absent. For example 1,1,2,2-tetrachloroethane and 1,1,2,2-tetrabromoethane both prefer the gauche conformation,[205] even though 1,1,2,2-tetrafluoroethane prefers the anti.[206] Also, both 2,3-dimethylpentane and 3,4-dimethylhexane prefer the gauche conformation,[207] and 2,3-dimethylbutane shows no preference for either.[208] Furthermore, the solvent can exert a powerful effect. For example, the compound 2,3-dinitro-2,3-dimethylbutane exists entirely in the gauche conformation in the solid state, but in benzene, the gauche–anti ratio is 79:21; while in CCl_4 the anti form is actually favored (gauche–anti ratio 42:58).[209]

In one case two conformational isomers of a single aliphatic hydrocarbon, 3,4-di(1-adamantyl)-2,2,5,5-tetramethylhexane, have proven stable enough for isolation at room temperature.[210] The two isomers **M** and **N** were separately crystallized, and the structures proved by x-ray crystallography. (The actual dihedral angles are distorted from the 60° angles shown in the drawings, owing to steric hindrance between the large groups.)



All the conformations so far discussed have involved rotation about sp^3–sp^3 bonds. Many studies have also been made of compounds with sp^3–sp^2 bonds.[211] For example, propanal (or any similar molecule) has four extreme conformations, two of which are called *eclipsing* and the other two *bisecting*. For propanal the eclipsing conformations have lower energy than the other two, with **P** favored over **Q** by about 1 kcal/mol (4 kJ/mol).[212] As has already been pointed out (p. 128), for a few of these compounds, rotation is slow enough to permit cis–trans isomerism, though for simple compounds rotation is rapid. For example, acetaldehyde has a lower rotational barrier (about 1 kcal/mol or 4 kJ/mol) than ethane.[213]



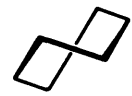
[204]Griffith; Roberts *Tetrahedron Lett.* **1974,** 3499.
[205]Kagarise *J. Chem. Phys.* **1956,** *24,* 300.
[206]Brown; Beagley *J. Mol. Struct.* **1977,** *38,* 167.
[207]Ritter; Hull; Cantow *Tetrahedron Lett.* **1978,** 3093.
[208]Lunazzi; Macciantelli; Bernardi; Ingold *J. Am. Chem. Soc.* **1977,** *99,* 4573.
[209]Tan; Chia; Huang; Kuok; Tang *J. Chem. Soc., Perkin Trans. 2* **1984,** 1407.
[210]Flamm-ter Meer; Beckhaus; Peters; von Schnering; Fritz; Rüchardt *Chem. Ber.* **1986,** *119,* 1492; Rüchardt; Beckhaus *Angew. Chem. Int. Ed. Engl.* **1985,** *24,* 529-538 [*Angew. Chem. 97,* 531-540].
[211]For reviews, see Sinegovskaya; Keiko; Trofimov *Sulfur Rep.* **1987,** *7,* 337-378 (for enol ethers and thioethers); Karabatsos; Fenoglio *Top. Stereochem.* **1970,** *5,* 167-203; Jones; Owen *J. Mol. Struct.* **1973,** *18,* 1-32 (for carboxylic esters). See also Schweizer; Dunitz *Helv. Chim. Acta* **1982,** *65,* 1547; Chakrabarti; Dunitz *Helv. Chim. Acta* **1982,** *65,* 1555; Cossé-Barbi; Massat; Dubois *Bull. Soc. Chim. Belg.* **1985,** *94,* 919; Dorigo; Pratt; Houk *J. Am. Chem. Soc.* **1987,** *109,* 6591.
[212]Butcher; Wilson *J. Chem. Phys.* **1964,** *40,* 1671; Allinger; Hickey *J. Mol. Struct.* **1973,** *17,* 233; Gupta *Can. J. Chem.* **1985,** *63,* 984.
[213]Davidson; Allen *J. Chem. Phys.* **1971,** *54,* 2828.

Conformation in Six-membered Rings[214]

For cyclohexane there are two extreme conformations in which all the angles are tetrahedral.[215] These are called the *boat* and the *chair* conformations and in each the ring is said to be *puckered*. The chair conformation is a rigid structure, but the boat form is flexible[216]

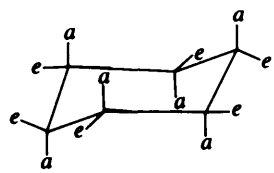
Boat

Chair



Twist

and can easily pass over to a somewhat more stable form known as the *twist* conformation. The twist form is about 1.5 kcal/mol (6.3 kJ/mol) more stable than the boat because it has less eclipsing interaction (see p. 156).[217] The chair form is more stable than the twist form by about 5 kcal/mol (21 kJ/mol).[218] In the vast majority of compounds containing a cyclohexane ring, the molecules exist almost entirely in the chair form. Yet it is known that the boat or twist form exists transiently. An inspection of the chair form shows that six of its bonds are directed differently from the other six:



On each carbon, one bond is directed up or down and the other more or less in the "plane" of the ring. The up or down bonds are called *axial* and the others *equatorial*. The axial bonds point alternately up and down. If a molecule were frozen into a chair form, there would be isomerism in monosubstituted cyclohexanes. For example, there would be an equatorial methylcyclohexane and an axial isomer. However, it has never been possible to isolate isomers of this type at room temperature.[219] This proves the transient existence of the boat or twist form, since in order for the two types of methylcyclohexane to be nonseparable, there must be rapid interconversion of one chair form to another (in which all axial bonds become equatorial and vice versa) and this is possible only through a boat or twist conformation. Conversion of one chair form to another requires an activation energy of about 10 kcal/mol (42 kJ/mol)[220] and is very rapid at room temperature.[221] However, by

[214]For reviews, see Jensen; Bushweller *Adv. Alicyclic Chem.* **1971,** *3*, 139-194; Robinson; Theobald *Q. Rev., Chem. Soc.* **1967,** *21*, 314-330; Eliel *Angew. Chem. Int. Ed. Engl.* **1965,** *4*, 761-774 [*Angew. Chem.* 77, 784-797].

[215]The C—C—C angles in cyclohexane are actually 111.5° [Davis; Hassel *Acta Chem. Scand.* **1963,** *17*,1181; Geise; Buys; Mijlhoff *J. Mol. Struct.* **1971,** *9*, 447; Bastiansen; Fernholt; Seip; Kambara; Kuchitsu *J. Mol. Struct.* **1973,** *18*, 163], but this is within the normal tetrahedral range (see p. 20).

[216]See Dunitz *J. Chem. Educ.* **1970,** *47*, 488.

[217]For a review of nonchair forms, see Kellie; Riddell *Top. Stereochem.* **1974,** *8*, 225-269.

[218]Margrave; Frisch; Bautista; Clarke; Johnson *J. Am. Chem. Soc.* **1963,** *85*, 546; Squillacote; Sheridan; Chapman; Anet *J. Am. Chem. Soc.* **1975,** *97*, 3244.

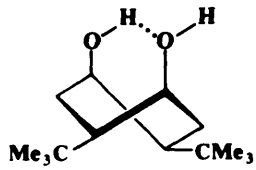
[219]Wehle; Fitjer *Tetrahedron Lett.* **1986,** *27*, 5843, have succeeded in producing two conformers that are indefinitely stable in solution at room temperature. However, the other five positions of the cyclohexane ring in this case are all spirosubstituted with cyclobutane rings, greatly increasing the barrier to chair–chair interconversion.

[220]Jensen; Noyce; Sederholm; Berlin *J. Am. Chem. Soc.* **1962,** *84*, 386; Anet; Ahmad; Hall *Proc. Chem. Soc.* **1964,** 145; Bovey; Hood; Anderson; Kornegay *J. Chem. Phys.* **1964,** *41*, 2041; Anet; Bourn *J. Am. Chem. Soc.* **1967,** *89*, 760. See also Strauss *J. Chem. Educ.* **1971,** *48*, 221.

[221]For reviews of chair–chair interconversions, see Ōki, Ref. 49, pp. 287-307; Anderson *Top. Curr. Chem.* **1974,** *45*, 139-167.

working at low temperatures, Jensen and Bushweller were able to obtain the pure equatorial conformers of chlorocyclohexane and trideuteriomethoxycyclohexane as solids and in solution.[222] Equatorial chlorocyclohexane has a half-life of 22 years in solution at −160°C.

In some molecules the twist conformation is actually preferred. An example is **76**, in which hydrogen bonding stabilizes the otherwise high-energy form.[223] Of course, in certain



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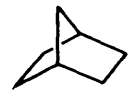
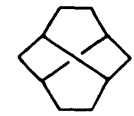


norbornane



twistane

bicyclic compounds, the six-membered ring is forced to maintain a boat or twist conformation, as in norbornane or twistane.

In monosubstituted cyclohexanes, the substituent normally prefers the equatorial position because in the axial position there is interaction between the substituent and the axial hydrogens in the 3 and 5 positions, but the extent of this preference depends greatly on the nature of the group. Alkyl groups have a greater preference than polar groups and for alkyl groups the preference increases with size. For polar groups, size seems to be unimportant. Both the large $HgBr$[224] and $HgCl$[225] groups and the small F group have been reported to have little or no conformational preference (the HgCl group actually shows a slight preference for the axial position). Table 4.3 gives approximate values of the free energy required for various groups to go from the equatorial position to the axial (these are called *A* values),[226] though it must be kept in mind that they vary somewhat with physical state, temperature, and solvent.[227]

In disubstituted compounds, the rule for alkyl groups is that the conformation is such that as many groups as possible adopt the equatorial position. How far it is possible depends on the configuration. In a *cis*-1,2-disubstituted cyclohexane, one substituent must be axial and the other equatorial. In a *trans*-1,2 compound both may be equatorial or both axial. This is also true for 1,4-disubstituted cyclohexanes, but the reverse holds for 1,3 compounds: the trans isomer must have the *ae* conformation and the cis isomer may be *aa* or *ee*. For alkyl groups, the *ee* conformation predominates over the *aa* but for other groups this is not necessarily so. For example, both *trans*-1,4-dibromocyclohexane and the corresponding dichloro compound have the *ee* and *aa* conformations about equally populated[228] and most *trans*-1,2-dihalocyclohexanes exist predominantly in the *aa* conformation.[229] Note that in the

[222]Jensen; Bushweller *J. Am. Chem. Soc.* **1966,** *88*, 4279; **1969,** *91*, 3223.

[223]Stolow *J. Am. Chem. Soc.* **1961,** *83*, 2592, **1964,** *86*, 2170; Stolow; McDonagh; Bonaventura *J. Am. Chem. Soc.* **1964,** *86*, 2165. For some other examples, see Camps; Iglesias *Tetrahedron Lett.* **1985,** *26*, 5463; Fitjer; Scheuermann; Klages; Wehle; Stephenson; Binsch *Chem. Ber.* **1986,** *119*, 1144.

[224]Jensen; Gale *J. Am. Chem. Soc.* **1959,** *81*, 6337.

[225]Anet; Krane; Kitching; Dodderel; Praeger *Tetrahedron Lett.* **1974,** 3255.

[226]Except where otherwise indicated, these values are from Jensen; Bushweller, Ref. 214. See also Ref. 238.

[227]See, for example, Ford; Allinger *J. Org. Chem.* **1970,** *35*, 3178. For a critical review of the methods used to obtain these values, see Jensen; Bushweller, Ref. 214.

[228]Atkinson; Hassel *Acta Chem. Scand.* **1959,** *13*, 1737; Abraham; Rossetti *Tetrahedron Lett.* **1972,** 4965, *J. Chem. Soc., Perkin Trans. 2* **1973,** 582. See also Hammarström; Berg; Liljefors *Tetrahedron Lett.* **1987,** *28*, 4883.

[229]Hageman; Havinga *Recl. Trav. Chim. Pays-Bas* **1969,** *88*, 97; Klaeboe *Acta Chem. Scand.* **1971,** *25*, 695; Abraham; Xodo; Cook; Cruz *J. Chem. Soc., Perkin Trans. 2* **1982,** 1503; Samoshin; Svyatkin; Zefirov *J. Org. Chem. USSR* **1988,** *24*, 1080, and references cited in these papers. *trans*-1,2-Difluorocyclohexane exists predominantly in the *ee* conformation: see Zefirov; Samoshin; Subbotin; Sergeev *J. Org. Chem. USSR* **1981,** *17*, 1301.

TABLE 4.3 Free-energy differences between equatorial and axial substituents on a cyclohexane ring (*A* values)[226]

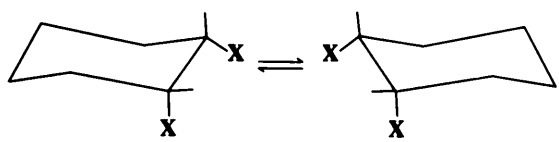
Group	Approximate $-\Delta G°$, kcal/mole	kJ/mole	Group	Approximate $-\Delta G°$, kcal/mole	kJ/mole
HgCl[225]	−0.25	−1.0	NO_2	1.1	4.6
HgBr	0	0	COOEt	1.1–1.2	4.6–5.0
D[237]	0.008	0.03	COOMe	1.27–1.31	5.3–5.5
CN	0.15–0.25	0.6–1.0	COOH	1.36–1.46	5.7–6.1
F	0.25	1.0	NH_2[230]	1.4	5.9
C≡CH	0.41	1.7	$CH{=}CH_2$[231]	1.7	7.1
I	0.46	1.9	CH_3[232]	1.74	7.28
Br	0.48–0.62	2.0–2.6	C_2H_5	~1.75	~7.3
OTs	0.515	2.15	iso-Pr	~2.15	~9.0
Cl	0.52	2.2	C_6H_{11}[233]	2.15	9.0
OAc	0.71	3.0	$SiMe_3$[234]	2.4–2.6	10–11
OMe[238]	0.75	3.1	C_6H_5[235]	2.7	11
OH	0.92–0.97	3.8–4.1	*t*-Bu[236]	4.9	21

latter case the two halogen atoms are anti in the *aa* conformation but gauche in the *ee* conformation.[239]

Since compounds with alkyl equatorial substituents are generally more stable, *trans*-1,2 compounds, which can adopt the *ee* conformation, are thermodynamically more stable than their *cis*-1,2 isomers, which must exist in the *ae* conformation. For the 1,2-dimethylcyclohexanes, the difference in stability is about 2 kcal/mol (8 kJ/mol). Similarly, *trans*-1,4 and *cis*-1,3 compounds are more stable than their steroisomers.

An interesting anomaly is *all-trans*-1,2,3,4,5,6-hexaisopropylcyclohexane, in which the six isopropyl groups prefer the axial position, although the six ethyl groups of the corresponding hexaethyl compound prefer the equatorial position.[240] The alkyl groups of these compounds can of course only be all axial or all equatorial, and it is likely that the molecule prefers the all-axial conformation because of unavoidable strain in the other conformation.

Incidentally, we can now see, in one case, why the correct number of stereoisomers could be predicted by assuming planar rings, even though they are not planar (p. 130). In the



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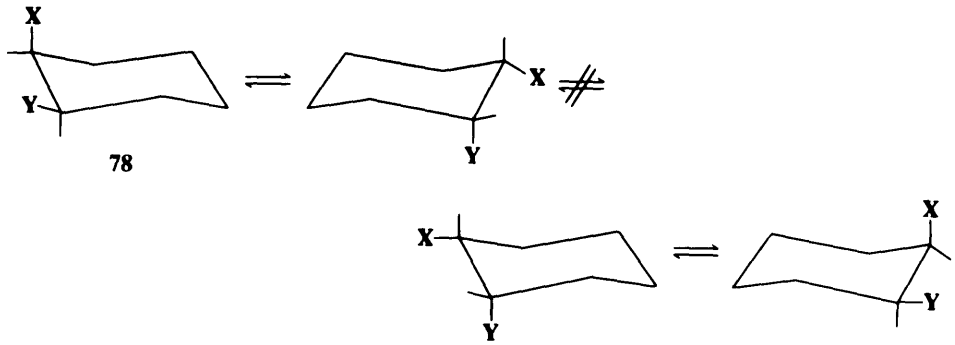
[230]Buchanan; Webb *Tetrahedron Lett.* **1983,** *24*, 4519.
[231]Eliel; Manoharan *J. Org. Chem.* **1981,** *46*, 1959.
[232]Booth; Everett *J. Chem. Soc., Chem. Commun.* **1976,** 278.
[233]Hirsch *Top. Stereochem.* **1967,** *1*, 199-222.
[234]Kitching; Olszowy; Drew; Adcock *J. Org. Chem.* **1982,** *47*, 5153.
[235]Squillacote; Neth *J. Am. Chem. Soc.* **1987,** *109*, 198.
[236]Manoharan; Eliel *Tetrahedron Lett.* **1984,** *25*, 3267.
[237]Anet; O'Leary *Tetrahedron Lett.* **1989,** *30*, 1059.
[238]Schneider; Hoppen *Tetrahedron Lett.* **1974,** 579.
[239]For a case of a preferential diaxial conformation in 1,3 isomers, see Ochiai; Iwaki; Ukita; Matsuura; Shiro; Nagao *J. Am. Chem. Soc.* **1988,** *110*, 4606.
[240]Golan; Goren; Biali *J. Am. Chem. Soc.* **1990,** *112*, 9300.

case of both a *cis*-1,2-XX-disubstituted and a *cis*-1,2-XY-disubstituted cyclohexane, the molecule is nonsuperimposable on its mirror image; neither has a plane of symmetry. However, in the former case (**77**) conversion of one chair form to the other (which of course happens rapidly) turns the molecule into its mirror image, while in the latter case (**78**) rapid interconversion does not give the mirror image but merely the conformer in which the original axial and equatorial substituents exchange places. Thus the optical inactivity of **77**



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is not due to a plane of symmetry but to a rapid interconversion of the molecule and its mirror image. A similar situation holds for *cis*-1,3 compounds. However, for *cis*-1,4 isomers (both XX and XY) optical inactivity arises from a plane of symmetry in both conformations. All *trans*-1,2- and *trans*-1,3-disubstituted cyclohexanes are chiral (whether XX or XY), while *trans*-1,4 compounds (both XX and XY) are achiral, since all conformations have a plane of symmetry.

The conformation of a group can be frozen into a desired position by putting into the ring a large alkyl group (most often *t*-butyl), which greatly favors the equatorial position.[241]

The principles involved in the conformational analysis of six-membered rings containing one or two trigonal atoms, e.g., cyclohexanone and cyclohexene, are similar.[242]

Conformation in Six-Membered Rings Containing Hetero Atoms

In six-membered rings containing hetero atoms,[243] the basic principles are the same; i.e., there are chair, twist, and boat forms, axial and equatorial groups, etc., but in certain compounds a number of new factors enter the picture. We deal with only two of these.[244]

1. In 5-alkyl-substituted 1,3-dioxanes, the 5-substituent has a much smaller preference for the equatorial position than in cyclohexane derivatives;[245] the *A* values are much lower.

[241]This idea was suggested by Winstein; Holness *J. Am. Chem. Soc.* **1955,** *77*, 5561. There are a few known compounds in which a *t*-butyl group is axial. See, for example, Vierhapper *Tetrahedron Lett.* **1981,** *22*, 5161.

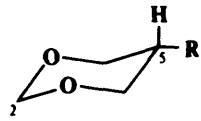
[242]For a monograph, see Rabideau *The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*; VCH: New York, 1989. For reviews, see Vereshchagin *Russ. Chem. Rev.* **1983,** *52*, 1081-1095; Johnson *Chem. Rev.* **1968,** *68*, 375-413. See also Lambert; Clikeman; Taba; Marko; Bosch; Xue *Acc. Chem. Res.* **1987,** *20*, 454-458; Ref. 185; Ref. 214.

[243]For monographs, see Glass *Conformational Analysis of Medium-Sized Heterocycles*; VCH: New York, 1988; Riddell *The Conformational Analysis of Heterocyclic Compounds*; Academic Press: New York, 1980. For reviews, see Juaristi *Acc. Chem. Res.* **1989,** *22*, 357-364; Crabb; Katritzky *Adv. Heterocycl. Chem.* **1984,** *36*, 1-173; Eliel *Angew. Chem. Int. Ed. Engl.* **1972,** *11*, 739-750 [*Angew. Chem. 84*, 779-791], *Pure Appl. Chem.* **1971,** *25*, 509-525, *Acc. Chem. Res.* **1970,** *3*, 1-8; Lambert *Acc. Chem. Res.* **1971,** *4*, 87-94; Romers; Altona; Buys; Havinga *Top. Stereochem.* **1969,** *4*, 39-97; Bushweller; Gianni, Ref. 185, pp. 232-274.

[244]These factors are discussed by Eliel, Ref. 243.

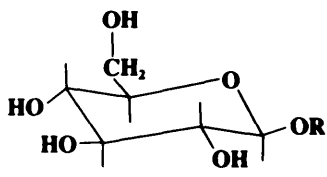
[245]Riddell; Robinson *Tetrahedron* **1967,** *23*, 3417; Eliel; Knoeber *J. Am. Chem. Soc.* **1968,** *90*, 3444. See also Abraham; Banks; Eliel; Hofer; Kaloustian *J. Am. Chem. Soc.* **1972,** *94*, 1913; Eliel; Alcudia *J. Am. Chem. Soc.* **1974,** *96*, 1939.

This indicates that the lone pairs on the oxygens have a smaller steric requirement than the C—H bonds in the corresponding cyclohexane derivatives. Similar behavior is found in the



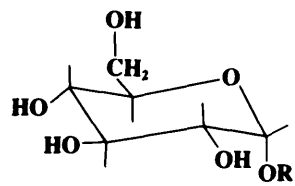
1,3-dithianes.[246] With certain nonalkyl substituents (e.g., F, NO_2, SOMe, NMe_3^+) the axial position is actually preferred.[247]

2. An alkyl group located on a carbon α to a hetero atom prefers the equatorial position, which is of course the normally expected behavior, but a *polar* group in such a location prefers the *axial* position. An example of this phenomenon, known as the *anomeric effect*,[248] is the greater stability of a α-glucosides over β-glucosides. A number of explanations have



A β-glucoside

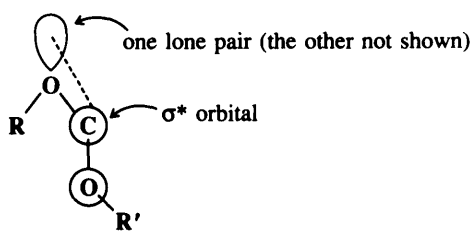
79



An α-glucoside

80

been offered for the anomeric effect. The one[249] that has received the most acceptance[250] is that one of the lone pairs of the polar atom connected to the carbon (an oxygen atom in the case of **80**) can be stabilized by overlapping with an antibonding orbital of the bond between the carbon and the other polar atom:



[246]Hutchins; Eliel *J. Am. Chem. Soc.* **1969,** *91*, 2703.

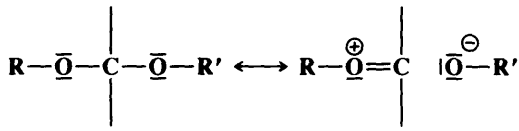
[247]Kaloustian; Dennis; Mager; Evans; Alcudia; Eliel *J. Am. Chem. Soc.* **1976,** *98*, 956. See also Eliel; Kandasamy; Sechrest *J. Org. Chem.* **1977,** *42*, 1533.

[248]For books on this subject, see Kirby *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer: New York, 1983; Szarek; Horton *Anomeric Effect*; American Chemical Society: Washington, 1979. For reviews see Deslongchamps *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Elmsford, NY, 1983, pp. 4-26; Zefirov *Tetrahedron* **1977,** *33*, 3193-3202; Zefirov; Shekhtman *Russ. Chem. Rev.* **1971,** *40*, 315-329; Lemieux *Pure Appl. Chem.* **1971,** *27*, 527-547; Angyal *Angew. Chem. Int. Ed. Engl.* **1969,** *8*, 157-166 [*Angew. Chem. 81*, 172-182]; Martin *Ann. Chim.* (*Paris*) [14] **1971,** *6*, 205-218.

[249]See Romers; Altona; Buys; Havinga *Top. Stereochem.* **1969,** *4*, 39-97, pp. 73-77; Wolfe; Whangbo; Mitchell *Carbohydr. Res.* **1979,** *69*, 1.

[250]For some evidence for this explanation, see Fuchs; Ellencweig; Tartakovsky; Aped *Angew. Chem. Int. Ed. Engl.* **1986,** *25*, 287 [*Angew. Chem. 98*, 289]; Praly; Lemieux *Can. J. Chem.* **1987,** *65*, 213; Booth; Khedhair; Readshaw *Tetrahedron* **1987,** *43*, 4699. For evidence against it, see Box *Heterocycles* **1990,** *31*, 1157-1181.

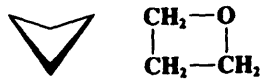
This can happen only if the two orbitals are in the positions shown. The situation can also be represented by this type of hyperconjugation (called "negative hyperconjugation"):



It is possible that simple repulsion between parallel dipoles in **79** also plays a part in the greater stablity of **80.**

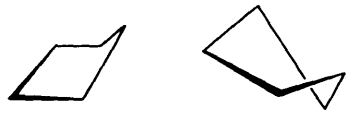
Conformation in Other Rings

Three-membered rings must be planar, but they seem to be the only saturated rings that generally are. Cyclobutane[251] is not planar but exists as in **81,** with an angle between the planes of about 35°.[252] The deviation from planarity is presumably caused by eclipsing in the planar form (see p. 156). Oxetane, in which eclipsing is less, is closer to planarity, with



81 Oxetane

an angle between the planes of about 10°.[253] Cyclopentane might be expected to be planar, since the angles of a regular pentagon are 108°, but it is not so, also because of eclipsing effects.[254] There are two puckered conformations, the *envelope* and the *half-chair*. There is little energy difference between these two forms and many five-membered ring systems have conformations somewhere in between them.[255] Although in the envelope conformation one



Envelope Half-chair

carbon is shown above the others, ring motions cause each of the carbons in rapid succession to assume this position. The puckering rotates around the ring in what may be called a *pseudorotation*.[256] In substituted cyclopentanes and five-membered rings in which at least

[251]For reviews of the stereochemistry of four-membered rings, see Legon *Chem. Rev.* **1980,** *80*, 231-262; Moriarty *Top. Stereochem.* **1974,** *8*, 271-421; Cotton; Frenz *Tetrahedron* **1974,** *30*, 1587-1594.

[252]Dows; Rich *J. Chem. Phys.* **1967,** *47*, 333; Stone; Mills *Mol. Phys.* **1970,** *18*, 631; Miller; Capwell *Spectrochim. Acta, Part A* **1971,** *27*, 947; Miller; Capwell; Lord; Rea *Spectrochim. Acta, Part A* **1972,** *28*, 603. However, some cyclobutane derivatives are planar, at least in the solid state: for example, see Margulis; Fischer *J. Am. Chem. Soc.* **1967,** *89*, 223; Margulis *Chem. Commun.* **1969,** 215; *J. Am. Chem. Soc.* **1971,** *93*, 2193.

[253]Luger; Buschmann *J. Am. Chem. Soc.* **1984,** *106*, 7118.

[254]For reviews of the conformational analysis of five-membered rings, see Fuchs *Top. Stereochem.* **1978,** *10*, 1-94; Legon, Ref. 251.

[255]Willy; Binsch; Eliel *J. Am. Chem. Soc.* **1970,** *92*, 5394; Lipnick *J. Mol. Struct.* **1974,** *21*, 423.

[256]Kilpatrick; Pitzer; Spitzer *J. Am. Chem. Soc.* **1947,** *69*, 2438; Pitzer; Donath *J. Am. Chem. Soc.* **1959,** *81*, 3213; Durig; Wertz *J. Chem. Phys.* **1968,** *49*, 2118; Lipnick *J. Mol. Struct.* **1974,** *21*, 411; Poupko; Luz; Zimmermann *J. Am. Chem. Soc.* **1982,** *104*, 5307.

one atom does not contain two substituents (such as tetrahydrofuran, cyclopentanone, etc.), one conformer may be more stable than the others. The barrier to planarity in cyclopentane has been reported to be 5.2 kcal/mol (22 kJ/mol).[257]

Rings larger than six-membered are always puckered[258] unless they contain a large number of sp^2 atoms (see the section on strain in medium rings, p. 155). It should be noted that axial and equatorial hydrogens are found only in the chair conformations of six-membered rings. In rings of other sizes the hydrogens protrude at angles that generally do not lend themselves to classification in this way,[259] though in some cases the terms "pseudo-axial" and "pseudo-equatorial" have been used to classify hydrogens in rings of other sizes.[260]

Molecular Mechanics

Molecular mechanics (also known as *force field calculations*)[261] is a method for the calculation of conformational geometries.[262] It is used to calculate bond angles and distances, as well as total potential energies, for each conformation of a molecule.[263] Molecular orbital calculations (p. 28) can also give such information, but molecular mechanics is generally easier, cheaper (requires less computer time), and/or more accurate. In mo calculations, positions of the nuclei of the atoms are assumed, and the wave equations take account only of the electrons. Molecular mechanics calculations ignore the electrons, and study only the positions of the nuclei. Another important difference is that in an mo calculation each molecule is treated individually, but in molecular mechanics, parameters are obtained for small, simple molecules and then used in the calculations for larger or more complicated ones.

Molecular mechanics calculations use an empirically devised set of equations for the potential energy of molecules. These include terms for vibrational bond stretching, bond angle bending, and other interactions between atoms in a molecule. All these are summed up:

$$V = \Sigma V_{stretch} + \Sigma V_{bend} + \Sigma V_{torsion} + \Sigma V_{VDW}$$

V_{VDW} sums up the interactions (van der Waals) between atoms of a molecule that are not bonded to each other. The set of functions, called the force field, contains adjustable pa-

[257]Carreira; Jiang; Person; Willis *J. Chem. Phys.* **1972,** *56*, 1440.

[258]For reviews of conformations in larger rings, see Arshinova *Russ. Chem. Rev.* **1988,** *57*, 1142-1161; Ounsworth; Weiler *J. Chem. Educ.* **1987,** *64*, 568-572; Ōki, Ref. 49, pp. 307-321; Casanova; Waegell *Bull. Soc. Chim. Fr.* **1975,** 911-921; Anet *Top. Curr. Chem.* **1974,** *45*, 169-220; Dunitz *Pure Appl. Chem.* **1971,** *25*, 495-508, *Perspect. Struct. Chem.* **1968,** *2*, 1-70; Tochtermann *Fortchr. Chem. Forsch.* **1970,** *15*, 378-444; Dale *Angew. Chem. Int. Ed. Engl.* **1966,** *5*, 1000-1021 [*Angew. Chem. 78*, 1070-1093]. For a monograph, see Glass *Conformational Analysis of Medium-Sized Heterocycles*; VCH: New York, 1988. Also see the monographs by Hanack and Eliel; Allinger; Angyal; Morrison, Ref. 185.

[259]For definitions of axial, equatorial, and related terms for rings of any size, see Anet *Tetrahedron Lett.* **1990,** *31*, 2125.

[260]For a discussion of the angles of the ring positions, see Cremer *Isr. J. Chem.* **1980,** *20*, 12.

[261]Sometimes called the *Westheimer method*, because of the pioneering work of F. H. Westheimer: Westheimer; Mayer *J. Chem. Phys.* **1946,** *14*, 733; Westheimer *J. Chem. Phys.* **1947,** *15*, 252; Rieger; Westheimer *J. Am. Chem. Soc.* **1950,** *72*, 19.

[262]For a monograph, see Burkert; Allinger *Molecular Mechanics*; American Chemical Society: Washington, 1982. For reviews, see Osawa; Musso *Angew. Chem. Int. Ed. Engl.* **1983,** *22*, 1-12 [*Angew. Chem. 95*, 1-12], *Top. Stereochem.* **1982,** *13*, 117-193; Boyd; Lipkowitz *J. Chem. Educ.* **1982,** *59*, 269-274; Cox *J. Chem. Educ.* **1982,** *59*, 275-278; Ermer *Struct. Bonding (Berlin)* **1976,** *27*, 161-211; Allinger *Adv. Phys. Org. Chem.* **1976,** *13*, 1-82; Altona; Faber *Top. Curr. Chem.* **1974,** *45*, 1-38. For worked out calculations, using the MMP2 program, see Clark *A Handbook of Computational Chemistry*; Wiley: New York, 1985. See also the series *Advances in Molecular Modeling*.

[263]For an alternative approach, that gives geometries based on electrostatic forces, see Kirpichenok; Zefirov *J. Org. Chem. USSR* **1987,** *23* 607, 623; Zefirov; Samoshin; Svyatkin; Mursakulov *J. Org. Chem. USSR* **1987,** *23*, 634.

rameters that are optimized to get the best fit of known properties of the molecules. The assumption is made that corresponding parameters and force constants can be transferred from one molecule to another. Molecular mechanics is therefore based on experimental data.

In a typical molecular mechanics calculation for a molecule[264] a trial geometrical structure is assumed (bond distances, angles, torsion angles, etc.). Hydrogen atoms are generally not explicitly considered (their positions are calculated later, from standard geometric parameters). The computer searches the trial structure and constructs a list of interaction terms: bond distances, atoms attached to a common atom (bond angles), atoms attached to adjacent atoms (torsion angles), and nonbonded interactions, and then chooses the force field parameters for these interactions from a list stored in the program. It then calculates the potential energy of the trial structure, using the V equation given above. The computer next goes through an energy minimization process by plotting small changes in geometrical coordinates against energy, looking for places in the curve where the first derivatives of V are equal to zero, which means that the total energy V is at a minimum. This must be done separately for each stable conformation, since there is no known method for finding the lowest V for a molecule (e.g., the anti conformation of *n*-butane). If appropriate trial structures are entered, the computer will find the lowest V for the anti and gauche conformations, separately. This can be a handicap for large molecules (e.g., 2,3-dimethylundecane) which may have many stable conformations (that is, energy minima). The computer will find only those minima recognized by the investigator.[265] Molecular mechanics can also be used to study energy maxima (barriers), but in much less detail.[266] A number of force field computer programs are available, among them the Allinger MM2, MMP2, and MM3[267] force fields, and the Bartell MUB-2 force field.[268]

A molecular mechanics calculation gives the total potential energy of each conformation. If the mole fractions of all the conformations are known, or can be calculated, the enthalpy of formation of the compound can be obtained.[269]

Even though molecular mechanics has given satisfactory results (that is, results that agree with experimental measurements) for many molecules, it is still not totally reliable, since it does fail in certain cases. A further limitation is that it can be used only in cases for which transferable parameters can be obtained from simple molecules. Molecular orbital calculations do not have this limitation.

STRAIN

Steric strain[270] exists in a molecule when bonds are forced to make abnormal angles. This results in a higher energy than would be the case in the absence of angle distortions. There

[264]This description is from Burkert; Allinger, Ref. 262, pp. 63-65.

[265]For methods of dealing with this difficulty, see Li; Scheraga *Proc. Natl. Acad. Sci. USA* **1987,** *84*, 6611; Saunders *J. Am. Chem. Soc.* **1987,** *109*, 3150; Wilson; Cui; Moskowitz; Schmidt *Tetrahedron Lett.* **1988,** *29*, 4373; Billeter; Howard; Kuntz; Kollman *J. Am. Chem. Soc.* **1988,** *110*, 8385.

[266]See Burkert; Allinger, Ref. 262, pp. 72-76.

[267]See Allinger; Yuh; Lii *J. Am. Chem. Soc.* **1989,** *111*, 8551; Allinger; Chen; Rahman; Pathiaseril *J. Am. Chem. Soc.* **1991,** *113*, 4505.

[268]For a list of programs and sources, see Burkert; Allinger, Ref. 262, pp. 317-319. See also Clark, Ref. 262, p. 10. Improved MM2 parameters for aldehydes and ketones are reported by Bowen; Pathiaseril; Profeta; Allinger *J. Org. Chem.* **1987,** *52*, 5162. For extensions of MM2 to other systems, see Bowen; Reddy; Patterson; Allinger *J. Org. Chem.* **1988,** *53*, 5471; Frierson; Imam; Zalkow; Allinger *J. Org. Chem.* **1988,** *53*, 5248; Tai; Allinger *J. Am. Chem. Soc.* **1988,** *110*, 2050; Podlogar; Raber *J. Org. Chem.* **1989,** *54*, 5032.

[269]See Clark, Ref. 262, pp. 173-184. See also DeTar *J. Org. Chem.* **1987,** *52*, 1851.

[270]For a monograph, see Greenberg; Liebman *Strained Organic Molecules*; Academic Press: New York, 1978. For reviews, see Wiberg *Angew. Chem. Int. Ed. Engl.* **1986,** *25*, 312-322 [*Angew. Chem. 98*, 312-322]; Greenberg; Stevenson *Mol. Struct. Energ.* **1986,** *3*, 193-266; Liebman; Greenberg *Chem. Rev.* **1976,** *76*, 311-365. For a review of the concept of strain, see Cremer; Kraka *Mol. Struct. Energ.* **1988,** *7*, 65-138.

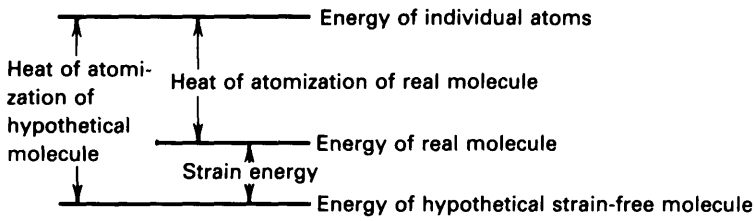


FIGURE 4.5 Strain energy calculation.

are, in general, two kinds of structural features that result in sterically caused abnormal bond angles. One of these is found in small-ring compounds, where the angles must be less than those resulting from normal orbital overlap. Such strain is called *small-angle strain*. The other arises when nonbonded atoms are forced into close proximity by the geometry of the molecule. These are called *nonbonded interactions*.

Strained molecules possess *strain energy*. That is, their potential energies are higher than they would be if strain were absent.[271] The strain energy for a particular molecule can be estimated from heat of atomization or heat of combustion data. A strained molecule has a lower heat of atomization than it would have if it were strain-free (Figure 4.5). As in the similar case of resonance energies (p. 29), strain energies can not be known exactly, because the energy of a real molecule can be measured, but not the energy of a hypothetical unstrained model. It is also possible to calculate strain energies by molecular mechanics, not only for real molecules, but also for those that cannot be made.[272]

Strain in Small Rings

Three-membered rings have a great deal of angle strain, since 60° angles represent a large departure from the tetrahedral angles. In sharp contrast to other ethers, ethylene oxide is quite reactive, the ring being opened by many reagents (see p. 353). Ring opening, of course, relieves the strain.[273] Cyclopropane,[274] which is even more strained[275] than ethylene oxide, is also cleaved more easily than would be expected for an alkane.[276] Thus, pyrolysis at 450 to 500°C converts it to propene, bromination gives 1,3-dibromopropane,[277] and it can be hydrogenated to propane (though at high pressure).[278] Other three-membered rings are similarly reactive.[279]

There is much evidence, chiefly derived from nmr coupling constants, that the bonding in cyclopropanes is not the same as in compounds that lack small-angle strain.[280] For a

[271]For discussions, see Wiberg; Bader; Lau *J. Am. Chem. Soc.* **1987,** *109*, 985, 1001.

[272]For a review, see Rüchardt; Beckhaus, Ref. 210. See also Burkert; Allinger, Ref. 262, pp. 169-194; Allinger, Ref. 262, pp. 45-47.

[273]For reviews of reactions of cyclopropanes and cyclobutanes, see Trost *Top. Curr. Chem.* **1986,** *133*, 3-82; Wong; Lau; Tam *Top. Curr. Chem.* **1986,** *133*, 83-157.

[274]For a treatise, see Rappoport *The Chemistry of the Cyclopropyl Group*, 2 pts.; Wiley: New York, 1987.

[275]For reviews of strain in cyclopropanes, see, in Ref. 274, the papers by Wiberg, pt. 1., pp. 1-26; Liebman; Greenberg, pt. 2, pp. 1083-1119; Liebman; Greenberg *Chem. Rev.* **1989,** *89*, 1225-1246.

[276]For reviews of ring-opening reactions of cyclopropanes, see Wong; Hon; Tse; Yip; Tanko; Hudlicky *Chem. Rev.* **1989,** *89*, 165-198; Reissig, in Ref. 274, pt. 1, pp. 375-443.

[277]Ogg; Priest *J. Am. Chem. Soc.* **1938,** *60*, 217.

[278]Shortridge; Craig; Greenlee; Derfer; Boord *J. Am. Chem. Soc.* **1948,** *70*, 946.

[279]For a review of the pyrolysis of three- and four-membered rings, see Frey *Adv. Phys. Org. Chem.* **1966,** *4*, 147-193.

[280]For discussions of bonding in cyclopropanes, see Bernett *J. Chem. Educ.* **1967,** *44*, 17-24; de Meijere *Angew. Chem. Int. Ed. Engl.* **1979,** *18*, 809-826 [*Angew. Chem. 91*, 867-884]; Honegger; Heilbronner; Schmelzer *Nouv. J. Chem.* **1982,** *6*, 519; Cremer; Kraka *J. Am. Chem. Soc.* **1985,** *107*, 3800, 3811; Slee *Mol. Struct. Energ.* **1988,** *5*, 63-114; Ref. 284.

normal carbon atom, one *s* and three *p* orbitals are hybridized to give four approximately equivalent sp^3 orbitals, each containing about 25% *s* character. But for a cyclopropane carbon atom, the four hybrid orbitals are far from equivalent. The two orbitals directed to the outside bonds have more *s* character than a normal sp^3 orbital, while the two orbitals involved in ring bonding have less, because the more *p*-like they are the more they resemble ordinary *p* orbitals, whose preferred bond angle is 90° rather than 109.5°. Since the small-angle strain in cyclopropanes is the difference between the preferred angle and the real angle of 60°, this additional *p* character relieves some of the strain. The external orbitals have about 33% *s* character, so that they are approximately sp^2 orbitals, while the internal orbitals have about 17% *s* character, so that they may be called approximately sp^5 orbitals.[281] Each of the three carbon–carbon bonds of cyclopropane is therefore formed by overlap of two sp^5 orbitals. Molecular-orbital calculations show that such bonds are not completely σ in character. In normal C—C bonds, sp^3 orbitals overlap in such a way that the straight line connecting the nuclei becomes an axis about which the electron density is symmetrical. But in cyclopropane, the electron density is directed *away from* the ring. Figure 4.6 shows the direction of orbital overlap.[282] For cylopropane, the angle (marked θ) is 21°. Cyclobutane exhibits the same phenomenon but to a lesser extent, θ being 7°.[282] Molecular orbital calculations also show that the maximum electron densities of the C—C σ orbitals are bent away from the ring, with θ = 9.4° for cyclopropane and 3.4° for cyclobutane.[283] The bonds in cyclopropane are called *bent bonds*, and are intermediate in character between σ and π, so that cyclopropanes behave in some respects like double-bond compounds.[284] For one thing, there is much evidence, chiefly from uv spectra,[285] that a cyclopropane ring is conjugated with an adjacent double bond and that this conjugation is greatest for the conformation shown in *a* in Figure 4.7 and least or absent for the conformation shown in *b*, since overlap of the double-bond π orbital with two of the *p*-like orbitals of the cyclopropane ring is greatest in conformation *a*. However, the conjugation between a cyclopropane ring and a double bond is less than that between two double bonds.[286] For other examples of the similarities in behavior of a cyclopropane ring and a double bond, see p. 755.

Four-membered rings also exhibit angle strain, but much less, and are less easily opened.

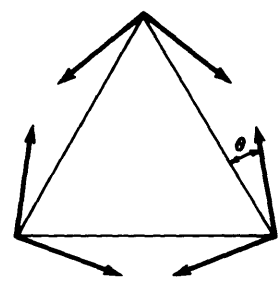


FIGURE 4.6 Orbital overlap in cyclopropane. The arrows point toward the center of electron density.

[281]Randić; Maksić *Theor. Chim. Acta* **1965,** *3*, 59; Foote *Tetrahedron Lett.* **1963,** 579; Weigert; Roberts *J. Am. Chem. Soc.* **1967,** *89*, 5962.

[282]Coulson; Moffitt *Philos. Mag.* **1949,** *40*, 1; Coulson; Goodwin *J. Chem. Soc.* **1962,** 2851, **1963,** 3161; Peters *Tetrahedron* **1963,** *19*, 1539; Hoffmann; Davidson *J. Am. Chem. Soc.* **1971,** *93*, 5699.

[283]Wiberg; Bader; Lau, Ref. 271; Cremer; Kraka, Ref. 280.

[284]For reviews, see Tidwell, in Ref. 274, pt. 1, pp. 565-632; Charton, in Zabicky *The Chemistry of Alkenes*, vol. 2, pp. 511-610, Wiley: New York, 1970.

[285]See, for example, Cromwell; Hudson *J. Am. Chem. Soc.* **1953,** *75*, 872; Kosower; Ito *Proc. Chem. Soc.* **1962,** 25; Dauben; Berezin *J. Am. Chem. Soc.* **1967,** *89*, 3449; Jorgenson; Leung *J. Am. Chem. Soc.* **1968,** *90*, 3769; Heathcock; Poulter *J. Am. Chem. Soc.* **1968,** *90*, 3766; Tsuji; Shibata; Hienuki; Nishida *J. Am. Chem. Soc.* **1978,** *100*, 1806; Drumright; Mas; Merola; Tanko *J. Org. Chem.* **1990,** *55*, 4098.

[286]Staley *J. Am. Chem. Soc.* **1967,** *89*, 1532; Pews; Ojha *J. Am. Chem. Soc.* **1969,** *91*, 5769. See, however, Noe; Young *J. Am. Chem. Soc.* **1982,** *104*, 6218.

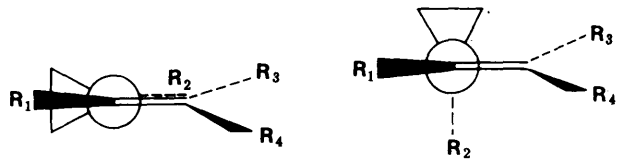
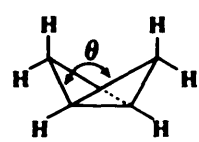


FIGURE 4.7 Conformations of α-cyclopropylalkenes. Conformation *a* leads to maximum conjugation and conformation *b* to minimum conjugation.

Cyclobutane is more resistant than cyclopropane to bromination, and though it can be hydrogenated to butane, more strenuous conditions are required. Nevertheless, pyrolysis at 420°C gives two molecules of ethylene. As mentioned earlier (p. 148), cyclobutane is not planar.

Many highly strained compounds containing small rings in fused systems have been prepared,[287] showing that organic molecules can exhibit much more strain than simple cyclopropanes or cyclobutanes.[288] Table 4.4 shows a few of these compounds.[289] Perhaps the most interesting are cubane, prismane, and the substituted tetrahedrane, since preparation of these ring systems had been the object of much endeavor. Prismane has the structure that Ladenburg proposed as a possible structure for benzene. The bicyclobutane molecule is bent, with the angle θ between the planes equal to 126 ± 3°.[290] The rehybridization effect,



described above for cyclopropane, is even more extreme in this molecule. Calculations have shown that the central bond is essentially formed by overlap of two *p* orbitals with little or no *s* character.[291] *Propellanes* are compounds in which two carbons, directly connected, are also connected by three other bridges. The one in the table is the smallest possible propellane,[292] and is in fact more stable than the larger [2.1.1]propellane and [2.2.1]propellane, which have been isolated only in solid matrixes at low temperature.[293]

In certain small-ring systems, including small propellanes, the geometry of one or more carbon atoms is so constrained that all four of their valences are directed to the same side of a plane ("inverted tetrahedron"), as in **81**.[294] An example is 1,3-dehydroadamantane, **82**

[287]For reviews discussing the properties of some of these as well as related compounds, see the reviews in *Chem. Rev.* **1989,** *89*, 975-1270, and the following: Jefford *J. Chem. Educ.* **1976,** *53*, 477-482; Seebach *Angew. Chem. Int. Ed. Engl.* **1965,** *4*, 121-131 [*Angew. Chem. 77*, 119-129]; Greenberg; Liebman, Ref. 270, pp. 210-220. For a review of bicyclo[*n.m.*0]alkanes, see Wiberg *Adv. Alicyclic Chem.* **1968,** *2*, 185-254.

[288]For a useful classification of strained polycyclic systems, see Gund; Gund *J. Am. Chem. Soc.* **1981,** *103*, 4458.

[289]For a computer program that generates IUPAC names for complex bridged systems, see Rücker; Rücker *Chimia* **1990,** *44*, 116.

[290]Haller; Srinivasan *J. Chem. Phys.* **1964,** *41*, 2745.

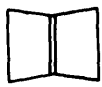
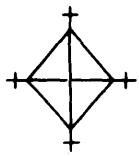
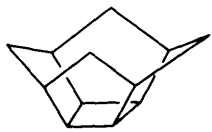
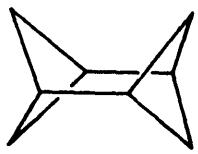
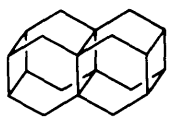
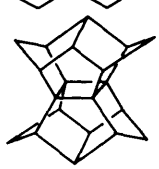
[291]Schulman; Fisanick *J. Am. Chem. Soc.* **1970,** *92*, 6653; Newton; Schulman *J. Am. Chem. Soc.* **1972,** *94*, 767.

[292]Wiberg; Walker *J. Am. Chem. Soc.* **1982,** *104*, 5239; Wiberg; Waddell *J. Am. Chem. Soc.* **1990,** *112*, 2194; Seiler *Helv. Chim. Acta* **1990,** *73*, 1574; Bothe; Schlüter *Chem. Ber.* **1991,** *124*, 587. For reviews of small-ring propellanes, see Wiberg *Chem. Rev.* **1989,** *89*, 975-983; Ginsburg, in Ref. 274, pt. 2, pp. 1193-1221. For a discussion of the formation of propellanes, see Ginsburg *Top. Curr. Chem.* **1987,** *137*, 1-17.

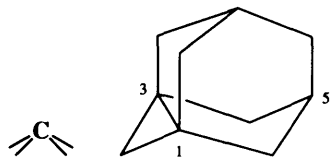
[293]Walker; Wiberg; Michl *J. Am. Chem. Soc.* **1982,** *104*, 2056; Wiberg; Walker; Pratt; Michl *J. Am. Chem. Soc.* **1983,** *105*, 3638.

[294]For a review, see Wiberg *Acc. Chem. Res.* **1984,** *17*, 379-386.

TABLE 4.4 Some strained small-ring systems

Structural formula of compound prepared	Systematic name of ring system	Common name if any	Ref.
	Bicyclo[1.1.0]butane	Bicyclobutane	303
	$\Delta^{1,4}$-Bicyclo[2.2.0]hexene		304
	Tricyclo[1.1.0.$0^{2,4}$]butane	Tetrahedrane	305
	Pentacyclo[5.1.0.$0^{2,4}$.$0^{3,5}$.$0^{6,8}$]octane	Octabisvalene	306
	Tricyclo[1.1.1.$0^{1,3}$]pentane	A [1.1.1]propellane	292
	Tetracyclo[2.2.0.$0^{2,6}$.$0^{3,5}$]hexane	Prismane	295
	Pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane	Cubane	296
	Pentacyclo[5.4.1.$0^{3,1}$.$0^{5,9}$.$0^{8,11}$]dodecane	4[Peristylane]	297
	Hexacyclo[5.3.0.$0^{2,6}$.$0^{3,10}$.$0^{4,9}$.$0^{5,8}$]decane	Pentaprismane	298
	Tricyclo[3.1.1.$1^{2,4}$]octane	Diasterane	299
	Hexacyclo[4.4.0.$0^{2,4}$.$0^{3,9}$.$0^{5,8}$.$0^{7,10}$]decane		300
	Nonacyclo[10.8.0.$0^{2,11}$.$0^{4,9}$.$0^{4,19}$.$0^{6,17}$.$0^{7,16}$-.$0^{9,14}$.$0^{14,19}$]eicosane	A double tetraasterane	301
	Undecacyclo[9.9.0.$0^{1,5}$.$0^{2,12}$.$0^{2,18}$.$0^{3,7}$.$0^{6,10}$-.$0^{8,12}$.$0^{11,15}$.$0^{13,17}$.$0^{16,20}$]eicosane	Pagodane	302

(which is also a propellane).[307] X-ray crystallography of the 5-cyano derivative of **82** shows that the four carbon valences at C-1 and C-3 are all directed "into" the molecule and none



81 **82**

point outside.[308] **82** is quite reactive; it is unstable in air, readily adds hydrogen, water, bromine, or acetic acid to the C_1—C_3 bond, and is easily polymerized. When two such atoms are connected by a bond (as in **82**), the bond is very long (the C_1—C_3 bond length in the 5-cyano derivative of **82** is 1.64 Å), as the atoms try to compensate in this way for their enforced angles. The high reactivity of the C_1—C_3 bond of **82** is not only caused by strain, but also by the fact that reagents find it easy to approach these atoms since there are no bonds (e.g., C—H bonds on C-1 or C-3) to get in the way.

Strain in Medium Rings[309]

In rings larger than four-membered, there is no small-angle strain, but there are three other kinds of strain. In the chair form of cyclohexane, which does not exhibit any of the three kinds of strain, all six carbon–carbon bonds have the two attached carbons in the gauche conformation. However, in five-membered rings and in rings containing from 7 to 13 carbons any conformation in which all the ring bonds are gauche contains transannular interactions,

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[295]Katz; Acton *J. Am. Chem. Soc.* **1973,** *95*, 2738. See also Viehe; Merényi; Oth; Senders; Valange *Angew. Chem. Int. Ed. Engl.* **1964,** *3*, 755 [*Angew. Chem. 76*, 923]; Wilzbach; Kaplan *J. Am. Chem. Soc.* **1965,** *87*, 4004.

[296]Eaton; Cole *J. Am. Chem. Soc.* **1964,** *86*, 3157; Barborak; Watts; Pettit *J. Am. Chem. Soc.* **1966,** *88*, 1328; Hedberg; Hedberg; Eaton; Nodari; Robiette *J. Am. Chem. Soc.* **1991,** *113*, 1514. For a review of cubanes, see Griffin; Marchand *Chem. Rev.* **1989,** *89*, 997-1010.

[297]Paquette; Fischer; Browne; Doecke *J. Am. Chem. Soc.* **1985,** *105*, 686.

[298]Eaton; Or; Branca; Shankar *Tetrahedron* **1986,** *42*, 1621. See also Dauben; Cunningham *J. Org. Chem.* **1983,** *48*, 2842.

[299]Otterbach; Musso *Angew. Chem. Int. Ed. Engl.* **1987,** *26*, 554 [*Angew. Chem. 99*, 588].

[300]Allred; Beck *J. Am. Chem. Soc.* **1973,** *95*, 2393.

[301]Hoffmann; Musso *Angew. Chem. Int. Ed. Engl.* **1987,** *26*, 1006 [*Angew. Chem. 99*, 1036].

[302]Rihs *Tetrahedron Lett.* **1983,** *24*, 5857.

[303]Lemal; Menger; Clark *J. Am. Chem. Soc.* **1963,** *85*, 2529; Wiberg; Lampman *Tetrahedron Lett.* **1963,** 2173. For reviews of preparations and reactions of this system, see Hoz, in Ref. 274, pt. 2, pp. 1121-1192; Wiberg; Lampman; Ciula; Connor; Schertler; Lavanish *Tetrahedron* **1965,** *21*, 2749-2769; Wiberg *Rec. Chem. Prog.* **1965,** *26*, 143-154; Wiberg, Ref. 287. For a review of [*n*.1.1] systems, see Meinwald; Meinwald *Adv. Alicyclic Chem.* **1966,** *1*, 1-51.

[304]Casanova; Bragin; Cottrell *J. Am. Chem. Soc.* **1978,** *100*, 2264.

[305]Maier; Pfriem; Schäfer; Malsch; Matusch *Chem. Ber.* **1981,** *114*, 3965; Maier; Pfriem; Malsch; Kalinowski; Dehnicke *Chem. Ber.* **1981,** *114*, 3988; Irngartinger; Goldmann; Jahn; Nixdorf; Rodewald; Maier; Malsch; Emrich *Angew. Chem. Int. Ed. Engl.* **1984,** *23*, 993 [*Angew. Chem. 96*, 967]; Maier; Fleischer *Tetrahedron Lett.* **1991,** *32*, 57. For reviews of attempts to synthesize tetrahedrane, see Maier *Angew. Chem. Int. Ed. Engl.* **1988,** *27*, 309-332 [*Angew. Chem. 100*, 317-341]; Zefirov; Koz'min; Abramenkov *Russ. Chem. Rev.* **1978,** *47*, 163-171. For a review of tetrahedranes and other cage molecules stabilized by steric hindrance, see Maier; Rang; Born, in Olah *Cage Hydrocarbons*; Wiley: New York, 1990, pp. 219-259. See also Maier; Born *Angew. Chem. Int. Ed. Engl.* **1989,** *28*, 1050 [*Angew. Chem. 101*, 1085].

[306]Rücker; Trupp *J. Am. Chem. Soc.* **1988,** *110*, 4828.

[307]Pincock and Torupka *J. Am. Chem. Soc.* **1969,** *91*, 4593; Pincock; Schmidt; Scott; Torupka *Can. J. Chem.* **1972,** *50*, 3958; Scott; Pincock *J. Am. Chem. Soc.* **1973,** *95*, 2040.

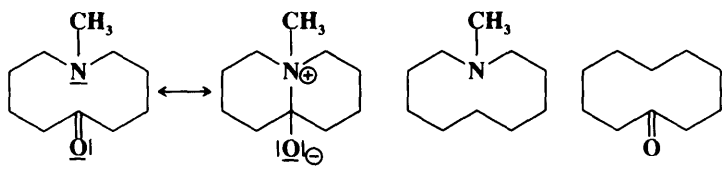
[308]Gibbons; Trotter *Can. J. Chem.* **1973,** *51*, 87.

[309]For reviews, see Gol'dfarb; Belen'kii *Russ. Chem. Rev.* **1960,** *29*, 214-235; Raphael *Proc. Chem. Soc.* **1962,** 97-105; Sicher *Prog. Stereochem.* **1962,** *3*, 202-264.

i.e., interactions between the substituents on C-1 and C-3 or C-1 and C-4, etc. These interactions occur because the internal space is not large enough for all the quasi-axial hydrogen atoms to fit without coming into conflict. The molecule can adopt other conformations in which this *transannular strain* is reduced, but then some of the carbon–carbon bonds must adopt eclipsed or partially eclipsed conformations. The strain resulting from eclipsed conformations is called *Pitzer strain*. For saturated rings from 3- to 13-membered (except for the chair form of cyclohexane) there is no escape from at least one of these two types of strain. In practice each ring adopts conformations that minimize both sorts of strain as much as possible. For cyclopentane, as we have seen (p. 148), this means that the molecule is not planar. In rings larger than 9-membered, Pitzer strain seems to disappear, but transannular strain is still present.[310] For 9- and 10-membered rings, some of the transannular and Pitzer strain may be relieved by the adoption of a third type of strain, *large-angle strain*. Thus, C—C—C angles of 115 to 120° have been found in x-ray diffraction of cyclononylamine hydrobromide and 1,6-diaminocyclodecane dihydrochloride.[311]

The amount of strain in cycloalkanes is shown in Table 4.5,[312] which lists heats of combustion per CH_2 group. As can be seen, cycloalkanes larger than 13-membered are as strain-free as cyclohexane.

Transannular interactions can exist across rings from 8- to 11-membered and even larger.[313] Such interactions can be detected by dipole and spectral measurements. For example, that the carbonyl group in **83a** is affected by the nitrogen (**83b** is probably another canonical form) has been demonstrated by photoelectron spectroscopy, which shows that



83a **83b** **84** **85**

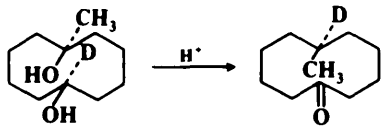
the ionization potentials of the nitrogen *n* and C=O π orbitals in **83** differ from those of the two comparison molecules **84** and **85**,[314] It is significant that when **83** accepts a proton,

TABLE 4.5 Heats of combustion in the gas phase for cycloalkanes, per CH_2 group[312]

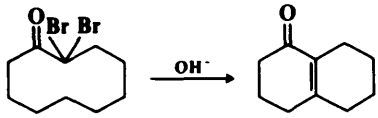
	$-\Delta H_c$, (g)			$-\Delta H_c$, (g)	
Size of ring	**kcal/mol**	**kJ/mol**	**Size of ring**	**kcal/mol**	**kJ/mol**
3	166.3	695.8	10	158.6	663.6
4	163.9	685.8	11	158.4	662.7
5	158.7	664.0	12	157.8	660.2
6	157.4	658.6	13	157.7	659.8
7	158.3	662.3	14	157.4	658.6
8	158.6	663.6	15	157.5	659.0
9	158.8	664.4	16	157.5	659.0

[310]Huber-Buser; Dunitz *Helv. Chim. Acta* **1960**, *43*, 760.
[311]Bryan; Dunitz *Helv. Chim. Acta* **1960**, *43*, 1; Dunitz; Venkatesan *Helv. Chim. Acta* **1961**, *44*, 2033.
[312]Gol'dfarb; Belen'kii, Ref. 309, p. 218.
[313]For a review, see Cope; Martin; McKervey *Q. Rev., Chem. Soc.* **1966**, *20*, 119-152.
[314]Spanka; Rademacher *J. Org. Chem.* **1986**, *51*, 592. See also Spanka; Rademacher; Duddeck *J. Chem. Soc., Perkin Trans. 2* **1988**, 2119; Leonard; Fox; Ōki *J. Am. Chem. Soc.* **1954**, *76*, 5708.

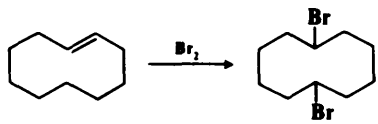
it goes to the oxygen rather than to the nitrogen. Many examples of transannular reactions are known. A few are:



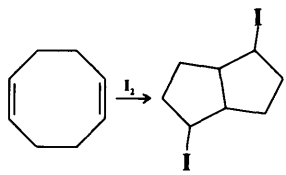
Ref. 315



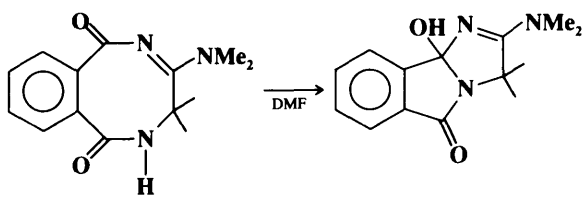
Ref. 316



Ref. 317



Ref. 318



Ref. 319

In summary, we can divide saturated rings into four groups, of which the first and third are more strained than the other two.[320]

1. *Small rings* (3- and 4-membered). Small-angle strain predominates.

2. *Common rings* (5-, 6-, and 7-membered). Largely unstrained. The strain that is present is mostly Pitzer strain.

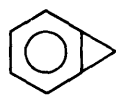
3. *Medium rings* (8- to 11-membered). Considerable strain; Pitzer, transannular, and large-angle strain.

4. *Large rings* (12-membered and larger). Little or no strain.

[315]Prelog; Küng *Helv. Chim. Acta* **1956,** *39*, 1394.
[316]Schenker; Prelog *Helv. Chim. Acta* **1953,** *36*, 896.
[317]Sicher; Závada; Svoboda *Collect. Czech. Chem. Commun.* **1962,** *27*, 1927.
[318]Uemura; Fukuzawa; Toshimitsu; Okano; Tezuka; Sawada *J. Org. Chem.* **1983,** *48*, 270.
[319]Schläpfer-Dähler; Prewo; Bieri; Germain; Heimgartner *Chimia* **1988,** *42*, 25.
[320]For a review on the influence of ring size on the properties of cyclic systems, see Granik *Russ. Chem. Rev.* **1982,** *51*, 119-134.

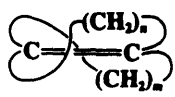
Unsaturated Rings[321]

Double bonds can exist in rings of any size. As expected, the most highly strained are the three-membered rings. Small-angle strain, which is so important in cyclopropane, is even greater in cyclopropene[322] because the ideal angle is greater. In cyclopropane, the bond angle is forced to be 60°, about 50° smaller than the tetrahedral angle; but in cyclopropene, the angle, also about 60°, is now about 60° smaller than the ideal angle of 120°. Thus, the angle is cyclopropene is about 10° more strained than in cyclopropane. However, this additional strain is offset by a decrease in strain arising from another factor. Cyclopropene, lacking two hydrogens, has none of the eclipsing strain present in cyclopropane. Cyclopropene has been prepared[323] and is stable at liquid–nitrogen temperatures, though on warming even to −80°C it rapidly polymerizes. Many other cyclopropenes are stable at room temperature and above.[322] The highly strained benzocyclopropene,[324] in which the cyclopropene ring is fused to a benzene ring, has been prepared[325] and is stable for weeks at room temperature, though it decomposes on distillation at atmospheric pressure.

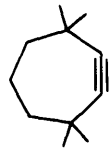


benzocyclopropene

As previously mentioned, double bonds in relatively small rings must be cis. A stable trans double bond[326] first appears in an eight-membered ring (*trans*-cyclooctene, p. 104), though the transient existence of *trans*-cyclohexene and cycloheptene has been demonstrated.[327] Above about 11 members, the trans isomer is more stable than the cis.[160] It has proved possible to prepare compounds in which a trans double bond is shared by two cycloalkene rings (e.g., **86**). Such compounds have been called [*m. n*]*betweenanenes*, and



86



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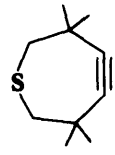


88

[321]For a review of strained double bonds, see Zefirov; Sokolov *Russ. Chem. Rev.* **1967,** *36*, 87-100. For a review of double and triple bonds in rings, see Johnson *Mol. Struct. Energ.* **1986,** *3*, 85-140.

[322]For reviews of cyclopropenes, see Baird *Top. Curr. Chem.* **1988,** *144*, 137-209; Halton; Banwell, in Ref. 274, pt. 2, pp. 1223-1339; Closs *Adv. Alicyclic Chem.* **1966,** *1*, 53-127; For a discussion of the bonding and hybridization, see Allen *Tetrahedron* **1982,** *38*, 645.

[323]Dem'yanov; Doyarenko *Bull. Acad. Sci. Russ.* **1922,** *16*, 297, *Ber.* **1923,** *56*, 2200; Schlatter *J. Am. Chem. Soc.* **1941,** *63*, 1733; Wiberg; Bartley *J. Am. Chem. Soc.* **1960,** *82*, 6375; Stigliani; Laurie; Li *J. Chem. Phys.* **1975,** *62*, 1890.

[324]For reviews of cycloproparenes, see Halton *Chem. Rev.* **1989,** *89*, 1161-1185, **1973,** *73*, 113-126; Billups; Rodin; Haley *Tetrahedron* **1988,** *44*, 1305-1338; Halton; Stang *Acc. Chem. Res.* **1987,** *20*, 443-448; Billups *Acc. Chem. Res.* **1978,** *11*, 245-251.

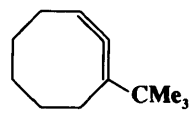
[325]Vogel; Grimme; Korte *Tetrahedron Lett.* **1965,** 3625. Also see Anet; Anet *J. Am. Chem. Soc.* **1964,** *86*, 526; Müller; Bernardinelli; Thi *Chimia* **1988,** *42*, 261; Neidlein; Christen; Poignée; Boese; Bläser; Gieren; Ruiz-Pérez; Hübner *Angew. Chem. Int. Ed. Engl.* **1988,** *27*, 294 [*Angew. Chem. 100*, 292].

[326]For reviews of trans cycloalkenes, see Nakazaki; Yamamoto; Naemura *Top. Curr. Chem.* **1984,** *125*, 1-25; Marshall *Acc. Chem. Res.* **1980,** *13*, 213-218.

[327]Bonneau; Joussot-Dubien; Salem; Yarwood *J. Am. Chem. Soc.* **1979,** *98*, 4329; Wallraff; Michl *J. Org. Chem.* **1986,** *51*, 1794; Squillacote; Bergman; De Felippis *Tetrahedron Lett.* **1989,** *30*, 6805.

several have been prepared with *m* and *n* values from 8 to 26.[328] The double bonds of the smaller betweenanenes, as might be expected from the fact that they are deeply buried within the bridges, are much less reactive than those of the corresponding cis–cis isomers.

The smallest unstrained cyclic triple bond is found in cyclononyne.[329] Cyclooctyne has been isolated,[330] but its heat of hydrogenation shows that it is considerably strained. There have been a few compounds isolated with triple bonds in seven-membered rings. 3,3,7,7-Tetramethylcycloheptyne (**87**) dimerizes within an hour at room temperature,[331] but the thia derivative **88**, in which the C—S bonds are longer than the corresponding C—C bonds in **87**, is indefinitely stable even at 140°C.[332] Cycloheptyne itself has not been isolated, though its transient existence has been shown.[333] Cyclohexyne[334] and its 3,3,6,6-tetramethyl derivative[335] have been trapped at 77 K, and in an argon matrix at 12 K, respectively, and ir spectra have been obtained. Transient six- and even five-membered rings containing triple bonds have also been demonstrated.[336] A derivative of cyclopentyne has been trapped in a matrix.[337] Although cycloheptyne and cyclohexyne have not been isolated at room temperatures, Pt(0) complexes of these compounds have been prepared and are stable.[338] The smallest cyclic allene[339] so far isolated is 1-*t*-butyl-1,2-cyclooctadiene **89**.[340] The parent 1,2-cyclooctadiene has not been isolated. It has been shown to exist transiently, but rapidly



89

dimerizes.[341] The presence of the *t*-butyl group apparently prevents this. The transient existence of 1,2-cycloheptadiene has also been shown,[342] and both 1,2-cyclooctadiene and 1,2-cycloheptadiene have been isolated in platinum complexes.[343] 1,2-Cyclohexadiene has been trapped at low temperatures, and its structure has been proved by spectral studies.[344]

[328]Marshall; Lewellyn *J. Am. Chem. Soc.* **1977,** *99*, 3508; Nakazaki; Yamamoto; Yanagi *J. Chem. Soc., Chem. Commun.* **1977,** 346; *J. Am. Chem. Soc.* **1979,** *101*, 147; Ceré; Paolucci; Pollicino; Sandri; Fava *J. Chem. Soc., Chem. Commun.* **1980,** 755; Marshall; Flynn *J. Am. Chem. Soc.* **1983,** *105*, 3360. For reviews, see Ref. 326. For a review of these and similar compounds, see Borden *Chem. Rev.* **1989,** *89*, 1095-1109.

[329]For reviews of triple bonds in rings, see Meier *Adv. Strain Org. Chem.* **1991,** *1*, 215-272; Krebs; Wilke *Top. Curr. Chem.* **1983,** *109*, 189-233; Nakagawa in Patai *The Chemistry of the C—C Triple Bond*, pt. 2; Wiley: New York, 1978, pp. 635-712; Krebs, in Viehe *Acetylenes*; Marcel Dekker: New York, 1969, pp. 987-1062. For a list of strained cycloalkynes that also have double bonds, see Meier; Hanold; Molz; Bissinger; Kolshorn; Zountsas *Tetrahedron* **1986,** *42*, 1711.

[330]Blomquist; Liu *J. Am. Chem. Soc.* **1953,** *75*, 2153. See also Bühl; Gugel; Kolshorn; Meier *Synthesis* **1978,** 536.

[331]Krebs; Kimling *Angew. Chem. Int. Ed. Engl.* **1971,** *10*, 509 [*Angew. Chem. 83*, 540]; Schmidt; Schweig; Krebs *Tetrahedron Lett.* **1974,** 1471.

[332]Krebs; Kimling *Tetrahedron Lett.* **1970,** 761.

[333]Wittig; Meske-Schüller *Liebigs Ann. Chem.* **1968,** *711*, 65; Krebs; Kimling, Ref. 331; Bottini; Frost; Anderson; Dev *Tetrahedron* **1973,** *29*, 1975.

[334]Wentrup; Blanch; Briehl; Gross *J. Am. Chem. Soc.* **1988,** *110*, 1874.

[335]See Sander; Chapman *Angew. Chem. Int. Ed. Engl.* **1988,** *27*, 398 [*Angew. Chem. 100*, 402]; Krebs; Colcha; Müller; Eicher; Pielartzik; Schnöckel *Tetrahedron Lett.* **1984,** *25*, 5027.

[336]See, for example, Wittig; Mayer *Chem. Ber.* **1963,** *96*, 329, 342; Wittig; Weinlich *Chem. Ber.* **1965,** *98*, 471; Bolster; Kellogg *J. Am. Chem. Soc.* **1981,** *103*, 2868; Gilbert; Baze *J. Am. Chem. Soc.* **1983,** *105*, 664.

[337]Chapman; Gano; West; Regitz; Maas *J. Am. Chem. Soc.* **1981,** *103*, 7033.

[338]Bennett; Robertson; Whimp; Yoshida *J. Am. Chem. Soc.* **1971,** *93*, 3797.

[339]For reviews of cyclic allenes, see Johnson *Adv. Theor. Interesting Mol.* **1989,** *1*, 401-436, *Chem. Rev.* **1989,** *89*, 1111-1124; Thies *Isr. J. Chem.* **1985,** *26*, 191-195; Schuster; Coppola *Allenes in Organic Synthesis*; Wiley: New York, 1984, pp. 38-56.

[340]Price; Johnson *Tetrahedron Lett.* **1986,** *27*, 4679.

[341]See Marquis; Gardner *Tetrahedron Lett.* **1966,** 2793.

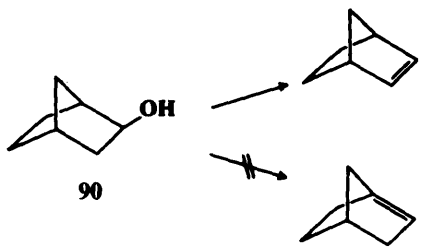
[342]Wittig; Dorsch; Meske-Schüller *Liebigs Ann. Chem.* **1968,** *711*, 55.

[343]Visser; Ramakers *J. Chem. Soc., Chem. Commun.* **1972,** 178.

[344]Wentrup; Gross; Maquestiau; Flammang *Angew. Chem. Int. Ed. Engl.* **1983,** *22*, 542 [*Angew. Chem. 95*, 551]. 1,2,3-Cyclohexatriene has also been trapped: Shakespeare; Johnson *J. Am. Chem. Soc.* **1990,** *112*, 8578.

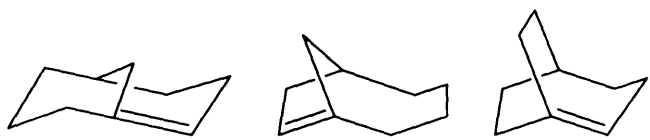
Cyclic allenes in general are less strained than their acetylenic isomers.[345] The cyclic cumulene 1,2,3-cyclononatriene has also been synthesized and is reasonably stable in solution at room temperature in the absence of air.[346]

In bridged bicyclic compounds double bonds at the bridgehead are impossible in small systems. This is the basis of *Bredt's rule*,[347] which states that elimination to give a double bond in a bridged bicyclic system (e.g., **90**) always leads away from the bridgehead. This rule no longer applies when the rings are large enough. In determining whether a bicyclic



90

system is large enough to accommodate a bridgehead double bond, the most reliable criterion is the size of the ring in which the double bond is located.[348] Bicyclo[3.3.1]non-1-ene[349] (**91**) and bicyclo[4.2.1]non-1(8)ene[350] (**92**) are stable compounds. Both can be looked upon as



91 **92** **93**

derivatives of *trans*-cyclooctene, which is of course a known compound. **91** has been shown to have a strain energy of the same order of magnitude as that of *trans*-cyclooctene.[351] On the other hand, in bicyclo[3.2.2]non-1-ene (**93**), the largest ring that contains the double bond is *trans*-cycloheptene, which is as yet unknown. **93** has been prepared, but dimerized before it could be isolated.[352] Even smaller systems ([3.2.1] and [2.2.2]), but with imine double bonds (**94-96**), have been obtained in matrixes at low temperatures.[353] These com-

[345]Moore; Ward *J. Am. Chem. Soc.* **1963,** *85*, 86.

[346]Angus; Johnson *J. Org. Chem.* **1984,** *49*, 2880.

[347]For reviews, see Shea *Tetrahedron* **1980,** *36*, 1683-1715; Buchanan *Chem. Soc. Rev.* **1974,** *3*, 41-63; Köbrich *Angew. Chem. Int. Ed. Engl.* **1973,** *12*, 464-473 [*Angew. Chem. 85*, 494-503]. For reviews of bridgehead olefins, see Billups; Haley; Lee *Chem. Rev.* **1989,** *89*, 1147-1159; Warner *Chem. Rev.* **1989,** *89*, 1067-1093; Szeimies *React. Intermed. (Plenum)* **1983,** *3*, 299-366; Keese *Angew. Chem. Int. Ed. Engl.* **1975,** *14*, 528-538 [*Angew. Chem. 87*, 568-578].

[348]For a discussion and predictions of stability in such compounds, see Maier; Schleyer *J. Am. Chem. Soc.* **1981,** *103*, 1891.

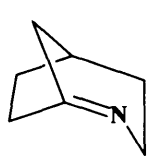
[349]Marshall; Faubl *J. Am. Chem. Soc.* **1967,** *89*, 5965, **1970,** *92*, 948; Wiseman *J. Am. Chem. Soc.* **1967,** *89*, 5966; Wiseman; Pletcher *J. Am. Chem. Soc.* **1970,** *92*, 956; Kim; White *J. Am. Chem. Soc.* **1975,** *97*, 451; Becker *Helv. Chim. Acta* **1977,** *60*, 81. For the preparation of optically active **91**, see Nakazaki; Naemura; Nakahara *J. Org. Chem.* **1979,** *44*, 2438.

[350]Wiseman; Chan; Ahola *J. Am. Chem. Soc.* **1969,** *91*, 2812; Carruthers; Qureshi *Chem. Commun.* **1969,** 832; Becker *Tetrahedron Lett.* **1975,** 2207.

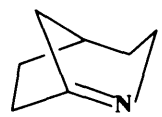
[351]Lesko; Turner *J. Am. Chem. Soc.* **1968,** *90*, 6888; Burkert *Chem. Ber.* **1977,** *110*, 773.

[352]Wiseman; Chong *J. Am. Chem. Soc.* **1969,** *91*, 7775.

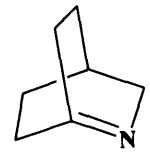
[353]Sheridan; Ganzer *J. Am. Chem. Soc.* **1983,** *105*, 6158; Ref. 354.



E isomer
94



Z isomer
95

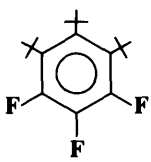


96

pounds are destroyed on warming. **94** and **95** are the first reported example of *E*-*Z* isomerism at a strained bridgehead double bond.[354]

Strain Due to Unavoidable Crowding[355]

In some molecules, large groups are so close to each other that they cannot fit into the available space in such a way that normal bond angles are maintained. It has proved possible to prepare compounds with a high degree of this type of strain. For example, success has been achieved in synthesizing benzene rings containing ortho *t*-butyl groups. The 1,2,3-tri-*t*-butyl compounds **97**[356] (see p. 873), **98**,[357] and **99**[358] have been prepared, as well as the 1,2,3,4-tetra-*t*-butyl compound **100**.[359] That these molecules are strained is demon-



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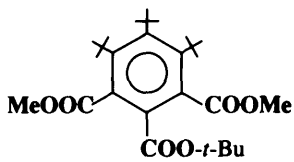

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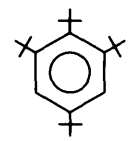

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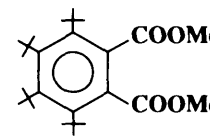


100

strated by uv and ir spectra, which show that the ring is not planar in 1,2,4-tri-*t*-butylbenzene, and by a comparison of the heats of reaction of this compound and its 1,3,5 isomer, which show that the 1,2,4 compound possesses about 22 kcal/mol (92 kJ/mol) more strain energy than its isomer[360] (see also p. 1117). X-ray diffraction of **98** shows a nonplanar, boat conformation for the ring.[357] $SiMe_3$ groups are larger than CMe_3 groups, and it has proven possible to prepare $C_6(SiMe_3)_6$. This compound has a chair-shaped ring in the solid state, and a mixture of chair and boat forms in solution.[361] Even smaller groups can sterically interfere in ortho positions. In hexaisopropylbenzene, the six isopropyl groups are so crowded that they cannot rotate but are lined up around the benzene ring, all pointed in

[354]Radziszewski; Downing; Wentrup; Kaszynski; Jawdosiuk; Kovacic; Michl *J. Am. Chem. Soc.* **1985,** *107*, 2799.

[355]For reviews, see Tidwell *Tetrahedron* **1978,** *34*, 1855-1868; Voronenkov; Osokin *Russ. Chem. Rev.* **1972,** *41*, 616-629. For a review of early studies, see Mosher; Tidwell *J. Chem. Educ.* **1990,** *67*, 9-14. For a review of van der Waals radii, see Zefirov; Zorkii *Russ. Chem. Rev.* **1989,** *58*, 421-440.

[356]Viehe; Merényi; Oth; Valange *Angew. Chem. Int. Ed. Engl.* **1964,** *3*, 746 [*Angew. Chem. 76*, 890].

[357]Maas; Fink; Wingert; Blatter; Regitz *Chem. Ber.* **1987,** *120*, 819.

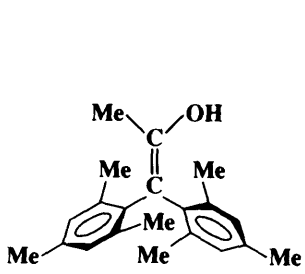
[358]Arnett; Bollinger *Tetrahedron Lett.* **1964,** 3803.

[359]Maier; Schneider *Angew. Chem. Int. Ed. Engl.* **1980,** *19*, 1022 [*Angew. Chem. 92*, 1056]. For another example, see Krebs; Franken; Müller *Tetrahedron Lett.* **1981,** *22*, 1675.

[360]Arnett; Sanda; Bollinger; Barber *J. Am. Chem. Soc.* **1967,** *89*, 5389; Krüerke; Hoogzand; Hübel *Chem. Ber.* **1961,** *94*, 2817; Dale *Chem. Ber.* **1961,** *94*, 2821. See also Barclay; Brownstein; Gabe; Lee *Can. J. Chem.* **1984,** *62*, 1358.

[361]Sakurai; Ebata; Kabuto; Sekiguchi *J. Am. Chem. Soc.* **1990,** *112*, 1799.

the same direction.[362] This compound is an example of a *geared molecule*.[363] The isopropyl groups fit into each other in the same manner as interlocked gears. Another example is **101** (which is a stable enol).[364] In this case each ring can rotate about its C—aryl bond only by forcing the other to rotate as well. In the case of triptycene derivatives such as **102**, a



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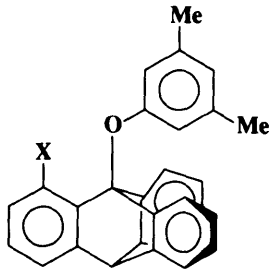
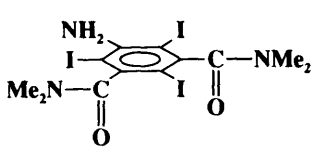
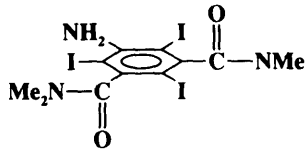


102

complete 360° rotation of the aryl group around the O—aryl bond requires the aryl group to pass over three rotational barriers; one of which is the C—X bond and other two the "top" C—H bonds of the other two rings. As expected, the C—X barrier is the highest, ranging from 10.3 kcal/mol (43.1 kJ/mol) for X = F to 17.6 kcal/mole (73.6 kJ/mol) for X = *t*-butyl.[365] In another instance, it has proved possible to prepare cis and trans isomers of 5-amino-2,4,6-triiodo-N,N,N′,N′-tetramethylisophthalamide because there is no room for the $CONMe_2$ groups to rotate, caught as they are between two bulky iodine atoms.[366]



cis



trans

The trans isomer is chiral and has been resolved, while the cis isomer is a meso form. Another example of cis–trans isomerism resulting from restricted rotation about single bonds[367] is found in 1,8-di-*o*-tolylnapthalene[368] (see also p. 128).

[362]Arnett; Bollinger *J. Am. Chem. Soc.* **1964,** *86*, 4730; Hopff; Gati *Helv. Chim. Acta* **1965,** *48*, 509; Siegel; Gutiérrez; Schweizer; Ermer; Mislow *J. Am. Chem. Soc.* **1986,** *108*, 1569. For the similar structure of hexakis(dichloromethyl)benzene, see Kahr; Biali; Schaefer; Buda; Mislow *J. Org. Chem.* **1987,** *52*, 3713.

[363]For reviews, see Iwamura; Mislow *Acc. Chem. Res.* **1988,** *21*, 175-182; Mislow *Chemtracts: Org. Chem.* **1989,** *2*, 151-174, *Chimia* **1986,** *40*, 395-402; Berg; Liljefors; Roussel; Sandström *Acc. Chem. Res.* **1985,** *18*, 80-86.

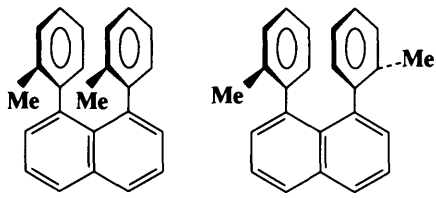
[364]Nugiel; Biali; Rappoport *J. Am. Chem. Soc.* **1984,** *106*, 3357.

[365]Yamamoto; Ōki *Bull. Chem. Soc. Jpn.* **1986,** *59*, 3597. For reviews of similar cases, see Yamamoto *Pure Appl. Chem.* **1990,** *62*, 569-574; Ōki, Ref. 49, pp. 269-284.

[366]Ackerman; Laidlaw; Snyder *Tetrahedron Lett.* **1969,** 3879; Ackerman; Laidlaw *Tetrahedron Lett.* **1969,** 4487. See also Cuyegkeng; Mannschreck *Chem. Ber.* **1987,** *120*, 803.

[367]For a monograph on restricted rotation about single bonds, see Ōki, Ref. 49. For reviews, see Förster; Vögtle *Angew. Chem. Int. Ed. Engl.* **1977,** *16*, 429-441 [*Angew. Chem. 89*, 443-455]; Ōki *Angew. Chem. Int. Ed. Engl.* **1976,** *15*, 87-93 [*Angew. Chem. 88*, 67-74].

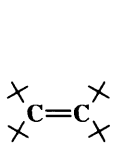
[368]Clough; Roberts *J. Am. Chem. Soc.* **1976,** *98*, 1018. For a study of rotational barriers in this system, see Cosmo; Sternhell *Aust. J. Chem.* **1987,** *40*, 1107.



cis trans

There are many other cases of intramolecular crowding that result in the distortion of bond angles. We have already mentioned hexahelicene (p. 103) and bent benzene rings (p. 37). The compounds tri-*t*-butylamine and tetra-*t*-butylmethane are as yet unknown. In the latter, there is no way for the strain to be relieved and it is questionable whether this compound can ever be made. In tri-*t*-butylamine the crowding can be eased somewhat if the three bulky groups assume a planar instead of the normal pyramidal configuration. In tri-*t*-butylcarbinol, coplanarity of the three *t*-butyl groups is prevented by the presence of the OH group, and yet this compound has been prepared.[369] Tri-*t*-butylamine should have less steric strain than tri-*t*-butylcarbinol and it should be possible to prepare it.[370] The tetra-*t*-butylphosphonium cation $(t\text{-Bu})_4P^+$ has been prepared.[371] Although steric effects are nonadditive in crowded molecules, a quantitative measure has been proposed by D. F. DeTar, based on molecular mechanics calculations. This is called *formal steric enthalpy* (FSE), and values have been calculated for alkanes, alkenes, alcohols, ethers, and methyl esters.[372] For example, some FSE values for alkanes are: butane 0.00; 2,2,3,3-tetramethylbutane 7.27; 2,2,4,4,5-pentamethylhexane 11.30; and tri-*t*-butylmethane 38.53.

The two carbon atoms of a C=C double bond and the four groups attached to them are normally in a plane, but if the groups are large enough, significant deviation from planarity can result.[373] The compound tetra-*t*-butylethene(**103**) has not been prepared,[374] but the tetraaldehyde **104,** which should have about the same amount of strain, has been made. X-ray crystallography shows that **104** is twisted out of a planar shape by an angle of 28.6°.[375]



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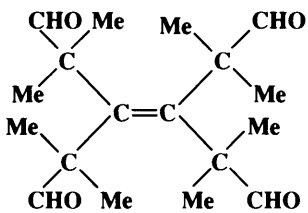

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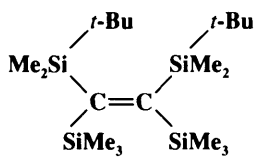


105

[369]Bartlett; Lefferts *J. Am. Chem. Soc.* **1955,** *77,* 2804; Bartlett; Tidwell *J. Am. Chem. Soc.* **1968,** *90,* 4421.

[370]For attempts to prepare tri-*t*-butylamine, see Back; Barton *J. Chem. Soc., Perkin Trans 1* **1977,** 924. For the preparation of di-*t*-butylmethylamine and other sterically hindered amines, see Kopka; Fataftah; Rathke *J. Org. Chem.* **1980,** *45,* 4616; Audeh; Fuller; Hutchinson; Lindsay Smith *J. Chem. Res. (S)* **1979,** 270.

[371]Schmidbaur; Blaschke; Zimmer-Gasser; Schubert *Chem. Ber.* **1980,** *113,* 1612.

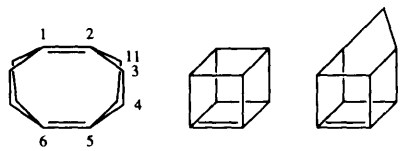
[372]DeTar; Binzet; Darba *J. Org. Chem.* **1985,** *50,* 2826, 5298, 5304.

[373]For reviews, see Luef; Keese *Top. Stereochem.* **1991,** *20,* 231-318; Sandström, Ref. 164, pp. 160-169.

[374]For a list of crowded alkenes that have been made, see Drake; Rabjohn; Tempesta; Taylor *J. Org. Chem.* **1988,** *53,* 4555. See also Garratt; Payne; Tocher *J. Org. Chem.* **1990,** *55,* 1909.

[375]Krebs; Nickel; Tikwe; Kopf *Tetrahedron Lett.* **1985,** *26,* 1639.

Also, the C=C double bond distance is 1.357 Å, significantly longer than a normal C=C bond of 1.32 Å (Table 1.5). *Z*-1,2-Bis(*t*-butyldimethylsilyl)-1,2-bis(trimethylsilyl)ethene (**105**) has an even greater twist, but could not be made to undergo conversion to the *E* isomer, probably because the groups are too large to slide past each other.[376] A different kind of double bond strain is found in tricyclo[4.2.2.$2^{2,5}$]dodeca-1,5-diene (**106**),[377] cubene (**107**),[378] and homocub-4(5)-ene (**108**).[379] In these molecules, the four groups on the double bond are all forced to be on one side of the double-bond plane.[380] In **106** the angle between



106 **107** **108**

the line C_1–C_2 (extended) and the plane defined by C_2, C_3, and C_{11} is 27°. An additional source of strain in this molecule is the fact that the two double bonds are pushed into close proximity by the four bridges. In an effort to alleviate this sort of strain the bridge bond distances (C_3–C_4) are 1.595 Å, which is considerably longer than the 1.53 Å expected for a normal sp^3–sp^3 C—C bond (Table 1.5). **107** and **108** have not been isolated, but have been generated as intermediates that were trapped by reaction with other compounds.[378,379]

[376]Sakurai; Ebata; Kabuto; Nakadaira *Chem. Lett.* **1987**, 301.

[377]Wiberg; Matturo; Okarma; Jason *J. Am. Chem. Soc.* **1984**, *106*, 2194; Wiberg; Adams; Okarma; Matturo; Segmuller *J. Am. Chem. Soc.* **1984**, *106*, 2200.

[378]Eaton; Maggini *J. Am. Chem. Soc.* **1988**, *110*, 7230.

[379]Hrovat; Borden *J. Am. Chem. Soc.* **1988**, *110*, 7229.

[380]For a review of such molecules, see Borden *Chem. Rev.* **1989**, *89*, 1095-1109. See also Hrovat; Borden *J. Am. Chem. Soc.* **1988**, *110*, 4710.