CHAPTER 4

Stereochemistry

In Chapters 1–3, we discussed electron distribution in organic molecules. In this chapter, we discuss the 3D 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 3D structures that are not interchangeable. These 3D 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

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[1] For books on this subject, see Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***; Sokolov, V.I. *Introduction to Theoretical Stereochemistry*, Gordon and Breach, NY, ***1991***; Bassindale, A. *The Third Dimension in Organic Chemistry*, Wiley, NY, ***1984***; Nógrádi, M. *Sterochemistry*, Pergamon, Elmsford, NY, ***1981***; Kagan, H. *Organic Sterochemistry*, Wiley, NY, ***1979***; Testa, B. *Principles of Organic Stereochemistry*, Marcel Dekker, NY, ***1979***; Izumi, Y.; Tai, A. *Stereo-Differentiating Reactions*, Academic Press, NY, Kodansha Ltd., Tokyo, ***1977***; Natta, G.; Farina, M. *Stereochemistry*, Harper and Row, NY, ***1972***; Eliel, E.L. *Elements of Stereochemistry*, Wiley, NY, ***1969***; Mislow, K. *Introduction to Stereochemistry*, W. A. Benjamin, NY, ***1965***. Two excellent treatments of stereochemistry that, though not recent, contain much that is valid and useful, are Wheland, G.W. *Advanced Organic Chemistry*, 3rd ed., Wiley, NY, ***1960***, pp. 195–514; Shriner, R.L.; Adams, R.; Marvel, C.S. in Gilman, H. *Advanced Organic Chemistry*; Vol. 1, 2nd ed., Wiley, NY, ***1943***, pp. 214–488. For a historical treatment, see Ramsay, O.B. *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 and in *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, ***1979*** (the "Blue Book").

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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. 141). 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. Note that parity violation represents an essential property of particle and atomic handedness, and has been related to chirality.[4]

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 their orientations (Fig. 4.1). Enantiomers have identical[5] physical and chemical properties except in two important respects:

1. They rotate the plane of polarized light in opposite directions, although in equal amounts. The isomer that rotates the plane to the left (counterclockwise)

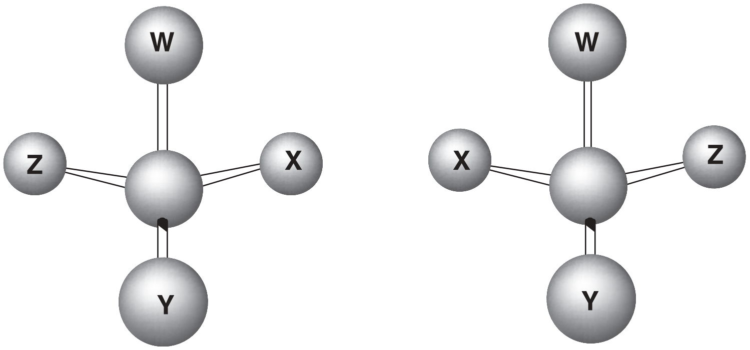

Fig. 4.1. Enantiomers.

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

[4] Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J.L.; Palacios, J.C. *Tetrahedron Asymmetry* ***2000***, *11*, 2845.

[5] 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, G.E. *J. Chem. Soc. Chem. Commun. 1986*, 60, and references cited therein. See also Barron, L.D. *Chem. Soc. Rev.* ***1986***, *15*, 189.

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.[6]

In general, it may be said that enantiomers have identical properties in a symmetrical environment, but their properties may differ in an unsymmetrical environment.[7] 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*, and so on. 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*[8] or *racemates*.[9] 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,[10] 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 $206\,\mathrm{g\,L^{-1}}$, while for the (+) or the (−) enantiomer, the corresponding figures are 170°C and $1390\,\mathrm{g\,L^{-1}}$. 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. 142).

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

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

[8] 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.

[9] For a monograph on the properties of racemates and their resolution, see Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates, and Resolutions*, Wiley, NY, ***1981***.

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

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[11] and concentration (for solutions), the pressure (for gases), and the wavelength of light.[12] 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 a is linear with this. Therefore, a number is defined, called the *specific rotation* $[\alpha]$, which is

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

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: $[\alpha]_{546}^{25}$. 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; that is, $\lambda = 589$ nm. The molar rotation $[M]_{\lambda}^{t}$ is the specific rotation times the molecular weight divided by 100.

It must be emphasized that although the value of a 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, although 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.[13] 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, $[\alpha]_D^{24}$ for (−)-2-ethyl-2-methylsuccinic acid in $CHCl_3$ is $-5.0°$ at $c = 16.5\ \text{g}\ 100\ \text{mL}^{-1}$ ($0.165\ \text{g mL}^{-1}$), $-0.7°$ at $c = 10.6$, $+1.7°$ at $c = 8.5$, and $+18.9°$ at $c = 2.2$.[14] Note that the concentration is sometimes reported in $\text{g}\ 100\ \text{mL}^{-1}$ (as shown) or as g dL^{-1} (decaliters) rather than the standard grams per milliliter (g mL^{-1}). One should always check the concentration term to be certain. Noted that calculation of the optical rotation of (*R*)-(−)-3-chloro-1-butene found a remarkably large dependence on the C=C–C–C torsional angle.[15]

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

[12] For a review of polarimetry, see Lyle, G.G.; Lyle, R.E., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 13–27.

[13] For examples, see Shriner, R.L.; Adams, R.; Marvel, C.S., in Gilman, H. *Advanced Organic Chemistry*, Vol. 1, 2nd ed. Wiley, NY, ***1943***, pp. 291–301.

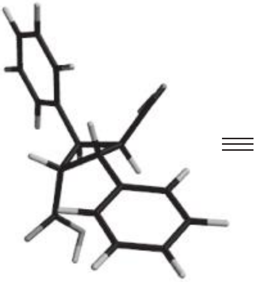
[14] Krow, G.; Hill, R.K. *Chem. Commun.* ***1968***, 430.

[15] Wiberg, K. B.; Vaccaro, P. H.; Cheeseman, J. R. *J. Am. Chem. Soc.* ***2003***, *125*, 1888.

However, the observed rotations are a factor of 2.6 smaller than the calculated values, independent of both conformation and wavelength from 589 to 365 nm.

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.*[16] A plane of symmetry[17] (also called a *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**.[18] A center of symmetry[17] is a point within an object such that a straight 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[17] 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.



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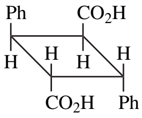
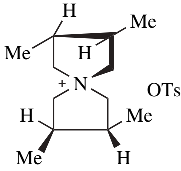


α-Truxillic acid



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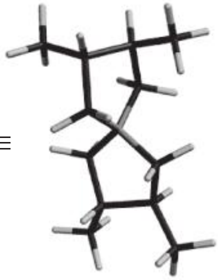

A molecule that contains just one *chiral (stereogenic) carbon atom* (defined as a carbon atom connected to four different groups; also called an *asymmetric carbon atom*) is always chiral, and hence optically active.[19] As seen in Fig. 4.1, such a

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[16] For a theoretical discussion of the relationship between symmetry and chirality, including parity violation (Ref. 5), see Barron L.D. *Chem. Soc. Rev.* ***1986***, *15*, 189.

[17] The definitions of plane, center, and alternating axis of symmetry are taken from Eliel, E.L. *Elements of Stereochemistry*, Wiley, NY, ***1969***, pp. 6,7. See also Lemière, G.L.; Alderweireldt, F.C. *J. Org. Chem.* ***1980***, *45*, 4175.

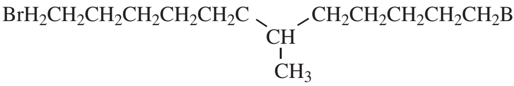
[18] McCasland, G.E.; Proskow, S. *J. Am. Chem. Soc.* ***1955***, *77*, 4688.

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

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[20] 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.

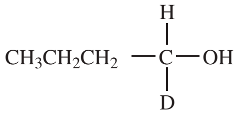
Optically active compounds may be classified into several categories.

1. *Compounds with a Stereogenic 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



$$BrH_2CH_2CH_2CH_2CH_2CH_2C{-}\underset{\displaystyle CH_3}{CH}{-}CH_2CH_2CH_2CH_2CH_2Br$$

   Optical activity has been detected even in cases,[21] such as 1-butanol-1-*d*, where one group is hydrogen and another deuterium.[22]



$$CH_3CH_2CH_2{-}\overset{\displaystyle H}{\underset{\displaystyle D}{C}}{-}OH$$

   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[23] and the optical activity of 5-ethyl-5-propylundecane is too low to be measurable at any wavelength between 280 and 580 nm.[24]

2. *Compounds with Other Quadrivalent Stereogenic Atoms.*[25] 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,[26] Ge, Sn,[27] and N (in quaternary salts or

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[20] For a review of such molecules, see Nakazaki, M. *Top. Stereochem.* ***1984***, *15*, 199.

[21] For reviews of compounds where chirality is due to the presence of deuterium or tritium, see Barth, G.; Djerassi, C. *Tetrahedron* ***1981***, *24*, 4123; Arigoni, D.; Eliel, E.L. *Top. Stereochem.* ***1969***, *4*, 127; Verbit, L. *Prog. Phys. Org. Chem.* ***1970***, *7*, 51. For a review of compounds containing chiral methyl groups, see Floss, H.G.; Tsai, M.; Woodard, R.W. *Top. Stereochem.* ***1984***, *15*, 253.

[22] Streitwieser, Jr., A.; Schaeffer, W.D. *J. Am. Chem. Soc.* ***1956***, *78*, 5597.

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

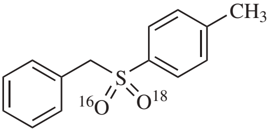
[24] Ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* ***1980***, *45*, 2754.

[25] For reviews of compounds with asymmetric atoms other than carbon, see Aylett, B.J. *Prog. Stereochem.* ***1969***, *4*, 213; Belloli, R. *J. Chem. Educ.* ***1969***, *46*, 640; Sokolov, V.I.; Reutov, O.A. *Russ. Chem. Rev.* ***1965***, *34*, 1.

[26] For reviews of stereochemistry of silicon, see Corriu, R.J.P.; Guérin, C.; Moreau, J.J.E., in Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds*, pt. 1, Wiley, NY, ***1989***, pp. 305–370, *Top. Stereochem.* ***1984***, *15*, 43; Maryanoff, C.A.; Maryanoff, B.E., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, ***1984***, pp. 355–374.

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

N-oxides).[28] In sulfones, the sulfur bonds with a tetrahedral array, but since two of the groups are always oxygen, no chirality normally results. However, the preparation[29] of 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.[30] Optically active chiral phosphates **4** have similarly been made.[31]



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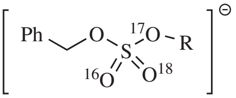

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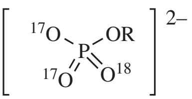

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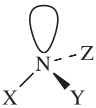
3. *Compounds with Tervalent Stereogenic Atoms*. Atoms with pyramidal bonding[32] might be expected to give rise to optical activity if the atom is connected to three different groups, since the unshared pair of electrons is analogous to a fourth group, necessarily different from the others. For example, 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.[33] For ammonia, there are 2×10^{11} inversions every second. The inversion is less rapid in substituted ammonia derivatives[34] (amines,

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[28] For a review, see Davis, F.A.; Jenkins, Jr., R.H., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, ***1984***, pp. 313–353. The first resolution of a quaternary ammonium salt of this type was done by Pope, W, J.; Peachey, S.J. *J. Chem. Soc.* ***1899***, *75*, 1127.

[29] Stirling, C.J.M. *J. Chem. Soc.* ***1963***, 5741; Sabol, M.A.; Andersen, K.K. *J. Am. Chem. Soc.* ***1969***, *91*, 3603; Annunziata, R.; Cinquini, M.; Colonna, S. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 2057.

[30] Lowe, G.; Parratt, M.J. *J. Chem. Soc. Chem. Commun.* ***1985***, 1075.

[31] Abbott, S.J.; Jones, S.R.; Weinman, S.A.; Knowles, J.R. *J. Am. Chem. Soc.* ***1978***, *100*, 2558; Cullis, P.M.; Lowe, G. *J. Chem. Soc. Chem. Commun.* ***1978***, 512. For a review, see Lowe, G. *Acc. Chem. Res.* ***1983***, *16*, 244.

[32] For a review of the stereochemistry at trivalent nitrogen, see Raban, M.; Greenblatt, J., in Patai, S. *The Chemistry of Functional Groups*, *Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 53–83.

[33] For reviews of the mechanism of, and the effect of structure on, pyramidal inversion, see Lambert, J.B. *Top. Stereochem.* ***1971***, *6*, 19; Rauk, A.; Allen, L.C.; Mislow, K. *Angew. Chem. Int. Ed.* ***1970***, *9*, 400; Lehn, J.M. *Fortschr. Chem. Forsch.* ***1970***, *15*, 311.

[34] For example, see Stackhouse, J.; Baechler, R.D.; Mislow, K. *Tetrahedron Lett.* ***1971***, 3437, 3441.

amides, etc.). The interconversion barrier for endo vesus exo methyl in *N*-methyl-2-azabicyclo[2.2.1]heptane, for example, is 0.3 kcal.[35] In this case, torsional strain plays a significant role, along with angle strain, in determining inversion barriers. 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[28] 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.[36] In suitable cases this barrier to inversion can result in compounds that are optically active solely because of a chiral tervalent nitrogen atom. For example, **7** has been resolved into its separate enantiomers.[37] 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,[38] diaziridines (e.g., **8**)[39] triaziridines (e.g., **9**),[40] and 1,2-oxazolidines (e.g., **10**)[41] even although 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 ($[\alpha]^{20}_{D} \approx \pm 3°$).[42] This compound and

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[35] Forsyth, D.A.; Zhang, W.; Hanley, J.A. *J. Org. Chem.* ***1996***, *61*, 1284. Also see Adams, D.B. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 567.

[36] Brois, S.J. *J. Am. Chem. Soc.* ***1968***, *90*, 506, 508. See also Shustov, G.V.; Kadorkina, G.K.; Kostyanovsky, R.G.; Rauk, A. *J. Am. Chem. Soc.* ***1988***, *110*, 1719; Lehn, J.M.; Wagner, J. *Chem. Commun.* ***1968***, 148; Felix, D.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1968***, *7*, 224; Kostyanovsky, R.G.; Samoilova, Z.E.; Chervin, I.I. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1968***, 2705, *Tetrahedron Lett.* ***1969***, 719. For a review, see Brois, S.J. *Trans. N.Y. Acad. Sci.* ***1969***, *31*, 931.

[37] Schurig, V.; Leyrer, U. *Tetrahedron: Asymmetry* ***1990***, *1*, 865.

[38] Boyd, D.R. *Tetrahedron Lett.* ***1968***, 4561; Boyd, D.R.; Spratt, R.; Jerina, D.M. *J. Chem. Soc. C* ***1969***, 2650; Montanari, F.; Moretti, I.; Torre, G. *Chem. Commun.* ***1968***, 1694; ***1969***, 1086; Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G.; Brückner, S.; Malpezzi, L. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1595. See also Mannschreck, A.; Linss, J.; Seitz, W. *Liebigs Ann. Chem.* ***1969***, *727*, 224; Forni, A.; Moretti, I.; Torre, G.; Brückner, S.; Malpezzi, L.; Di Silvestro, G.D. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 791. For a review of oxaziridines, see Schmitz, E. *Adv. Heterocycl. Chem.* ***1979***, *24*, 63.

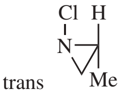
[39] Shustov, G.V.; Denisenko, S.N.; Chervin, I.I.; Asfandiarov, N.L.; Kostyanovsky, R.G. *Tetrahedron* ***1985***, *41*, 5719 and cited references. See also Mannschreck, A.; Radeglia, R.; Gründemann, E.; Ohme, R. *Chem. Ber.* ***1967***, *100*, 1778.

[40] Hilpert, H.; Hoesch, L.; Dreiding, A.S. *Helv. Chim. Acta* ***1985***, *68*, 1691, ***1987***, *70*, 381.

[41] Müller, K.; Eschenmoser, A. *Helv. Chim. Acta* ***1969***, *52*, 1823; Dobler, M.; Dunitz, J.D.; Hawley, D.M. *Helv. Chim. Acta* ***1969***, *52*, 1831.

[42] Kostyanovsky, R.G.; Rudchenko, V.F.; Shtamburg, V.G.; Chervin, I.I.; Nasibov, S.S. *Tetrahedron* ***1981***, *37*, 4245; Kostyanovsky, R.G.; Rudchenko, V.F. *Doklad. Chem.* ***1982***, *263*, 121. See also Rudchenko, V.F.; Ignatov, S.M.; Chervin, I.I.; Kostyanovsky, R.G. *Tetrahedron* ***1988***, *44*, 2233.

several similar ones reported in the same paper are the first examples of



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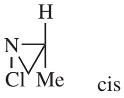

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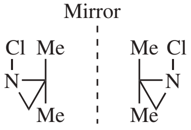

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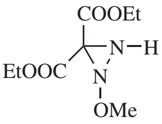

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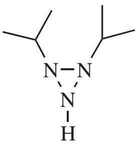

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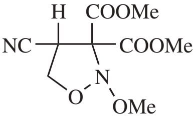

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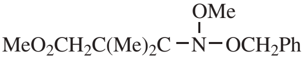
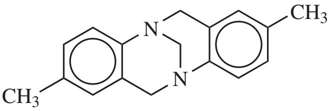


$\mathrm{MeO_2CH_2C(Me)_2C{-}\overset{OMe}{N}{-}OCH_2Ph}$

11

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 h. A similar compound (**11**, with $\mathrm{OCH_2Ph}$ replaced by OEt) has a longer half-life, 37.5 h at 20°C.



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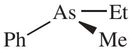
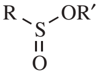
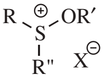
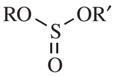


13

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) has been prepared.[43] Phosphorus inverts more slowly and arsenic still more slowly.[44] Nonbridgehead phosphorus,[45] arsenic, and antimony compounds have also been resolved, for example, **13**.[46] Sulfur exhibits pyramidal bonding in sulfoxides, sulfinic







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[43] Prelog, V.; Wieland, P. *Helv. Chim. Acta* ***1944***, *27*, 1127.

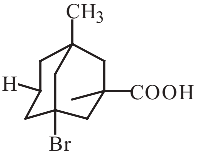
[44] For reviews, see Yambushev, F.D.; Savin, V.I. *Russ. Chem. Rev.* ***1979***, *48*, 582; Gallagher, M.J.; Jenkins, I.D. *Top. Stereochem.* ***1968***, *3*, 1; Kamai, G.; Usacheva, G.M. *Russ. Chem. Rev.* ***1966***, *35*, 601.

[45] For a review of chiral phosphorus compounds, see Valentine, Jr., D.J., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, ***1984***, pp. 263–312.

[46] Horner, L.; Fuchs, H. *Tetrahedron Lett.* ***1962***, 203.

esters, sulfonium salts, and sulfites. Examples of each of these have been resolved.[47] 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 $[\alpha]280 = +0.71°$.[48] A computational study indicates that base-catalyzed inversion at sulfur in sulfoxides is possible via a tetrahedral intermediate.[49]

4. *Suitably Substituted Adamantanes.* Adamantanes bearing four different substituents at the bridgehead positions are chiral and optically active and **14**, for example, has been resolved.[50] 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 Fig. 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



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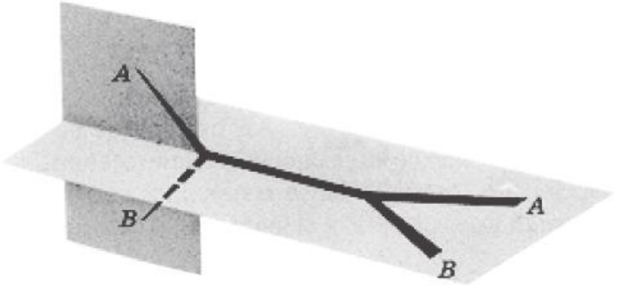

Fig. 4.2. Perpendicular disymmetric planes.

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[47] For reviews of chiral organosulfur compounds, see Andersen, K.K., in Patai, S. Rappoport, Z. Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 55–94; and, in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, ***1981***, pp. 229–312; Barbachyn, M.R.; Johnson, C.R., in Morrison, J.D. *Asymmetric Synthesis* Vol. 4, Academic Press, NY, ***1984***, pp. 227–261; Cinquini, M.; Cozzi, F.; Montanari, F., in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*; Elsevier, NY, ***1985***, pp. 355–407; Mikoł ajczyk, M.; Drabowicz, J. *Top. Stereochem.* ***1982***, *13*, 333.

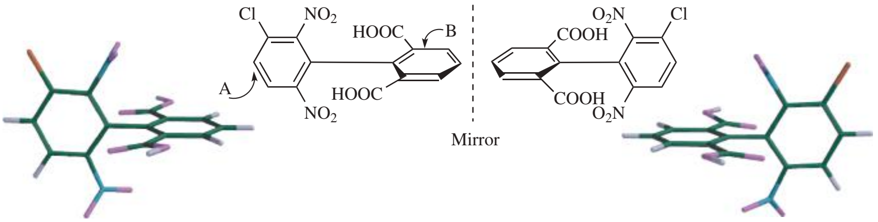
[48] Andersen, K.K.; Colonna, S.; Stirling, C.J.M. *J. Chem. Soc. Chem. Commun.* ***1973***, 645.

[49] Balcells, D.; Maseras, F.; Khiar, N. *Org. Lett.* ***2004***, *6*, 2197.

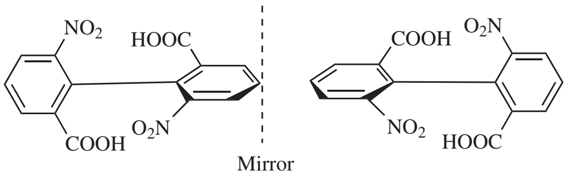
[50] Hamill, H.; McKervey, M.A. *Chem. Commun.* ***1969***, 864; Applequist, J.; Rivers, P.; Applequist, D.E. *J. Am. Chem. Soc.* ***1969***, *91*, 5705.

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.[51] For example, the activation energy (rotational barrier) for the enantiomerization process was determined, $\Delta G^{\ddagger} = 21.8 \pm 0.1\,\text{kcal mol}^{-1}$, for the chiral 2-carboxy-2′-methoxy-6-nitrobiphenyl.[52] 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 the biaryls:



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 can be separated only because rotation about single bonds is prevented or greatly slowed are called *atropisomers*.[53] 9,9′-Bianthryls also show hindered rotation and exhibit atropisomers.[54]

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′-bis-sulfonic acid.[55] In some cases, the groups may be large enough to slow rotation greatly but not to prevent it

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[51] 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, D.M. *Prog. Stereochem.* ***1969***, *4*, 1.

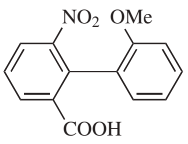
[52] Ceccacci, F.; Mancini, G.; Mencarelli, P.; Villani, C. *Tetrahedron Asymmetry* ***2003***, *14*, 3117.

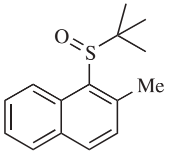
[53] For a review, see Ō ki, M. *Top. Stereochem.* ***1983***, *14*, 1.

[54] Becker, H.-D.; Langer, V.; Sieler, J.; Becker, H.-C. *J. Org. Chem.* ***1992***, *57*, 1883.

[55] Patterson, W.I.; Adams, R. *J. Am. Chem. Soc.* ***1935***, *57*, 762.

completely. In such cases, optically active compounds can be prepared that


15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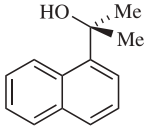
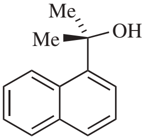
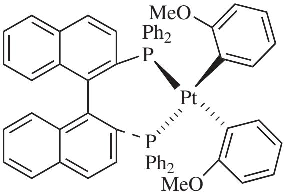
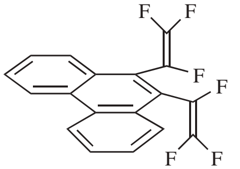

17a

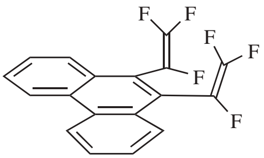

17b


18

slowly racemize on standing. Thus, **15** loses its optical activity with a half-life of 9.4 min in ethanol at 25°C.[56] 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.[57]

Atropisomerism occurs in other systems as well, including monopyrroles.[58] Sulfoxide **16**, for example, forms atropisomers with an interconversion barrier with its atropisomer of 18–19 kcal mol^{-1}.[59] The atropisomers of hindered naphthyl alcohols, such as **17** exist as the *sp*-atropisomer (**17a**) and the *ap*-atropisomer (**17b**).[60] Atropisomers can also be formed in organometallic compounds, such as the bis(phosphinoplatinum) complex (see **18**), generated by reaction with R-BINAP (see p. 1801).[61]


19a


19b

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[56] Stoughton, R.W.; Adams, R. *J. Am. Chem. Soc.* ***1932***, *54*, 4426.

[57] For a monograph on the detection and measurement of restricted rotations, see Ō ki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***.

[58] Boiadjiev, S.E.; Lightner, S.A. *Tetrahedron Asymmetry* ***2002***, *13*, 1721.

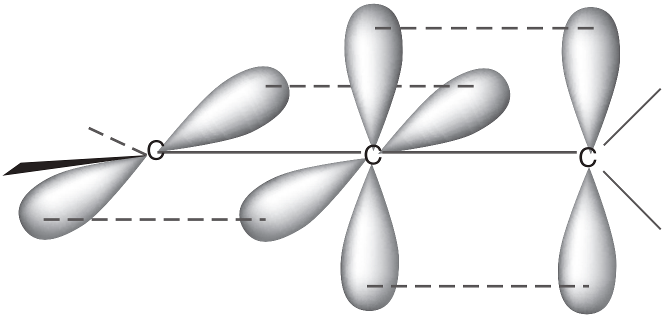
[59] Casarini, D.; Foresti, E.; Gasparrini, F.; Lunazzi, L.; Macciantelli, D.; Misiti, D.; Villani, C. *J. Org. Chem.* ***1993***, *58*, 5674.

[60] Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* ***1997***, *62*, 3315.

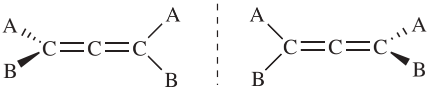
[61] Alcock, N.W.; Brown, J.M.; Pérez-Torrente, J.J. *Tetrahedron Lett.* ***1992***, *33*, 389. See also, Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J.J.; Yamanaka, M. *Synlett* ***2002***, 1561.

It is possible to isolate isomers in some cases, often due to restricted rotation. In 9,10-bis(trifluorovinyl)phenanthrene (**19**) torsional diastereomers (see p. 163) are formed. The value of K for interconversion of **19a** and **19b** is 0.48, with $\Delta G^\circ = 15.1\ \text{kcal mol}^{-1}$.[62] The ability to isolate atropisomers can depend on interactions with solvent, as in the isolation of atropisomeric colchicinoid alkaloids, which have been isolated, characterized, and their dichroic behavior described.[63]

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 Fig. 4.2: Like biphenyls, allenes are chiral only if both sides are unsymmetrically substituted.[64] For example,



These cases are completely different from the cis–trans isomerism of compounds with one double bond (p. 182). 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.



Mirror

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

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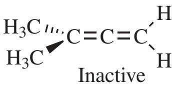
[62] Dolbier Jr., W.R.; Palmer, K.W. *Tetrahedron Lett.* ***1992***, *33*, 1547.

[63] Cavazza, M.; Zandomeneghi, M.; Pietra, F. *Tetrahedron Lett.* ***2000***, *41*, 9129.

[64] For reviews of allene chirality, see Runge, W., in Landor, S.R. *The Chemistry of the Allenes*, Vol. 3, Academic Press, NY, ***1982***, pp. 579–678, and, in Patai, S. *The Chemistry of Ketenes, Allenes, and Related Compounds*, pt. 1, Wiley, NY, ***1980***, pp. 99–154; Rossi, R.; Diversi, P. *Synthesis* ***1973***, 25.

exist, the situation is analogous to that in the allenes and optical activity is possible. Compound **20** has been resolved.[65]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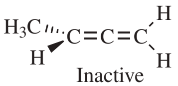
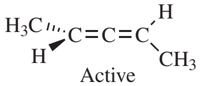
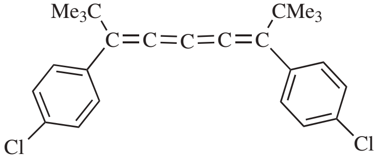

Inactive


Active

Among other types of compounds that contain the system illustrated in Fig. 4.2 and that are similarly chiral if both sides are dissymmetric are spiranes (e.g., **21**) and compounds with exocyclic double bonds (e.g., **22**). Atropisomerism exists in (1,5)-bridgedcalix[8]arenes (see p. 123).[66]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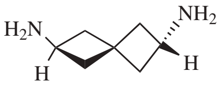
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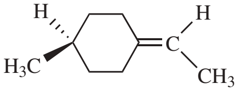
22

6. *Chirality Due to a Helical Shape*.[67] 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,[68] in which one side of the molecule must lie above the other because of crowding.[69] The rotational barrier for helicene is ~22.9 kcal mol^{-1}, and is significantly higher when substituents are present.[70] It has been shown that the dianion of helicene retains its chirality.[71] Chiral discrimination of helicenes is possible.[72] 1,16-Diazo[6]helicene has also been prepared and, interestingly, does not act as a proton sponge (see p. 386) because the helical structure leaves the basic nitrogen atoms too far apart. Heptalene is another compound that is not planar (p. 67). Its twisted structure makes it

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[65] Nakagawa, M.; Shing ū, K.; Naemura, K. *Tetrahedron Lett.* ***1961***, 802.

[66] Consoli, G.M.L.; Cunsolo, F.; Geraci, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* ***2002***, *4*, 2649.

[67] For a review, see Meurer, K.P.; Vögtle, F. *Top. Curr. Chem.* ***1985***, *127*, 1. See also Laarhoven, W.H.; Prinsen, W.J.C. *Top. Curr. Chem.* ***1984***, *125*, 63; Martin, R.H. *Angew. Chem. Int. Ed.* ***1974***, *13*, 649.

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

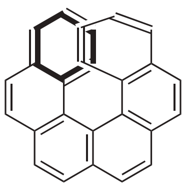
[69] For reviews of the helicenes, see Laarhoven, W.H.; Prinsen, W.J.C. *Top. Curr. Chem.* ***1984***, *125*, 63; Martin, R.H. *Angew. Chem. Int. Ed.* ***1974***, *13*, 649.

[70] Janke, R.H.; Haufe, G.; Würthwein, E.-U.; Borkent, J.H. *J. Am. Chem. Soc.* ***1996***, *118*, 6031.

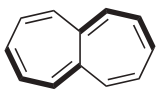
[71] Frim, R.; Goldblum, A.; Rabinovitz, M. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 267.

[72] Murguly, E.; McDonald, R.; Branda, N.R. *Org. Lett.* ***2000***, *2*, 3169.

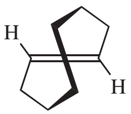
chiral, but the enantiomers rapidly interconvert.[73]



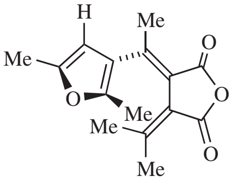
Hexahelicene



Heptalene



trans-Cyclooctene



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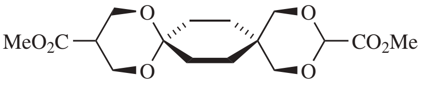
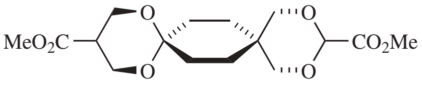


24a



24b

trans-Cyclooctene (see also, p. 184) also exhibits helical chirality because the carbon chain must lie above the double bond on one side and below it on the other.[74] Similar helical chirality also appears in fulgide **23**[75] and dispiro-1,3-dioxane, **24**, shows two enantiomers, **24a** and **24b**.[76]

7. *Optical Activity Caused by Restricted Rotation of Other Types*. Substituted paracyclophanes may be optically active[77] and **25**, for example, has been resolved.[78] In this case, chirality 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., **26**) have been prepared.[79] Another cyclophane[80] with a different type of chirality is [12][12]paracyclophane (**27**), where the chirality arises from the relative orientation of the two rings attached to the central benzene ring.[81] An aceytlenic cyclophane was shown to have helical chirality.[82] Metallocenes substituted with at least two different groups on one ring are also chiral.[83]

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[73] Staab, H.A.; Diehm, M.; Krieger, C. *Tetrahedron Lett.* ***1994***, *35*, 8357.

[74] Cope, A.C.; Ganellin, C.R.; Johnson Jr., H.W.; Van Auken, T.V.; Winkler, H.J.S. *J. Am. Chem. Soc.* ***1963***, *85*, 3276. Also see Levin, C.C.; Hoffmann, R. *J. Am. Chem. Soc.* ***1972***, *94*, 3446.

[75] Yokoyama, Y.; Iwai, T.; Yokoyama, Y.; Kurita, Y. *Chem. Lett.* ***1994***, 225.

[76] Grosu, I.; Mager, S.; Plé, G.; Mesaros, E. *Tetrahedron* ***1996***, *52*, 12783.

[77] For an example, see Rajakumar, P.; Srisailas, M. *Tetrahedron* ***2001***, *57*, 9749.

[78] Blomquist, A.T.; Stahl, R.E.; Meinwald, Y.C.; Smith, B.H. *J. Org. Chem.* ***1961***, *26*, 1687. For a review of chiral cyclophanes and related molecules, see Schlögl, K. *Top. Curr. Chem.* ***1984***, *125*, 27.

[79] Nakazaki, M.; Yamamoto, K.; Tanaka, S.; Kametani, H. *J. Org. Chem.* ***1977***, *42*, 287. Also see Pelter, A.; Crump, R.A.N.C.; Kidwell, H. *Tetrahedron Lett.* ***1996***, *37*, 1273. for an example of a chiral [2.2]paracyclophane.

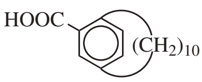
[80] For a treatise on the quantitative chirality of helicenes, see Katzenelson, O.; Edelstein, J.; Avnir, D. *Tetrahedron Asymmetry* ***2000***, *11*, 2695.

[81] Chan, T.-L.; Hung, C.-W.; Man, T.-O.; Leung, M.-k. *J. Chem. Soc. Chem. Commun.* ***1994***, 1971.

[82] Collins, S.K.; Yap, G.P.A.; Fallis, A.G. *Org. Lett.* ***2000***, *2*, 3189.

[83] For reviews on the stereochemistry of metallocenes, see Schlögl, K. *J. Organomet. Chem.* ***1986***, *300*, 219, *Top. Stereochem.* ***1967***, *1*, 39; *Pure Appl. Chem.* ***1970***, *23*, 413.

Several hundred such compounds have been resolved, one example



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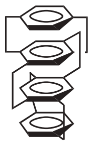

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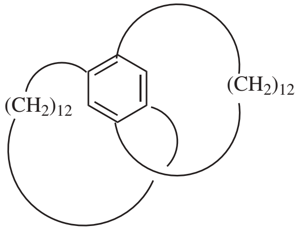

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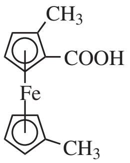

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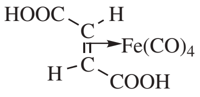

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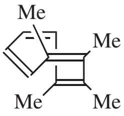
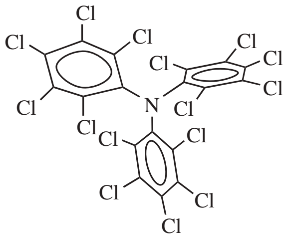
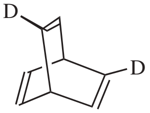


30

being **28**. Chirality is also found in other metallic complexes of suitable geometry.[84] For example, fumaric acid–iron tetracarbonyl (**29**) has been resolved.[85] 1,2,3,4-Tetramethylcyclooctatetraene (**30**) is also chiral.[86] This molecule, which exists in the tub form (p. 71), has



Perchlorotriphenylamine



31

neither a plane nor an alternating axis of symmetry. Another compound that is chiral solely because of hindered rotation is the propeller-shaped perchlorotriphenylamine, which has been resolved.[87] The 2,5-dideuterio

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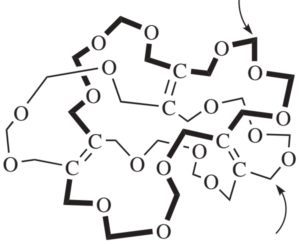
[84] For reviews of such complexes, see Paiaro, G. *Organomet. Chem. Rev. Sect. A* ***1970***, *6*, 319.

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

[86] Paquette, L.A.; Gardlik, J.M.; Johnson, L.K.; McCullough, K.J. *J. Am. Chem. Soc.* ***1980***, *102*, 5026.

[87] Okamoto, Y.; Yashima, E.; Hatada, K.; Mislow, K. *J. Org. Chem.* ***1984***, *49*, 557. For a conformational study concerning stereomutation of the helical enantiomers of trigonal carbon diaryl-substituted compounds by dynamic NMR, see Grilli, S.; Lunazzi, L.; Mazzanti, A.; Casarini, D.; Femoni, C. *J. Org. Chem.* ***2001***, *66*, 488.

derivative (**31**) of barrelene is chiral, although the parent hydrocarbon and the monodeuterio derivative are not. Compound **25** has been prepared in optically active form[88] and is another case where chirality is due to isotopic substitution.



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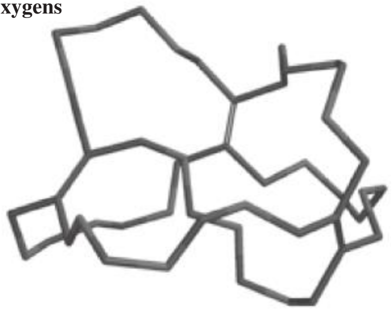
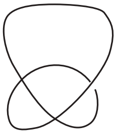


33

The main molecular chain in compound **32** has the form of a Möbius strip (see Fig. 15.7 and 3D model **33**).[89] This molecule has no stereogenic carbons, nor does it have a rigid shape a plane nor an alternating axis of symmetry. However, **32** has been synthesized and has been shown to be chiral.[90] Rings containing 50 or more members should be able to exist as knots (**34**, and see **39** on p. 133 in Chapter 3). Such a knot would be nonsuperimposable on its mirror image. Calixarenes,[91] crown ethers,[92] catenanes, and rotaxanes (see p. 131) can also be chiral if suitably substituted.[93] For example, **40** and **41** are nonsuperimposable mirror images.



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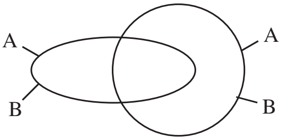

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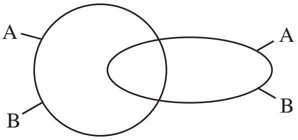

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[88] Lightner, D.A.; Paquette, L.A.; Chayangkoon, P.; Lin, H.; Peterson, J.R.*J. Org. Chem.* ***1988***, *53*, 1969.

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

[90] Walba, D.M.; Richards, R.M.; Haltiwanger, R.C. *J. Am. Chem. Soc.* ***1982***, *104*, 3219.

[91] Iwanek, W.; Wolff, C.; Mattay, J. *Tetrahedron Lett.* ***1995***, *36*, 8969.

[92] de Vries, E.F.J.; Steenwinkel, P.; Brussee, J.; Kruse, C.G.; van der Gen, A. *J. Org. Chem.* ***1993***, *58*, 4315; Pappalardo, S.; Palrisi, M.F. *Tetrahedron Lett.* ***1996***, *37*, 1493; Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* ***1996***, *37*, 7627.

[93] For a discussion of the stereochemistry of these compounds, see Schill, G. *Catenanes*, *Rotaxanes*, *and Knots*; Academic Press, NY, ***1971***, pp. 11–18.

Creation of a Stereogenic Center

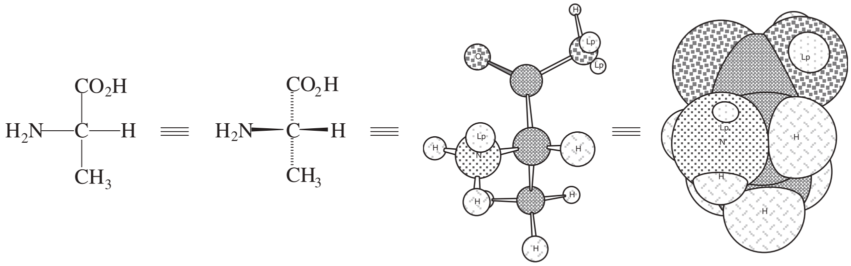
Any structural feature of a molecule that gives rise to optical activity may be called a *stereogenic center* (the older term is chiral center) In many reactions, a new chiral center is created, for example,

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

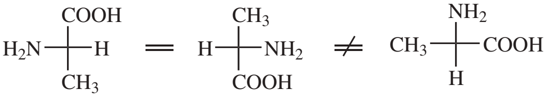
If the reagents and reaction conditions are all symmetrical, the product must be a racemic mixture. No optically active material can be created if all starting materials and conditions are optically inactive.[94] This statement also holds when one begins with a racemic mixture. Thus racemic 2-butanol, 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 Fig. 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.



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°, although 180° rotation is permissible:

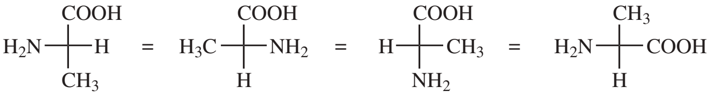


$$\begin{array}{c}COOH\\ H_2N-\!\!\!+\!\!\!-H\\ CH_3\end{array} \;=\; \begin{array}{c}CH_3\\ H-\!\!\!+\!\!\!-NH_2\\ COOH\end{array} \;\neq\; \begin{array}{c}NH_2\\ CH_3-\!\!\!+\!\!\!-COOH\\ H\end{array}$$

---

[94] 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, R.E.; Wilson, K.R. *J. Chem. Educ.* ***1973***, *50*, 455.

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):

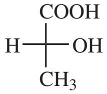


However, the *interchange* of any two groups results in the conversion of an enantiomer into its mirror image (this applies to models as well as to the Fischer projections).

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, 3D pictures must be used. With models or 3D 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 **37** and the other **38**. How do we know which is which? Chemists in the early part of the twentieth 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 **39** and given the label D. The (−) isomer, designated to be **39**, 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:



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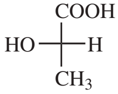

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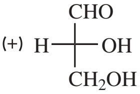

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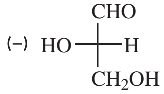

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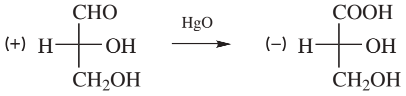

Since it is highly improbable that the configuration at the central carbon changed, it can be concluded that (−)-glyceric acid has the same configuration as (+)-glyceraldehyde and therefore (−)-glyceric acid is also called D. This example emphasizes that molecules with the same configuration need not 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 **37**, 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.[95] When a compound has been placed in the D or L series, its *absolute configuration* is said to be known.[96]

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.[97] 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.

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.[98] For our purposes, we confine ourselves to only a few

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[95] 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.

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

[97] Bijvoet, J.M.; Peerdeman, A.F.; van Bommel, A.J. *Nature (London)* ***1951***, *168*, 271. For a list of organic structures whose absolute configurations have been determined by this method, see Neidle, S.; Rogers, D.; Allen, F.H. *J. Chem. Soc. C* ***1970***, 2340.

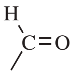
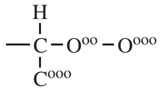
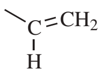
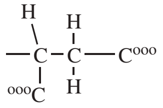
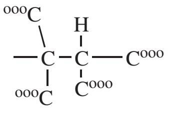
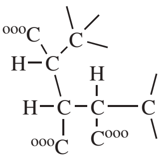
[98] For descriptions of the system and sets of sequence rules, see *Pure Appl. Chem.* ***19767***, *45*, 13; *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, ***1979*** (the Blue Book); Cahn, R.S.; Ingold, C.K.; Prelog, V. *Angew. Chem. Int. Ed.* ***1966***, *5*, 385; Cahn, R.S. *J. Chem. Educ.* ***1964***, *41*, 116; Fernelius, W.C.; Loening, K.; Adams, R.M. *J. Chem. Educ.* ***1974***, *51*, 735. See also, Prelog, V.; Helmchen, G. *Angew. Chem. Int. Ed.* ***1982***, *21*, 567. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 101–147. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 13–20.

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 although 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, and so on.
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 $–HNHMe_2$ 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 (e.g., ^{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). 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

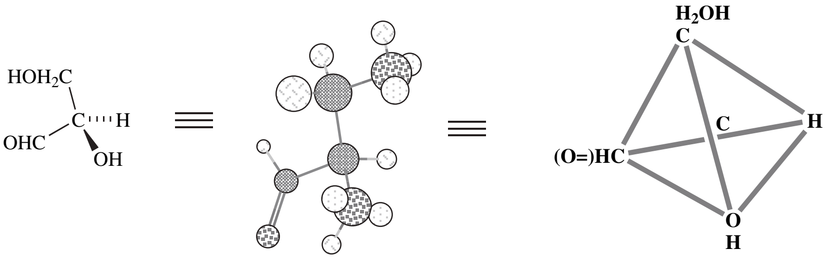
TABLE 4.1. How Four Common Groups Are Treated in the Cahn–Ingold–Prelog System

Group	Treated as If It Were	Group	Treated as If It Were
			
$—C\equiv C—H$		$—C_6H_5$	

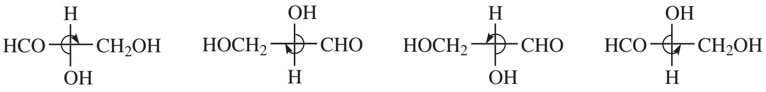
oxygen outranks three carbons and three carbons outrank two carbons and a hydrogen. To classify the remaining two groups we must proceed further along the chains. We note that $-C_6H_5$ has two of its (C, C, C) carbons connected to (C, C, H), while the third is ($_{000}$) and is thus preferred to $-C{\equiv}CH$, 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, $C{\equiv}CH$, *tert*-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*):

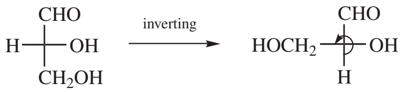


Note that when a compound is written in the Fischer projection, the configuration can easily be determined without constructing the model.[99] If the lowest ranking group is either at the top or the bottom (because these are the two positions pointing away from the viewer), the (*R*) configuration is present if the other three groups in descending order are clockwise, for example,



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

If the lowestranking 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, for example:



(*S*)-Glyceraldehyde

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

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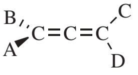
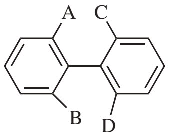
[99] For a discussion of how to determine (*R*) or (*S*) from other types of formula, see Eliel, E.L. *J. Chem. Educ.* ***1985***, *62*, 223.

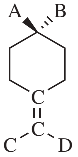
The Cahn–Ingold–Prelog system is unambiguous and easily applicable in most cases. Whether to call an enantiomer (*R*) or (*S*) does not depend on correlations, but the configuration must be known before the system can be applied and this does depend on correlations. The Cahn–Ingold–Prelog system has also been extended to chiral compounds that do not contain stereogenic centers, but have a chiral axis.[100] Compounds having a chiral axis include unsymmetrical allenes, biaryls that exhibit atropisomerism (see p. 146), and alkylidene cyclohexane derivatives, molecular propellers and gears, helicenes, cyclophanes, annulenes, *trans*-cycloalkenes, and metallocenes. A series of rules have been proposed to address the few cases where the rules can be ambiguous, as in cyclophanes and other systems.[101]



Allenes



Biaryls

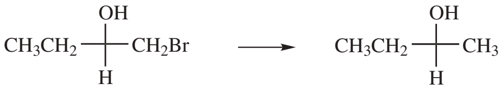


Alkylidenecyclohexanes

Methods of Determining Configuration[102]

In all the methods,[103] 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. 154). Since the chiral



$$CH_3CH_2\overset{OH}{\underset{H}{-\!\!\!\!+\!\!\!\!-}}CH_2Br \longrightarrow CH_3CH_2\overset{OH}{\underset{H}{-\!\!\!\!+\!\!\!\!-}}CH_3$$

(*R*) (*S*)

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[100] Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1119–1190. For a discussion of these rules, as well as for a review of methods for establishing configurations of chiral compounds not containing a stereogenic center, see Krow, G. *Top. Stereochem.* ***1970***, *5*, 31.

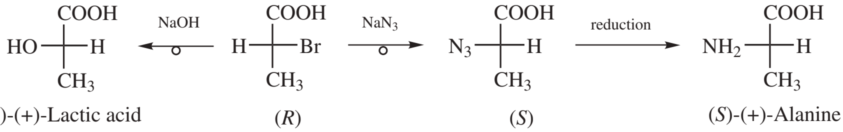
[101] Dodziuk, H.; Mirowicz, M. *Tetrahedron Asymmetry* ***1990***, *1*, 171; Mata, P.; Lobo, A.M.; Marshall, C.; Johnson, A.P. *Tetrahedron Asymmetry* ***1993***, *4*, 657; Perdih, M.; Razinger, M. *Tetrahedron Asymmetry* ***1994***, *5*, 835.

[102] For a monograph, see Kagan, H.B. *Determination of Configuration by Chemical Methods* (Vol. 3 of Kagan, H.B. *Stereochemistry*), Georg Thieme Publishers: Stuttgart, ***1977***. For reviews, see Brewster, J.H., in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 3, Wiley, NY, ***1972***, pp. 1–249; Klyne, W.; Scopes, P.M. *Prog. Stereochem.* ***1969***, *4*, 97; Schlenk Jr., W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 139. For a review of absolute configuration of molecules in the crystalline state, see Addadi, L.; Berkovitch-Yellin, Z.; Weissbuch, I.; Lahav, M.; Leiserowitz, L. *Top. Stereochem.* ***1986***, *16*, 1.

[103] Except the X-ray method of Bijvoet.

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 disturbing the chiral center, the product is the (*S*) isomer, even although 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 S_N2 mechanism proceeds with inversion of configuration at an asymmetric carbon (see p. 426) It was by a series of such transformations that lactic acid was related to alanine:

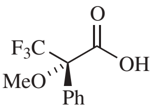


See also, the discussion on p. 427.

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.[86]



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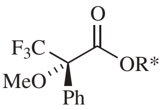

42

6. One of the most useful methods for determining enantiomeric composition is to derivatize the alcohol with a chiral nonracemic reagent and examine the ratio of resulting diastereomers by gas chromatography (gc).[104] There are many derivatizing agents available, but the most widely used are derivatives of α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA, Mosher's acid,

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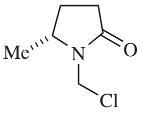
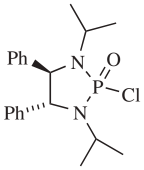
[104] Parker, D. *Chem. Rev.* ***1991***, *91*, 1441.

41).[105] Reaction with a chiral nonracemic alcohol (R*OH, where R* is a group containing a stereogenic center) generates a Mosher's ester (**42**) that can be analyzed for diastereomeric composition by ^{1}H or ^{19}F NMR, as well as by chromatographic techniques.[106] Alternatively, complexation with lanthanide shift reagents allow the signals of the MTPA ester to be resolved and used to determine enantiomeric composition.[107] This nmr method, as well as other related methods,[108] are effective for determining the absolute configuration of an alcohol of interest (R*OH).[109] Two, of many other reagents that have been developed to allow the enantiopurity of alcohols and amines to be determined include **43** and **44**. Chloromethyl lactam **43** reacts with R*OH or R*NHR (R*NH$_2$),[110] forming derivatives that allow analysis by ^{1}H NMR and **44** reacts with alkoxides (R*O^{-})[111] to form a derivative that can be analyzed by ^{31}P NMR. For a more detailed discussion of methods to determine optical purity (see p. 179).



43



44

7. Other methods have also been used for determining absolute configuration in a variety of molecules, including optical rotatory dispersion,[112] circular dichroism,[113,114] and asymmetric synthesis (see p. 166). Optical rotatory dispersion (ORD) is a measurement of specific rotation, [α], as a function of wavelength.[115] The change of specific rotation [α] or molar rotation [Φ]

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[105] Dale, J. A.; Dull, D.L.; Mosher, H. S. *J. Org. Chem.* ***1969***, 34, 2543; Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* ***1973***, *95*, 512.

[106] See Mori, K.; Akao, H. *Tetrahedron Lett.* ***1978***, 4127; Plummer, E.L.; Stewart, T.E.; Byrne, K.; Pearce, G.T.; Silverstein, R.M. *J. Chem. Ecol.* ***1976***, *2*, 307. See also Seco, J.M.; Quiñoá, E.; Riguera, R. *Tetrahedron Asymmetry* ***2000***, *11*, 2695.

[107] Yamaguchi, S.; Yasuhara, F.; Kabuto, K. *Tetrahedron* ***1976***, *32*, 1363; Yasuhara, F.; Yamaguchi, S. *Tetrahedron Lett.* ***1980***, *21*, 2827; Yamaguchi, S.; Yasuhara, F. *Tetrahedron Lett.* ***1977***, 89.

[108] Latypov, S.K.; Ferreiro, M.J.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* ***1998***, *120*, 4741; Latypov, S.K.; Seco, J.M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* ***1995***, *60*, 1538.

[109] Seco, J.M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* ***2004***, *104*, 17.

[110] Smith, M.B.; Dembofsky, B.T.; Son, Y.C. *J. Org. Chem.* ***1994***, *59*, 1719; Latypov, S.K.; Riguera, R.; Smith, M.B.; Polivkova, J. *J. Org. Chem.* ***1998***, *63*, 8682.

[111] Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* ***1992***, *57*, 1224.

[112] See Ref. 268 for books and reviews on optical rotatory dispersion and CD. For predictions about anomalous ORD, see Polavarapu, P.L.; Zhao, C. *J. Am. Chem. Soc.* ***1999***, *121*, 246.

[113] Gawroński, J.; Grajewski, J. *Org. Lett.* ***2003***, *5*, 3301. See Ref. 268.

[114] For a determination of the absolute configuration of chiral sulfoxides by vibrational circular dichroism spectroscopy, see Stephens, P.J.; Aamouche, A.; Devlin, F.J.; Superchi, S.; Donnoli, M.I.; Rosini, C. *J. Org. Chem.* ***2001***, *66*, 3671.

[115] Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1203, 999–1003.

with wavelength is measured, and a plot of either versus wavelength is often related to the sense of chirality or the substance under consideration. In general, the absolute value of the rotation increases as the wavelength decreases. The plot of circular dichroism (CD) is the differential absorption of left and right circularly polarized radiation by a nonracemic sample, taking place only in spectral regions in which absorption bands are found in the isotropic or visible electronic spectrum.[116] The primary application of both ORD and CD is for the assignment of configuration or conformation.[117] Configurational and conformational analysis have been carried out using infrared and vibrational circular dichroism (VCD) spectroscopies.[118]

In one example of the use of these techniques, one of the more effective methods for derivatizing 1,2-diols is the method employing dimolybdenum tetraacetate [$Mo_2(AcO)_4$] developed by Snatzke and Frelek.[119] Exposure of the resulting complex to air leads, in most cases, to a significant induced CD spectrum (known as ICD). The method can be used for a variety of 1,2-diols.[120]

8. Kishi and co-worker's[121] developed an NMR database of various molecules in chiral solvents, for the assignment of relative and absolute stereochemistry without derivatization or degradation. Kishi referred to this database as a "universal NMR database."[122] The diagram provided for diols **45** illustrates the method. The graph presents the difference in carbon chemical shifts between the average and the values for **45** (100 MHz) in DMBA (*N*,α-dimethylbenzylamine). Spectra were recorded in both enantiomers of the solvent, where the solid bar was recorded in (*R*)-DMBA and the shaded bar in (*S*)-DMBA. The *X*- and *Y*-axes represent carbon number and $\Delta\delta$ ($\delta_{\mathbf{45a\text{-}h}} - \delta_{ave}$ in ppm), respectively. The graphs are taken from "the ^{13}C NMR database in (*R*)- and (*S*)-DMBA as a deviation in chemical shift for each carbon of a given diastereomer from the average chemical shift of the carbon in question. Each diastereomer exhibits an almost identical NMR profile for (*R*)- and (*S*)-DMBA but shows an NMR profile distinct and differing from the other diastereomers, demonstrating that the database in (*R*)- and/or (*S*)-DMBA can

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[116] Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1195, 1003–1007.

[117] Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1007–1071; Nakanishi, K.; Berova, N.; Woody, R.W. *Circular Dichroism: Principles and Applications*, VCH, NY, ***1994***; Purdie, N.; Brittain, H.G. *Analytical Applications of Circular Dichroism*, Elsevier, Amsterdam, The Netherlands, ***1994***.

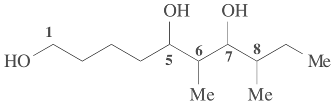
[118] Devlin, F.J.; Stephens, P.J.; Osterle, C.; Wiberg, K.B.; Cheeseman, J.R.; Frisch, M.J. *J. Org. Chem.* ***2002***, *67*, 8090.

[119] Frelek, J.; Geiger, M.; Voelter, W. *Curr. Org. Chem.* ***1999***, *3*, 117–146 and references cited therein.; Snatzke, G.; Wagner, U.; Wolff, H. P. *Tetrahedron* ***1981***, *37*, 349; Frelek, J.; Snatzke, G. *Fresenius̒ J. Anal. Chem.* ***1983***, *316*, 261; Frelek, J.; Pakulski, Z.; Zamojski, A. *Tetrahedron: Asymmetry* ***1996***, *7*, 1363; Frelek, J.; Ikekawa, N.; Takatsuto, S.; Snatzke, G. *Chirality* ***1997***, *9*, 578.

[120] Di Bari, L.; Pescitelli, G.; Pratelli, C.; Pini, D.; Salvadori, P. *J. Org. Chem.* ***2001***, *66*, 4819.

[121] Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2245; Hayashi, N.; Kobayashi, Y.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2249; Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2253.

[122] Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 2076.



45

(a) C5(S), C6(R), C7(S), C8(R)
(b) C5(S), C6(R), C7(R), C8(S)
(c) C5(S), C6(R), C7(S), C8(S)
(d) C5(S), C6(R), C7(R), C8(R)
(e) C5(S), C6(S), C7(R), C8(S)
(f) C5(R), C6(S), C7(R), C8(S)
(g) C5(R), C6(S), C7(S), C8(S)
(h) C5(R), C6(S), C7(R), C8(R)

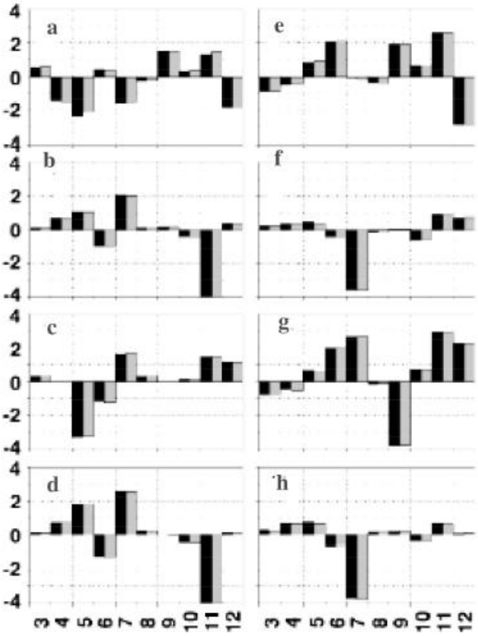


Fig. 4.3. Proton NMR analysis for assignment of stereochemistry.

be used for prediction of the relative stereochemistry of structural motifs in an intact form."[123]

A ^{1}H NMR analysis method has been developed that leads to the assignment of the stereochemistry of β-hydroxy ketones, by visual inspection of the ABX patterns for the (R)-methylene unit of the β-hydroxyketones.[124] Since β-hydroxy ketones are derived from the aldol reaction (see p. 1339), this new method is particularly useful in organic synthesis. A method has also been developed that uses ^{13}C NMR to determine the relative stereochemistry of 2,3-dialkylpentenoic acids.[125]

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.[126]

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[123] Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2245.

[124] Roush, W.R.; Bannister, T.D.; Wendt, M.D.; VanNieuwenhze, M.S.; Gustin, D.J.; Dilley, G.J.; Lane, G.C.; Scheidt, K.A.; Smith III, W.J. *J. Org. Chem.* ***2002***, *67*, 4284.

[125] Hong, S.-p.; McIntosh, M.C. *Tetrahedron* ***2002***, *57*, 5055.

[126] For longer, nontheoretical discussions, see Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 93–94, 992–999; Wheland, G.W. *Advanced Organic CHemistry*, 3rd ed., Wiley, NY, ***1960***, pp. 204–211. For theoretical discussions, see Caldwell, D.J.; Eyring, H. *The Theory of Optical Activity* Wiley, NY, ***1971***; Buckingham, A.D.; Stiles, P.J. *Acc. Chem. Res.* ***1974***, *7*, 258; Mason, S.F. *Q. Rev. Chem. Soc.* ***1963***, *17*, 20.

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- and the other is 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 toward 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,[127] 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 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, even though the molecules are present in large numbers 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 although 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.

An interesting phenomenon was observed when the CD of chiral molecules was measured in achiral solvents. The chiral solvent contributed as much as 10–20% to the CD intensity in some cases. Apparently, the chiral compound can induce a solvation structure that is chiral, even when the solvent molecules themselves are achiral.[128]

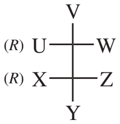
---

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

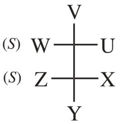
[128] Fidler, J.; Rodger, P.M.; Rodger, A. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 235.

MOLECULES WITH MORE THAN ONE STEREOGENIC CENTER

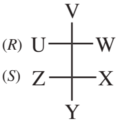
When a molecule has two stereogenic centers, each has its own configuration and can be classified (*R*) or (*S*) by the Cahn–Ingold–Prelog method. There are a total of four isomers, since the first center may be (*R*) or (*S*) and so may the second. Since a molecule can have only one mirror image, only 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]. Both **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*. Since **C** and **D** are enantiomers, they must have identical properties, except as noted on p. 138; 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).



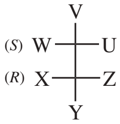
A



B

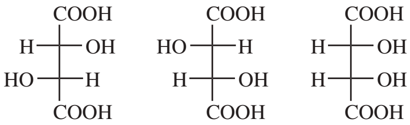


C



D

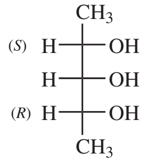
It is now possible to see why, as mentioned on p. 138, enantiomers react at different rates with other chiral molecules, but at the same rate with achiral molecules. In the latter case, the activated complex formed from the (*R*) enantiomer and the other molecule is the mirror image of the activated 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.



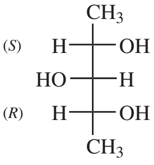
dl Pair meso

The three stereoisomers of tartaric acid

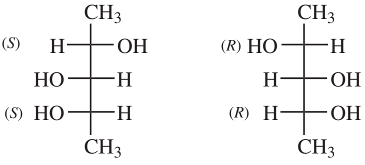
Although four is the maximum possible number of isomers when the compound has two stereogenic centers (chiral compounds without a chiral carbon, or with one chiral carbon and another type of stereogenic center, also follow the rules described here), some compounds have fewer. When the three groups on 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 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.



meso



meso



dl Pair

In most cases with more than two stereogenic 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.[129] 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 other is (*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 themselves, 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. 158–162 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 stereogenic center, but which does give relative configurations of all the stereogenic 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 (+) or (−). 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 aldohexoses are called glucose, mannose, idose, and so on, although they are all 2,3,4,5,6-pentahydroxyhexanal (in their open-chain forms). This practice was partially due to lack of knowledge

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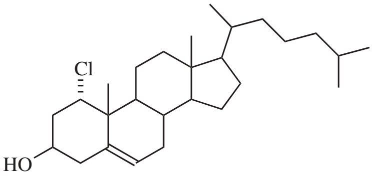
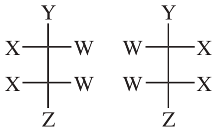
[129] For a method of generating all stereoisomers consistent with a given empirical formula, suitable for computer use, see Nourse, J.G.; Carhart, R.E.; Smith, D.H.; Djerassi, C. *J. Am. Chem. Soc.* ***1979***, *101*, 1216; ***1980***, *102*, 6289.

about which isomers had which configurations.[130] 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 a groups. An example is

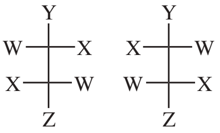


1α-Chloro-5-cholesten-3β-ol

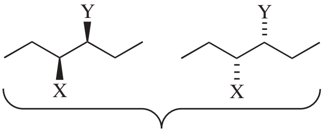
For many open-chain compounds, prefixes are used that are derived from the names of the corresponding sugars and that describe the whole system rather than each chiral center separately. Two such common prefixes are erythro- and threo-, which are applied to systems containing two asymmetric carbons when two of the groups are the same and the third is different.[131] 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[132] for designating stereoisomers[133] uses the terms syn and anti. The "main chain" of the molecule is drawn in the common zigzag manner. Then, if two non-hydrogen substituents are on the same side of the plane defined by the main chain, the designation is syn; otherwise it is anti.



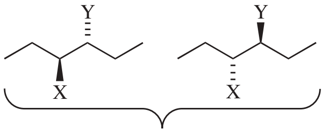
Erythro *dl* pair



Threo *dl* pair



syn *dl* Pair



anti *dl* Pair

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[130] A method has been developed for the determination of stereochemistry in six-membered chairlike rings using residual dipolar couplings. See Yan, J.; Kline, A. D.; Mo, H.; Shapiro, M. J.; Zartler, E. R. *J. Org. Chem.* ***2003***, *68*, 1786.

[131] For more general methods of designating diastereomers, see Carey, F.A.; Kuehne, M.E. *J. Org. Chem.* ***1982***, *47*, 3811; Boguslavskaya, L.S. *J. Org. Chem. USSR* ***1986***, *22*, 1412; Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed.* ***1982***, *21*, 654; Brewster, J.H. *J. Org. Chem.* ***1986***, *51*, 4751. See also Tavernier, D. *J. Chem. Educ.* ***1986***, *63*, 511; Brook, M.A. *J. Chem. Educ.* ***1987***, *64*, 218.

[132] For still another system, see Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed.* ***1982***, *21*, 654.

[133] Masamune, S.; Kaiho, T.; Garvey, D.S. *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.[134] The first way, which is more common, is to begin with a single stereoisomer, and to use a synthesis that does not affect the stereogenic center (or centers), as in the glyceraldehyde–glyceric acid example on p. 154. The optically active starting compound can be obtained by a previous synthesis, or by resolution of a racemic mixture (p. 172), 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.[135]

The other basic method is called *asymmetric synthesis*,[136] or *stereoselective synthesis*. As mentioned earlier, optically active materials cannot be created from

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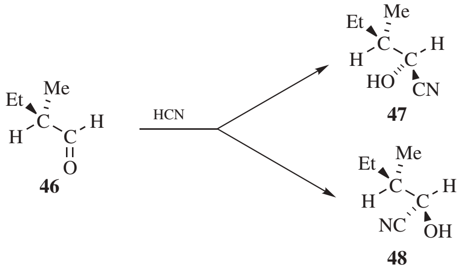
[134] For a monograph that covers both ways, including a list of commercially available optically active starting compounds, see Morrison, J.D.; Scott, J.W. *Asymmetric Synthesis* Vol. 4, Academic Press, NY, ***1984***. For a monograph covering a more limited area, see Williams, R.M. *Synthesis of Optically Active α-Amino Acids*, Pergamon, Elmsford, NY, ***1989***. For reviews on both ways, see Crosby, J. *Tetrahedron* ***1991***, *47*, 4789; Mori, K. *Tetrahedron* ***1989***, *45*, 3233.

[135] For books on the synthesis of optically active compounds starting from natural products, see Coppola, G.M.; Schuster, H.F. *Asymmetric Synthesis*, Wiley, NY, ***1987*** (amino acids as starting compounds); Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon, Elmsford, NY, ***1983*** (mostly carbohydrates as starting compounds). For reviews, see Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* ***1986***, *42*, 447; Hanessian, S. *Aldrichimica Acta* ***1989***, *22*, 3; Jurczak, J.; Gotebiowski, A. *Chem. Rev.* ***1989***, *89*, 149.

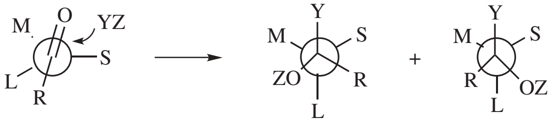
[136] For a treatise on this subject, see Morrison, J.D. *Asymmetric Synthesis* 5 vols. [Vol. 4 coedited by Scott, J.W.], Academic Press, NY, ***1983–1985***. For books, see Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***; Eliel, E.L.; Otsuka, S. *Asymmetric Reactions and Processes in Chemistry*, American Chemical Society, Washington, ***1982***; Morrison, J.D.; Mosher, H.S. *Asymmetric Organic Reactions*, Prentice-Hall, Englewood Cliffs, NJ, ***1971***, paperback reprint, American Chemical Society, Washington, ***1976***; Izumi,Y.; Tai, A. *Stereo-Differentiating Reactions*, Academic Press, NY, Kodansha Ltd. Tokyo, ***1977***. For reviews, see Ward, R.S. *Chem. Soc. Rev.* ***1990***, *19*, 1; Whitesell, J.K. *Chem. Rev.* ***1989***, *89*, 1581; Fujita, E.; Nagao, Y. *Adv. Heterocycl. Chem.* ***1989***, *45*, 1; Kochetkov, K.A.; Belikov, V.M. *Russ. Chem. Rev.* ***1987***, *56*, 1045; Oppolzer, W. *Tetrahedron* ***1987***, *43*, 1969; Seebach, D.; Imwinkelried, R.; Weber, T. *Mod. Synth. Methods* ***1986***, *4*, 125; ApSimon, J.W.; Collier, T.L. *Tetrahedron* ***1986***, *42*, 5157; Mukaiyama, T.; Asami, M. *Top. Curr. Chem.* ***1985***, *127*, 133; Martens, J. *Top. Curr. Chem.* ***1984***, *125*, 165; Duhamel, L.; Duhamel, P.; Launay, J.; Plaquevent, J. *Bull. Soc. Chim. Fr.* ***1984***, II-421; Mosher, H.S.; Morrison, J.D. *Science*, ***1983***, *221*, 1013; Schöllkopf, U. *Top. Curr. Chem.* ***1983***, *109*, 65; Quinkert, G.; Stark, H. *Angew. Chem. Int. Ed.* ***1983***, *22*, 637; Tramontini, M. *Synthesis* ***1982***, 605; Drauz, K.; Kleeman, A.; Martens, J. *Angew. Chem. Int. Ed.* ***1982***, *21*, 584; Wynberg, H. *Recl. Trav. Chim. Pays-Bas* ***1981***, *100*, 393; Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2; Valentine, Jr., D.; Scott, J.W. *Synthesis* ***1978***, 329; Kagan, H.B.; Fiaud, J.C. *Top. Stereochem.* ***1978***, *10*, 175; ApSimon, J., in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 3, Wiley, NY, ***1972***, pp. 251–408; Boyd, D.R.; McKervey, M.A. *Q. Rev. Chem. Soc*, ***1968***, *22*, 95; Goldberg, S.I. *Sel. Org. Transform.* ***1970***, *1*, 363; Klabunovskii, E.I.; Levitina, E.S. *Russ. Chem. Rev.* ***1970***, *39*, 1035; Inch, T.D. *Synthesis* ***1970***, 466; Mathieu, J.; Weill-Raynal, J. *Bull. Soc. Chim. Fr.* ***1968***, 1211; Amariglio, A.; Amariglio, H.; Duval, X. *Ann. Chim. (Paris) [14]* ***1968***, *3*, 5; Pracejus, H. *Fortschr. Chem. Forsch.* ***1967***, *8*, 493; Velluz, L.; Valls, J.; Mathieu, J. *Angew. Chem. Int. Ed.* ***1967***, *6*, 778.

inactive starting materials and conditions, except in the manner previously noted.[94] However, when a new stereogenic 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 asymmetric α carbon, *Cram's rule* predicts which of two diastereomers will predominate (diastereoselectivity).[137,138] The reaction of **46**, which has a stereogenic center at the α-carbon, and HCN can generate two possible diastereomers,



47 and **48**. If **46** is observed along its axis, it may be represented as in **49** (see p. 197), where S, M, and L stand for small, medium, and large, respectively. The oxygen of the carbonyl 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 **48** will be formed in larger amounts than **47**.



49 Major product Minor product

Another model can be used to predict diastereoselectivity, which assumes reactant-like transition states and that the separation of the incoming group

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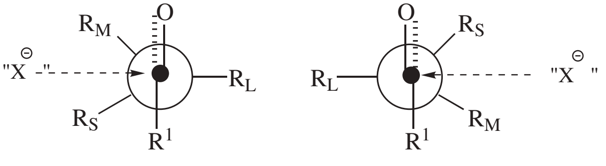
[137] Leitereg, T.J.; Cram, D.J. *J. Am. Chem. Soc.* ***1968***, *90*, 4019. For discussions, see Salem, L. *J. Am. Chem. Soc.* ***1973***, *95*, 94; Anh, N.T. *Top. Curr. Chem*, ***1980***, *88*, 145, 151–161; Eliel, E.L., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 125–155. See Smith, R.J.; Trzoss, M.; Bühl, M.; Bienz, S. *Eur. J. Org. Chem.* ***2002***, 2770.

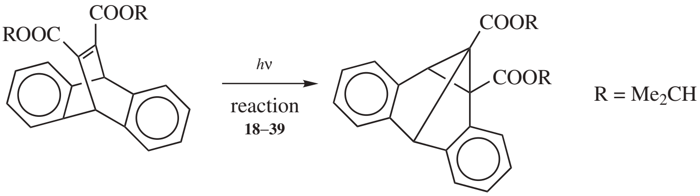
[138] For reviews, see Eliel, E.L. *The Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, ***1962***, pp. 68–74. For reviews of the stereochemistry of addition to carbonyl compounds, see Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2, pp. 22–28; Ashby, E.C.; Laemmle, J.T. *Chem. Rev.* ***1975***, *75*, 521; Goller, E.J. *J. Chem. Educ.* ***1974***, *51*, 182; Toromanoff, E. *Top. Stereochem.* ***1967***, *2*, 157.

and any electronegative substituent at the α-carbon is greatest. Transition state models **50** and **51** are used to predict diastereoselectivity in what is known as the *Felkin–Ahn Model*.[139] The so-called Cornforth model has also been presented as a model for carbonyl addition.[140]



50 **51**

Many reactions of this type are known, and in some the extent of favoritism approaches 100% (for an example see reaction **12-12**).[141] 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.



52 Not chiral **53** Optically active

In a special case of this type of asymmetric synthesis, a compound (**52**) with achiral molecules, but whose crystals are chiral, was converted by UV light to a single enantiomer of a chiral product (**53**).[142]

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, **55**.[143] In this case, >99% of the product was the (*S*) enantiomer. Compound **54** is called a *chiral auxiliary* because it is used to induce asymmetry and is then removed.

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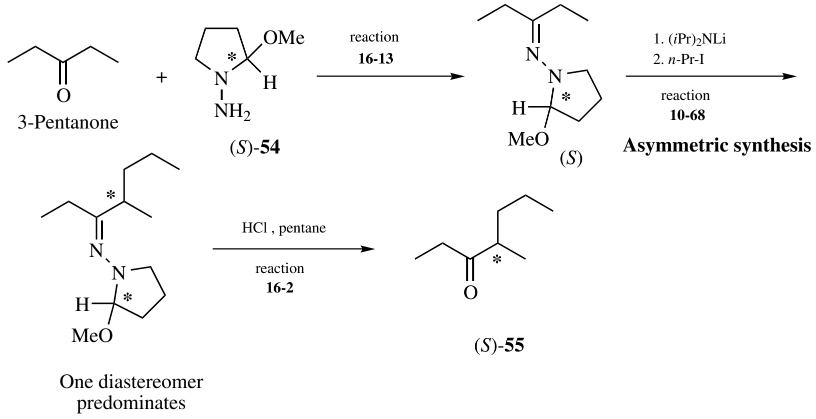
[139] Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* ***1968***, 2199.

[140] Evans, D.A.; Siska, S.J.; Cee, V.J. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1761.

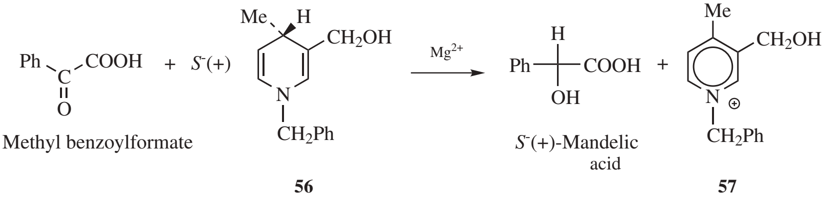
[141] For other examples and references to earlier work, see Eliel, E.L., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 125–155; Eliel, E.L.; Koskimies, J.K.; Lohri, B. *J. Am. Chem. Soc.* ***1978***, *100*, 1614; Still, W.C.; McDonald, J.H. *Tetrahedron Lett.* ***1980***, *21*, 1031; Still, W.C.; Schneider, J.A. *Tetrahedron Lett.* ***1980***, *21*, 1035.

[142] Evans, S.V.; Garcia-Garibay, M.; Omkaram, N.; Scheffer, J.R.; Trotter, J.; Wireko, F. *J. Am. Chem. Soc.* ***1986***, *108*, 5648; Garcia-Garibay, M.; Scheffer, J.R.; Trotter, J.; Wireko, F. *Tetrahedron Lett.* ***1987***, *28*, 4789. For an earlier example, see Penzien, K.; Schmidt, G.M.J. *Angew. Chem. Int. Ed.* ***1969***, *8*, 608.

[143] Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K.A.M. *Tetrahedron* ***1984***, *40*, 1345.



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.[144] Creation of a new chiral center in an inactive molecule can also be accomplished with an active reagent, although it is rare for 100% selectivity to be observed. An example[145,146] is the reduction of methyl benzoylformate



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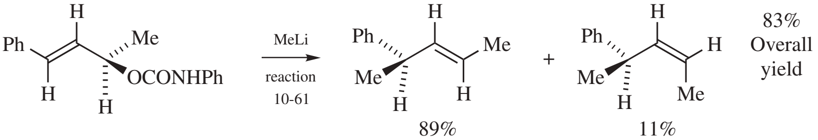
[144] See, for example, Horeau, A. *Tetrahedron Lett.* ***1961***, 506; Marquet, A.; Horeau, A. *Bull. Soc. Chim. Fr.* ***1967***, 124; Brockmann Jr., H.; Risch, N. *Angew. Chem. Int. Ed.* ***1974***, *13*, 664; Potapov, V.M.; Gracheva, R.A.; Okulova, V.F. *J. Org. Chem. USSR* ***1989***, *25*, 311.

[145] Meyers, A.I.; Oppenlaender, T. *J. Am. Chem. Soc.* ***1986***, *108*, 1989. For reviews of asymmetric reduction, see Morrison, J.D. *Surv. Prog. Chem.* ***1966***, *3*, 147; Yamada, S.; Koga, K. *Sel. Org. Transform.* ***1970***, *1*, 1. See also, Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***.

[146] For reviews, see, in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, ***1985***, the reviews by Halpern, J. pp. 41–69, Koenig, K.E. pp. 71–101, Harada, K. pp. 345–383; Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* ***1989***, *45*, 6901, pp. 6902–6916; Jardine, F.H. in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 751–775; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 53–87; Knowles, W.S. *Acc. Chem. Res.* ***1983***, *16*, 106; Brunner, H. *Angew. Chem. Int. Ed.* ***1983***, *22*, 897; Klabunovskii, E.I. *Russ. Chem. Rev.* ***1982***, *51*, 630; Čaplar, V.; Comisso, G.; Šunjić, V. *Synthesis* ***1981***, 85; Morrison, J.D.; Masler, W.F.; Neuberg, M.K. *Adv. Catal.* ***1976***, *25*, 81; Kagan, H.B. *Pure Appl. Chem.* ***1975***, *43*, 401; Bogdanović, B. *Angew. Chem. Int. Ed.* ***1973***, *12*, 954. See also Brewster, J.H. *Top. Stereochem.* ***1967***, *2*, 1, *J. Am. Chem. Soc.* ***1959***, *81*, 5475, 5483, 5493; Davis, D.D.; Jensen, F.R. *J. Org. Chem.* ***1970***, *35*, 3410; Jullien, F.R.; Requin, F.; Stahl-Larivière, H. *Nouv. J. Chim.* ***1979***, *3*, 91; Sathyanarayana, B.K.; Stevens, E.S. *J. Org. Chem.* ***1987***, *52*, 3170; Wroblewski, A.E.; Applequist, J.; Takaya, A.; Honzatko, R.; Kim, S.; Jacobson, R.A.; Reitsma, B.H.; Yeung, E.S.; Verkade, J.G. *J. Am. Chem. Soc.* ***1988***, *110*, 4144.

with optically active *N*-benzyl-3-(hydroxymethyl)-4-methyl-1,4-dihydropyridine (**56**) to produce mandelic acid that contained ~97.5% of the (*S*)-(+) isomer and 2.5% of the (*R*)-(−) isomer (for another example, see p. 1079). Note that the other product, **57**, is not chiral. Reactions like this, in which one reagent (in this case **56**) 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.[147]

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 stereogenic centers, it is possible for both centers to be created in the desired sense. This type of process is called *double asymmetric synthesis*[148] (for an example, see p. 1349).

3. *Active Catalyst or Solvent.*[149] 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 **16-23** and **15-11**),[150] the treatment of aldehydes or ketones with organometallic compounds in the presence of a chiral catalyst (see reaction **16-24**), and the conversion of alkenes to optically active epoxides by treatment with a hydroperoxide and a chiral catalyst (see reaction **15-50**). In some instances, notably in the homogeneous catalytic hydrogenation of alkenes (reaction **15-11**), the ratio of enantiomers prepared in this way is as high as 98:2.[151] Other examples of the use of a chiral catalyst or solvent are

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[147] Goering, H.L.; Kantner, S.S.; Tseng, C.C. *J. Org. Chem.* ***1983***, *48*, 715.

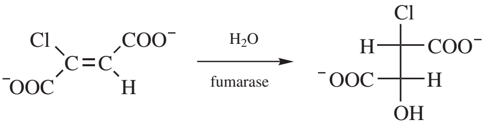
[148] For a review, see Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem. Int. Ed.* ***1985***, *24*, 1.

[149] For a monograph, see Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***. For reviews, see Tomioka, K. *Synthesis* ***1990***, 541; Consiglio, G.; Waymouth, R.M. *Chem. Rev.* ***1989***, *89*, 257; Brunner, H., in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 5, Wiley, NY, ***1989***, pp. 109–146; Noyori, R.; Kitamura, M. *Mod. Synth. Methods* ***1989***, *5*, 115; Pfaltz, A. *Mod. Synth. Methods* ***1989***, *5*, 199; Kagan, H.B. *Bull. Soc. Chim. Fr.* ***1988***, 846; Brunner, H. *Synthesis* ***1988***, 645; Wynberg, H. *Top. Stereochem.* ***1986***, *16*, 87.

[150] For reviews of these and related topics, see Zief, M.; Crane, L.J. *Chromatographic Separations*, Marcel Dekker, NY, ***1988***; Brunner, H. *J. Organomet. Chem.* ***1986***, *300*, 39; Bosnich, B.; Fryzuk, M.D. *Top. Stereochem.* ***1981***, *12*, 119.

[151] See Vineyard, B.D.; Knowles, W.S.; Sabacky, M.J.; Bachman, G.L.; Weinkauff, D.J. *J. Am. Chem. Soc.* ***1977***, *99*, 5946; Fryzuk, M.D.; Bosnich, B. *J. Am. Chem. Soc.* ***1978***, *100*, 5491.

the conversion of chlorofumaric acid (in the form of its diion) to the (−)-*threo* isomer of the di-ion of chloromalic acid by treatment with H_2O and the enzyme fumarase,[152] and the preparation of optically active aldols (aldol condensation, see reaction **16-35**) by the condensation of enolate anions with optically active substrates.[153]



(−)-*threo* Isomer

4. *Reactions in the Presence of Circularly Polarized Light.*[154] 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[155] (showing that the principle is valid), but up to now the extent of favoritism has always been <1%.

Methods of Resolution[156]

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.

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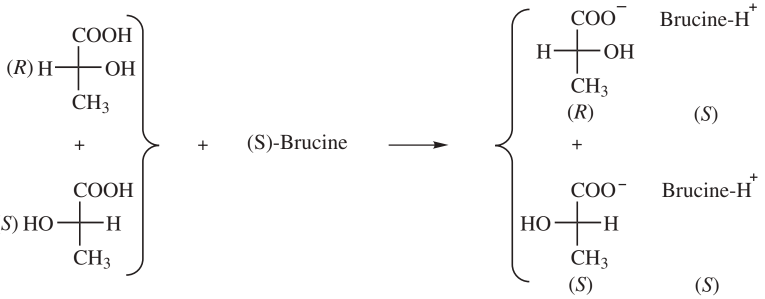
[152] Findeis, M.A.; Whitesides, G.M. *J. Org. Chem.* ***1987***, *52*, 2838. For a monograph on enzymes as chiral catalysts, see Réty, J.; Robinson, J.A. *Stereospecificity in Organic Chemistry and Enzymology*, Verlag Chemie: Deerfield Beach, FL, ***1982***. For reviews, see Klibanov, A.M. *Acc. Chem. Res.* ***1990***, *23*, 114; Jones, J.B., *Tetrahedron* ***1986***, *42*, 3351; Jones, J.B., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, pp. 309–344; Svedas, V.; Galaev, I.U. *Russ. Chem. Rev.* ***1983***, *52*, 1184. See also, Simon, H.; Bader, J.; Günther, H.; Neumann, S.; Thanos, J. *Angew. Chem. Int. Ed.* ***1985***, *24*, 539.

[153] Heathcock, C.H.; White, C.T. *J. Am. Chem. Soc.* ***1979***, *101*, 7076.

[154] For a review, See Buchardt, O. *Angew. Chem. Int. Ed.* ***1974***, *13*, 179. For a discussion, see Barron L.D. *J. Am. Chem. Soc.* ***1986***, *108*, 5539.

[155] See, for example, Bernstein, W.J.; Calvin, M.; Buchardt, O. *J. Am. Chem. Soc.* ***1972***, *94*, 494; ***1973***, *95*, 527, *Tetrahedron Lett.* ***1972***, 2195; Nicoud, J.F.; Kagan, J.F. *Isr. J. Chem.* ***1977***, *15*, 78. See also Zandomeneghi, M.; Cavazza, M.; Pietra, F. *J. Am. Chem. Soc.* ***1984***, *106*, 7261.

[156] For a monograph, see Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates, aand Resolutions*, Wiley, NY, ***1981***. For reviews, see Wilen, S.H.; Collet, A.; Jacques, J. *Tetrahedron* ***1977***, *33*, 2725; Wilen, S.H. *Top. Stereochem.* ***1971***, *6*, 107; Boyle, P.H. *Q. Rev. Chem. Soc.* ***1971***, *25*, 323; Buss, D.R.; Vermeulen, T. *Ind. Eng. Chem.* ***1968***, *60* (8), 12. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 297–424.



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 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 functional groups[157] may be coupled to an optically active reagent.[158] Racemic bases can be converted to diastereomeric salts with active acids. Alcohols[159] can be converted to diastereomeric esters, aldehydes to diastereomeric hydrazones, and so on. Amino alcohols have been resolved using boric acid and chiral

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[157] For summaries of methods used to resolve particular types of compounds, see Boyle, P.H. *Q. Rev. Chem. Soc.* ***1971***, *25*, 323; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 322–424.

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

[159] For a review of resolution of alcohols, see Klyashchitskii, B.A.; Shvets, V.I. *Russ. Chem. Rev.* ***1972***, *41*, 592.

bipaphthols.[160] Phosphine oxides[161] and chiral calix[4]arenes[162] have been resolved. Chiral crown ethers have been used to separate mixtures of enantiomeric alkyl- and arylammonium ions, by the formation of diastereomeric complexes[163] (see also category 3, below). Even hydrocarbons can be converted to diastereomeric inclusion compounds,[164] with urea. Urea is not chiral, but the cage structure is.[165] Racemic unsaturated hydrocarbons have been resolved as inclusion complex crystals with a chiral host compound derived from tartaric acid.[166] *trans*-Cyclooctene (p. 150) was resolved by conversion to a platinum complex containing an optically active amine.[167]

Fractional crystallization has always been the most common method for the separation of diastereomers. When it can be used, binary phase diagrams for the diastereomeric salts have been used to calculate the efficiency of optical resolution.[168] However, it is tediousness and the fact that it is limited to solids prompted a search for other methods. Fractional distillation has given only limited separation, but GC[169] and preparative

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[160] Periasamy, M.; Kumar, N. S.; Sivakumar, S.; Rao, V. D.; Ramanathan, C. R.; Venkatraman, L. *J. Org. Chem.* ***2001***, *66*, 3828.

[161] Andersen, N.G.; Ramsden, P.D.; Che, D.; Parvez, M.; Keay, B.A. *Org. Lett.* ***1999***, *1*, 2009; Andersen, N.G.; Ramsden, P.D.; Che, D.; Parvez, M.; Keay, B.A. *J. Org. Chem.* ***2001***, *66*, 7478.

[162] Caccamese, S.; Bottino, A.; Cunsolo, F.; Parlato, S.; Neri, P. *Tetrahedron Asymmetry* ***2000***, *11*, 3103.

[163] See, for example, Kyba, E.B.; Koga, K.; Sousa, L.R.; Siegel, M.G.; Cram, D.J. *J. Am. Chem. Soc.* ***1973***, *95*, 2692; Slingenfelter, D.S.; Helgeson, R.C.; Cram, D.J. *J. Org. Chem.* ***1981***, *46*, 393; Pearson, D.P.J.; Leigh, S.J.; Sutherland, I.O. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 3113; Bussman, W.; Lehn, J.M.; Oesch, U.; Plumeré, P.; Simon, W. *Helv. Chim. Acta* ***1981***, *64*, 657; Davidson, R.B.; Bradshaw, J.S.; Jones, B.A.; Dalley, N.K.; Christensen, J.J.; Izatt, R.M.; Morin, F.G.; Grant, D.M. *J. Org. Chem.* ***1984***, *49*, 353. See also Toda, F.; Tanaka, K.; Omata, T.; Nakamura, K.; Ōshima, T. *J. Am. Chem. Soc.* ***1983***, *105*, 5151.

[164] For reviews of chiral inclusion compounds, including their use for resolution, see Prelog, V.; Kovaćević, M.; Egli, M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1147; Worsch, D.; Vögtle, F. *Top. Curr. Chem.* ***1987***, *140*, 21; Toda, F. *Top. Curr. Chem.* ***1987***, *140*, 43; Stoddart, J.F. *Top. Stereochem.* ***1987***, *17*, 207; Sirlin, C. *Bull. Soc. Chim. Fr.* ***1984***, II-5–40; Arad-Yellin, R.; Green, B.S.; Knossow, M.; Tsoucaris, G., in Atwood; Davies; MacNicol *Inclusion Compounds*, Vol. 3; Academic Press, NY, ***1984***, pp. 263–295; Stoddart, J.F. *Prog. Macrocyclic Chem.* ***1981***, *2*, 173; Cram, D.J.; Helgeson, R.C.; Sousa, L.R.; Timko, J.M.; Newcomb, M.; Moreau, P.; DeJong, F.; Gokel, G.W.; Hoffman, D.H.; Domeier, L.A.; Peacock, S.C.; Madan, K.; Kaplan, L. *Pure Appl. Chem.* **1975**, *43*, 327.

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

[166] Miyamoto, H.; Sakamoto, M.; Yoskioka, K.; Takaoka, R.; Toda, F. *Tetrahedron Asymmetry* ***2000***, *11*, 3045.

[167] Cope, A.C.; Ganellin, C.R.; Johnson, Jr., H.W.; Van Auken, T.V.; Winkler, H.J.S. *J. Am. Chem. Soc.* ***1963***, *85*, 3276. For a review, see Tsuji, J. *Adv. Org. Chem.* ***1969***, *6*, 109, see p. 220.

[168] Amos, R.D.; Handy, N.C.; Jones, P.G.; Kirby, A.J.; Parker, J.K.; Percy, J.M.; Su, M.D. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 549.

[169] See, for example, Casanova, J.; Corey, E.J. *Chem. Ind. (London)* ***1961***, 1664; Gil-Av, E.; Nurok, D. *Proc. Chem. Soc.* ***1962***, 146; Gault, Y.; Felkin, H. *Bull. Soc. Chim. Fr.* ***1965***, 742; Vitt, S.V.; Saporovskaya, M.B.; Gudkova, I.P.; Belikov, V.M. *Tetrahedron Lett.* ***1965***, 2575; Westley, J.W.; Halpern, B.; Karger, B.L. *Anal. Chem.* ***1968***, *40*, 2046; Kawa, H.; Yamaguchi, F.; Ishikawa, N.*Chem. Lett.* ***1982***, 745.

liquid chromatography[170] have proved more useful. In many cases, they have supplanted fractional crystallization, especially where the quantities to be resolved are small.[171]

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.[171] This has been successfully accomplished with paper, column, thin-layer,[172] and gas and liquid chromatography.[173] For example, racemic mandelic acid has been almost completely resolved by column chromatography on starch.[174] Many workers have achieved separations with gas and liquid chromatography by the use of columns packed with chiral absorbents.[175] Columns packed with chiral materials are now commercially available and are capable of separating the enantiomers of certain types of compounds.[176]
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

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[170] For example, See Pirkle, W.H.; Hauske, J.R. *J. Org. Chem.* ***1977***, *42*, 1839; Helmchen, G.; Nill, G. *Angew. Chem. Int. Ed.* ***1979***, *18*, 65; Meyers, A.I.; Slade, J.; Smith, R.K.; Mihelich, E.D.; Hershenson, F.M.; Liang, C.D. *J. Org. Chem.* ***1979***, *44*, 2247; Goldman, M.; Kustanovich, Z.; Weinstein, S.; Tishbee, A.; Gil-Av, E. *J. Am. Chem. Soc.* ***1982***, *104*, 1093.

[171] For monographs on the use of liquid chromatography to effect resolutions, see Lough, W.J. *Chiral Liquid Chromatography*; Blackie and Sons: London, ***1989***; Krstulović, A.M. *Chiral Separations by HPLC*; Ellis Horwood: Chichester, ***1989***; Zief, M.; Crane, L.J. *Chromatographic Separations*, Marcel Dekker, NY, ***1988***. For a review, see Karger, B.L. *Anal. Chem.* ***1967***, *39* (8), 24A.

[172] Weinstein, S. *Tetrahedron Lett.* ***1984***, *25*, 985.

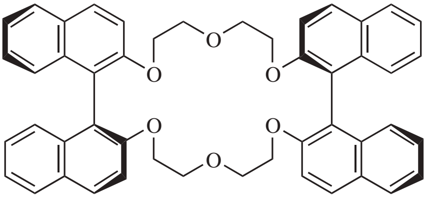
[173] For monographs, see Allenmark, S.G. *Chromatographic Enantioseparation*, Ellis Horwood, Chichester, ***1988***; König, W.A. *The Practice of Enantiomer Separation by Capillary Gas Chromatography*, Hüthig, Heidelberg, ***1987***. For reviews, see Schurig, V.; Nowotny, H. *Angew. Chem. Int. Ed.* ***1990***, *29*, 939; Pirkle, W.H.; Pochapsky, T.C. *Chem. Rev.* ***1989***, *89*, 347, *Adv. Chromatogr.*, ***1987***, *27*, 73; Okamoto, Y. *CHEMTECH* ***1987***, 176; Blaschke, G. *Angew. Chem. Int. Ed.* ***1980***, *19*, 13; Rogozhin, S.V.; Davankov, V.A. *Russ. Chem. Rev.* ***1968***, *37*, 565. See also many articles in the journal *Chirality*.

[174] Ohara, M.; Ohta, K.; Kwan, T. *Bull. Chem. Soc. Jpn.* ***1964***, *37*, 76. See also, Blaschke, G.; Donow, F. *Chem. Ber.* ***1975***, *108*, 2792; Hess, H.; Burger, G.; Musso, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 612.

[175] See, for example, Gil-Av, E.; Tishbee, A.; Hare, P.E. *J. Am. Chem. Soc.* ***1980***, *102*, 5115; Hesse, G.; Hagel, R. *Liebigs Ann. Chem.* ***1976***, 996; Schlögl, K.; Widhalm, M. *Chem. Ber.* ***1982***, *115*, 3042; Koppenhoefer, B.; Allmendinger, H.; Nicholson, G. *Angew. Chem. Int. Ed.* ***1985***, *24*, 48; Dobashi, Y.; Hara, S. *J. Am. Chem. Soc.* ***1985***, *107*, 3406, *J. Org. Chem.* ***1987***, *52*, 2490; Konrad, G.; Musso, H. *Liebigs Ann. Chem.* ***1986***, 1956; Pirkle, W.H.; Pochapsky, T.C.; Mahler, G.S.; Corey, D.E.; Reno, D.S.; Alessi, D.M. *J. Org. Chem.* ***1986***, *51*, 4991; Okamoto, Y.; Aburatani, R.; Kaida, Y.; Hatada, K. *Chem. Lett.* ***1988***, 1125; Ehlers, J.; König, W.A.; Lutz, S.; Wenz, G.; tom Dieck, H. *Angew. Chem. Int. Ed.* ***1988***, *27*, 1556; Hyun, M.H.; Park, Y.; Baik, I. *Tetrahedron Lett.* ***1988***, *29*, 4735; Schurig, V.; Nowotny, H.; Schmalzing, D. *Angew. Chem. Int. Ed.* ***1989***, *28*, 736; Ôi, S.; Shijo, M.; Miyano, S. *Chem. Lett.* *1990*, 59; Erlandsson, P.; Marle, I.; Hansson, L.; Isaksson, R.; Pettersson, C.; Pettersson, G. *J. Am. Chem. Soc.* ***1990***, *112*, 4573.

[176] See, for example, Pirkle, W.H.; Welch, C.J. *J. Org. Chem.* ***1984***, *49*, 138.

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 **58** partially to resolve the racemic amine salt **59**.[177] When an aqueous solution of **59** was mixed with a solution of optically active **58** in chloroform, and the layers separated, the chloroform layer contained about twice as much of the complex between **58** and (*R*)-**59** as of the diastereomeric complex. Many other chiral crown ethers and cryptands have been used, as have been cyclodextrins,[178] cholic acid,[179] and other kinds of hosts.[164] 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.



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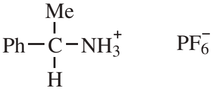

$\mathrm{Ph-\overset{Me}{\underset{H}{C}}-NH_3^+}\qquad \mathrm{PF_6^-}$

59

4. *Biochemical Processes*.[180] Biological molcules may react at different rates with the two enantiomers. For example, a certain bacterium may digest one enantiomer, but not the other. Pig liver esterase has been used for the selective cleavage of one enantiomeric ester.[181] 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*.[182] This is the method by which Pasteur proved that racemic acid was actually a mixture of (+)- and (−)-tartaric acids.[183] In the case of racemic sodium ammonium tartrate, the enantiomers crystallize

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[177] Cram, D.J.; Cram, J.M. *Science* ***1974***, *183*, 803. See also, Yamamoto, K.; Fukushima, H.; Okamoto, Y.; Hatada, K.; Nakazaki M. *J. Chem. Soc. Chem. Commun.* ***1984***, 1111; Kanoh, S.; Hongoh, Y.; Katoh, S.; Motoi, M.; Suda, H. *J. Chem. Soc. Chem. Commun.* ***1988***, 405; Bradshaw, J.S.; Huszthy, P.; McDaniel, C.W.; Zhu, C.Y.; Dalley, N.K.; Izatt, R.M.; Lifson, S. *J. Org. Chem.* ***1990***, *55*, 3129.

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

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

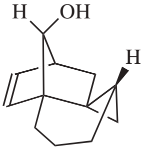
[180] For a review, see Sih, C.J.; Wu, S. *Top. Stereochem.* ***1989***, *19*, 63.

[181] For an example, see Gais, H.-J.; Jungen, M.; Jadhav, V. *J. Org. Chem.* ***2001***, *66*, 3384.

[182] For reviews, see Collet, A.; Brienne, M.; Jacques, J. *Chem. Rev.* ***1980***, *80*, 215; *Bull. Soc. Chim. Fr.* ***1972***, 127; ***1977***, 494. For a discussion, see Curtin, D.Y.; Paul, I.C. *Chem. Rev.* ***1981***, *81*, 525 pp. 535–536.

[183] 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).

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.[184] 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 <27°C. A more useful variation of the method, although still not very common, is the seeding of a racemic solution with something that will cause only one enantiomer to crystallize.[185] An interesting example of the mechanical separation technique was reported in the isolation of heptahelicene (p. 150). One enantiomer of this compound, which incidentally has the extremely high rotation of $[\alpha]_D^{20} = +6200°$, spontaneously crystallizes from benzene.[186] 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°C. A phase change from one crystal form to another takes place.[187] Note 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.[188]



60

Spontaneous resolution has also been achieved by sublimation. In the case of the norborneol derivative **60**, when the racemic solid is subjected to sublimation, the (+) molecules condense into one crystal and the (−)

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[184] 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.

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

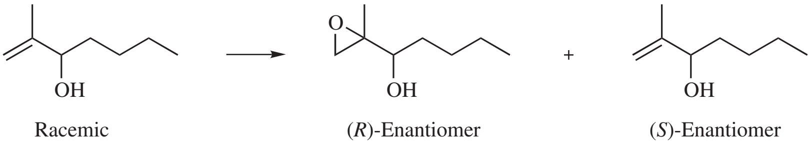
[186] Martin, R.H; Baes, M. *Tetrahedron* ***1975***, *31*, 2135. See also, Wynberg, H.; Groen, M.B. *J. Am. Chem. Soc.* ***1968***, *90*, 5339. For a discussion of other cases, see McBride, J.M.; Carter, R.L. *Angew. Chem. Int. Ed.* ***1991***, *30*, 293.

[187] Wilson, K.R.; Pincock, R.E. *J. Am. Chem. Soc.* ***1975***, *97*, 1474; Kress, R.B.; Duesler, E.N.; Etter, M.C.; Paul, I.C.; Curtin, D.Y. *J. Am. Chem. Soc.* ***1980***, *102*, 7709. See also, Lu, M.D.; Pincock, R.E. *J. Org. Chem.* ***1978***, *43*, 601; Gottarelli, G.; Spada, G.P. *J. Org. Chem.* ***1991***, *56*, 2096. For a discussion and other examples, see Agranat, I.; Perlmutter-Hayman, B.; Tapuhi, Y. *Nouv. J. Chem.* ***1978***, *2*, 183.

[188] Addadi, L.; Weinstein, S.; Gati, E.; Weissbuch, I.; Lahav, M. *J. Am. Chem. Soc.* ***1982***, *104*, 4610. See also, Weissbuch, I.; Addadi, L.; Berkovitch-Yellin, Z.; Gati, E.; Weinstein, S.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* ***1983***, *105*, 6615.

molecules into another.[189] 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*.[190] 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. 147. A method has been developed to evaluate the enantiomeric ratio of kinetic resolution using only the extent of substrate conversion.[191] An important application of this method is the resolution of racemic alkenes by treatment with optically active diisopinocampheylborane,[192] since alkenes do not easily lend themselves to conversion to diastereomers if no other functional groups are present. Another example



61

is the resolution of allylic alcohols, such as **61** with one enantiomer of a chiral epoxidation agent (see **15-50**).[193] In the case of **61**, the discrimination was extreme. One enantiomer was converted to the epoxide and the other was not, the rate ratio (hence the selectivity factor) being >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.

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[189] Paquette, L.A.; Lau, C.J. *J. Org. Chem.* ***1987***, *52*, 1634.

[190] For reviews, see Kagan, H.B.; Fiaud, J.C. *Top. Stereochem.* ***1988***, *18*, 249; Ward, R.S. *Tetrahedron Asymmetry* ***1995***, *6*, 1475; Pellissier, H. *Tetrahedron* ***2003***, *59*, 8291.

[191] Lu, Y.; Zhao, X.; Chen, Z.-N. *Tetrahedron Asymmetry* ***1995***, *6*, 1093.

[192] Brown, H.C.; Ayyangar, N.R.; Zweifel, G. *J. Am. Chem. Soc.* ***1964***, *86*, 397.

[193] Martin, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1981***, *103*, 6237. See also, Kobayashi, Y.; Kusakabe, M.; Kitano,Y.; Sato, F. *J. Org. Chem.* ***1988***, *53*, 1586; Kitano, Y.; Matsumoto, T.; Sato, F. *Tetrahedron* ***1988***, *44*, 4073; Carlier, P.R.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1988***, *110*, 2978; Discordia, R.P.; Dittmer, D.C. *J. Org. Chem.* ***1990***, *55*, 1414. For other examples, see Miyano, S.; Lu, L.D.; Viti, S.M.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 4350; Paquette, L.A.; DeRussy, D.T.; Cottrell, C.E. *J. Am. Chem. Soc.* ***1988***, *110*, 890; Weidert, P.J.; Geyer, E.; Horner, L. *Liebigs Ann. Chem.* ***1989***, 533; Katamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. *Tetrahedron: Assymetry* ***1990***, *1*, 1; Hayashi, M.; Miwata, H.; Oguni, N. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 1167.

Kinetic resolution of racemic allylic acetates[194] has been accomplished via asymmetric dihydroxylation (p. 1166), and 2-oxoimidazolidine-4-carboxylates have been developed as new chiral auxiliaries for the kinetic resolution of amines.[195] Reactions catalyzed by enzymes can be utilized for this kind of resolution.[196]

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, although an outside optically active substance is required. To effect the deracemization 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. When racemic thioesters were placed in solution with a specific optically active amide for 28 days, the solution contained 89% of one enantiomer and 11% of the other.[197] In this case, the presence of a base (Et_3N) was necessary for the interconversion to take place. Biocatalytic deracemization processes induce deracemization of chiral secondary alcohols.[198] In a specific example, *Sphingomonas paucimobilis* NCIMB 8195 catalyzes the efficient deracemization of many secondary alcohols in up to 90% yield of the (*R*)-alcohol.[199]

Optical Purity[200]

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 $[\alpha]$ 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, $[\alpha]$ for the sample will be $+48°$.[201]

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[194] Lohray, B.B.; Bhushan, V. *Tetrahedron Lett.* ***1993***, *34*, 3911.

[195] Kubota, H.; Kubo, A.; Nunami, K. *Tetrahedron Lett.* ***1994***, *35*, 3107.

[196] For example, see Nakamura, K.; Inoue, Y.; Ohno, A. *Tetrahedron Lett.* ***1994***, *35*, 4375; Mohr, P. Rösslein, L.; Tamm, C. *Tetrahedron Lett.* ***1989***, *30*, 2513; Kazlauskas, R.J. *J. Am. Chem. Soc.* ***1989***, *111*, 4953; Schwartz, A.; Madan, P.; Whitesell, J.K.; Lawrence, R.M. *Org. Synth.*, ***69***, 1; Francalanci, F.; Cesti, P.; Cabri, W.; Bianchi, D.; Martinengo, T.; Foá, M. *J. Org. Chem.* ***1987***, *52*, 5079.

[197] Pirkle, W.H.; Reno, D.S. *J. Am. Chem. Soc.* ***1987***, *109*, 7189. For another example, see Reider, P.J.; Davis, P.; Hughes, D.L.; Grabowski, E.J.J. *J. Org. Chem.* ***1987***, *52*, 955.

[198] Stecher, H.; Faber, K. *Synthesis* ***1997***, 1.

[199] Allan, G. R.; Carnell, A. J. *J. Org. Chem.* ***2001***, *66*, 6495.

[200] For a review, see Raban, M.; Mislow, K. *Top. Stereochem.* ***1967***, *2*, 199.

[201] 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 $[\alpha]$ is dependent on concentration (p. 139); see Horeau, A.*Tetrahedron Lett.* ***1969***, 3121.

We define *optical purity* as

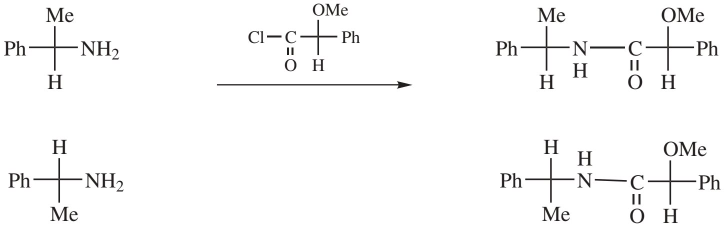
$$\text{Percent optical purity} = \frac{[\alpha]_{\text{obs}}}{[\alpha]_{\text{max}}} \times 100$$

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:

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

But how do we determine the value of $[\alpha]_{\text{max}}$? 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 $[\alpha]_{\text{max}}$. 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[202] (see p. 161). 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, for example,



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 spectra.[203] 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),[204] as well as other cases, but it is obvious that

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[202] Raban, M.; Mislow, K. *Tetrahedron Lett.* ***1965***, 4249, **1966**, 3961; Jacobus, J.; Raban, M. *J. Chem. Educ.* ***1969***, *46*, 351; Tokles, M.; Snyder, J.K. *Tetrahedron Lett.* ***1988***, *29*, 6063. For a review, see Yamaguchi, S., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 125–152. See also Raban, M.; Mislow, K. *Top. Stereochem.* ***1967***, *2*, 199.

[203] 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, T.; Pitcher, R.G.; Bommer, P.; Gutzwiller, J.; Uskoković, M. *J. Am. Chem. Soc.* ***1969***, *91*, 1871.

[204] Raban, M.; Mislow, K. *Top. Stereochem.* ***1967***, *2*, 199, see pp. 216–218.

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. The ^{13}C NMR can be used in a similar manner.[205] 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.[206] 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.[207] 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).[208] Lanthanide shift reagents have the property of spreading NMR peaks of compounds with which they can form coordination compounds, for example, alcohols, carbonyl compounds, and amines. Chiral lanthanide shift reagents shift the peaks of the two enantiomers of many such compounds to different extents.

Another method, involving GC,[209] 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 GC (p. 172) and the ratios determined from the peak areas.

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[205] For a method that relies on diastereomer formation without a chiral reagent, see Feringa, B.L.; Strijtveen, B.; Kellogg, R.M. *J. Org. Chem.* ***1986***, *51*, 5484. See also, Pasquier, M.L.; Marty, W. *Angew. Chem. Int. Ed.* ***1985***, *24*, 315; Luchinat, C.; Roelens, S. *J. Am. Chem. Soc.* ***1986***, *108*, 4873.

[206] See Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* ***1973***, *95*, 512; Rinaldi, P.L. *Prog. NMR Spectrosc.*, ***1982***, *15*, 291; Faghih, R.; Fontaine, C.; Horibe, I.; Imamura, P.M.; Lukacs, G.; Olesker, A.; Seo, S. *J. Org. Chem.* ***1985***, *50*, 4918; Trost, B.M.; Belletire, J.L.; Godleski, S.; McDougal, P.G.; Balkovec, J.M.; Baldwin, J.J.; Christy, M.E.; Ponticello, G.S.; Varga, S.L.; Springer, J.P. *J. Org. Chem.* ***1986***, *51*, 2370.

[207] For reviews of nmr chiral solvating agents, see Weisman, G.R., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 153–171; Pirkle, W.H.; Hoover, D.J. *Top. Stereochem.* ***1982***, *13*, 263. For literature references, see Sweeting, L.M.; Anet, F.A.L. *Org. Magn. Reson.* ***1984***, *22*, 539. See also, Pirkle, W.H.; Tsipouras, A. *Tetrahedron Lett.* ***1985***, *26*, 2989; Parker, D.; Taylor, R.J. *Tetrahedron* ***1987***, *43*, 5451.

[208] Sweeting, L.M.; Crans, D.C.; Whitesides, G.M. *J. Org. Chem.* ***1987***, *52*, 2273. For a monograph on chiral lanthanide shift reagents, see Morrill, T.C. *Lanthanide Shift Reagents in Stereochemical Analysis*, VCH, NY, ***1986***. For reviews, see Fraser, R.R., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 173–196; Sullivan, G.R. *Top. Stereochem.* ***1978***, *10*, 287.

[209] Charles, R.; Fischer, G.; Gil-Av, E. *Isr. J. Chem.* ***1963***, *1*, 234; Halpern, B.; Westley, J.W. *Chem. Commun.* ***1965***, 246; Vitt, S.V.; Saporovskaya, M.B.; Gudkova, I.P.; Belikov, V.M. *Tetrahedron Lett.* ***1965***, 2575; Guetté, J.; Horeau, A. *Tetrahedron Lett.* ***1965***, 3049; Westley, J.W.; Halpern, B. *J. Org. Chem.* ***1968***, *33*, 3978.

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.[210] The direct separation of enantiomers by gas or liquid chromatography on a chiral column has also been used to determine optical purity.[211]

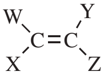
Other methods[212] involve isotopic dilution,[213] kinetic resolution,[214] ^{13}C NMR relaxation rates of diastereomeric complexes,[215] and circular polarization of luminescence.[216]

CIS–TRANS ISOMERISM

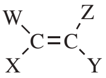
Compounds in which rotation is restricted may exhibit cis–trans isomerism.[217] These compounds do not rotate the plane of polarized light (unless they also happen to be chiral), and the properties of the isomers are not identical. The two most important types are isomerism resulting from double bonds and that resulting from rings.

Cis–Trans Isomerism Resulting from Double Bonds

It has been mentioned (p. 10) 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 $W \neq X$ and $Y \neq Z$. There are two and only two isomers (**62** and **63**), each superimposable on its mirror image unless one of the groups happens to carry a stereogenic center. Note that **62** and **63** are diastereomers, by the definition given on p. 155. There are two ways to name



62



63

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[210] For a review, see Pirkle, W.H.; Finn, J., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 87–124.

[211] For reviews, see in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, the articles by Schurig, V. pp. 59–86 and Pirkle, W.H.; Finn, J. pp. 87–124.

[212] See also Leitich, J. *Tetrahedron Lett.* ***1978***, 3589; Hill, H.W.; Zens, A.P.; Jacobus, J. *J. Am. Chem. Soc.* ***1979***, *101*, 7090; Matsumoto, M.; Yajima, H.; Endo, R. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 4139.

[213] Berson, J.A.; Ben-Efraim, D.A. *J. Am. Chem. Soc.* ***1959***, *81*, 4083. For a review, see Andersen, K.K.; Gash, D.M.; Robertson, J.D. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 45–57.

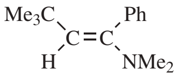
[214] Horeau, A.; Guetté, J.; Weidmann, R. *Bull. Soc. Chim. Fr.* ***1966***, 3513. For a review, see Schoofs, A.R.; Guetté, J., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 29–44.

[215] Hofer, E.; Keuper, R. *Tetrahedron Lett.* ***1984***, *25*, 5631.

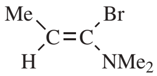
[216] Eaton, S.S. *Chem. Phys. Lett.* ***1971***, *8*, 251; Schippers, P.H.; Dekkers, H.P.J.M. *Tetrahedron* ***1982***, *38*, 2089.

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

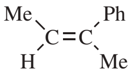
such isomers. In the older method, one isomer is called cis and the other trans. When W = Y, **62** is the cis and **63** the trans isomer. Unfortunately, there is no easy way to apply this method when the four groups are different. The newer method, which can be applied to all cases, is based on the Cahn–Ingold–Prelog system (p. 155). 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*).[218] 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., **64**, and **65**). Like *cis* and *trans*, (*E*) and (*Z*) are used as prefixes; for example, **65** is called (*E*)-1-bromo-1,2-dichloroethene.



(*E*)

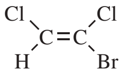


(*Z*)



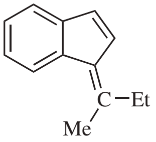
(*Z*)

64



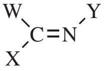
(*E*)

65



(*E*)

This type of isomerism is also possible with other double bonds, such as C=N,[219] N=N, or even C=S,[220] although 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, **66** may be called syn and **67** anti, although (*E*) and (*Z*) are often used here too.[221] In azo compounds, there is no ambiguity. Compound **68** is always *syn* or (*Z*) regardless of the nature of W and Y.



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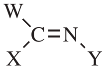

67

(*Z*) (*E*)

68

If there is more than one double bond[222] 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

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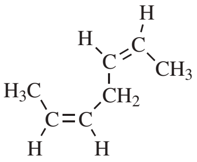
[218] For a complete description of the system, see *Pure Appl. Chem.* ***19767***, *45*, 13; *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, ***1979*** (the Blue Book).

[219] For reviews of isomerizations about C=N bonds, see, in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*; Wiley, NY, ***1970***, the articles by McCarty, C.G., 363–464 (pp. 364–408), and Wettermark, G. 565–596 (pp. 574–582).

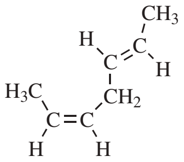
[220] King, J.F.; Durst, T. *Can. J. Chem.* ***1966***, *44*, 819.

[221] A mechanism has been reported for the acid-catalyzed (*Z*/*E*) isomerization of imines. See Johnson, J.E.; Morales, N.M.; Gorczyca, A.M.; Dolliver, D.D.; McAllister, M.A. *J. Org. Chem.* ***2001***, *66*, 7979.

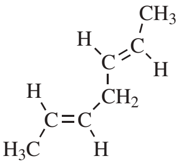
[222] This rule does not apply to allenes, which do not show cis–trans isomerism at all (see p. 148).



cis–cis or
(*Z*, *Z*)

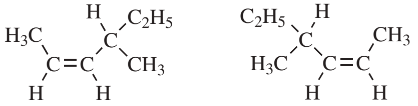


cis–trans or
(*Z*, *E*)

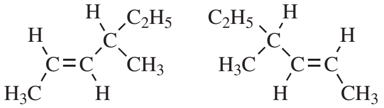


trans–trans or
(*E*, *E*)

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

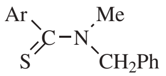


(*Z*) or cis *dl* pair



(*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. 151), and for rings larger than 10- or 11-membered, trans isomers are more stable[223] (see also, p. 225).



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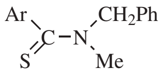

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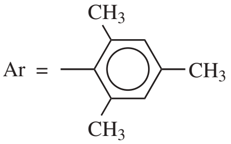
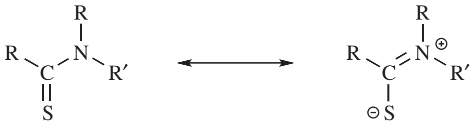


In a few cases, single-bond rotation is so slowed that cis and trans isomers can be isolated even where no double bond exists[224] (see also p. 230). One example is *N*-methyl-*N*-benzylthiomesitylide (**69** and **70**),[225] the isomers of which are stable in the crystalline state but interconvert with a half-life of ~25 h in $CDCl_3$ at 50°C.[226] This 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.[53] (For other examples of restricted rotation about single bonds, see pp. 230–233).



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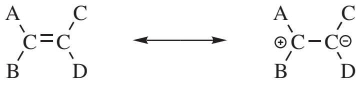
[223] Cope, A.C.; Moore, P.T.; Moore, W.R. *J. Am. Chem. Soc.* ***1959***, *81*, 3153.

[224] For a review, see Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 41–71.

[225] Mannschreck, A. *Angew. Chem. Int. Ed.* ***1965***, *4*, 985. See also, Toldy, L.; Radics, L. *Tetrahedron Lett.* ***1966***, 4753; Völter, H.; Helmchen, G. *Tetrahedron Lett.* ***1978***, 1251; Walter, W.; Hühnerfuss, H. *Tetrahedron Lett.* ***1981***, *22*, 2147.

[226] This is another example of atropisomerism (p. 145).

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 (**71**).[227] The contribution of di-ionic canonical forms, such as the one shown decreases the double-bond character and allows easier rotation. For example, compound **72** has a barrier to rotation of 13 kcal mol^{-1} (55 kJ mol^{-1}),[228] compared to a typical value of ~62–65 kcal mol^{-1} (260–270 kJ mol^{-1}) for simple alkenes.



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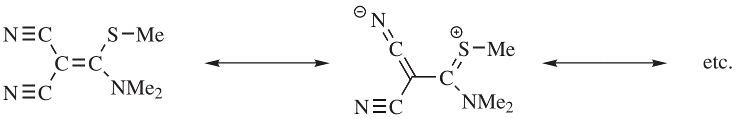
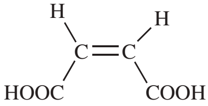
A, B = electron withdrawing
C, D = electron donating



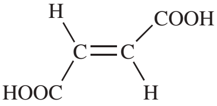
72

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. Since they generally have more symmetry than cis isomers, trans isomers in most cases have higher melting points and lower

TABLE 4.2. Some Properties of Maleic and Fumaric Acids



Maleic acid



Fumaric acid

Property	Maleic Acid	Fumaric Acid
Melting point, °C	130	286
Solubility in water at 25°C, g L^{-1}	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}

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[227] For reviews, see Sandström, J. *Top. Stereochem.* ***1983***, *14*, 83; Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 111–125.

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

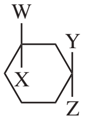
solubilities in inert solvents. The *cis* isomer usually has a higher heat of combustion, which indicates a lower thermochemical stability. Other noticeably different properties are densities, acid strengths, boiling points, and various types of spectra, but the differences are too involved to be discussed here.

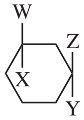
It is also important to note that *trans*-alkenes are often more stable than *cis*-alkenes due to diminished steric hindrance (p. 232), but this is not always the case. It is known, for example, that *cis*-1,2-difluoroethene is thermodynamically more stable than *trans*-1,2-difluoroethene. This appears to be due to delocalization of halogen lone-pair electrons and an antiperiplanar effect between vicinal antiperiplanar bonds.[229]

Cis–Trans Isomerism of Monocyclic Compounds

Although rings of four carbons and larger are not generally planar (see p. 211), they will be treated as such in this section, since the correct number of isomers can be determined when this is done[230] and the principles are easier to visualize (see p. 204).

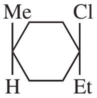
The presence of a ring, like that of a double bond, prevents rotation. Cis and trans isomers are possible whenever there are two carbons on a ring, each of which is substituted by two different groups. The two carbons need not be adjacent. Examples are





In some cases, the two stereoisomers can interconvert. In *cis*- and *trans*-disubstituted cyclopropanones, for example, there is reversible interconversion that favors the more stable trans isomer. This fluxional isomerization occurs via ring opening to an unseen oxyallyl *valence bond* isomer.[231]

As with double bonds, cis and trans isomers are possible, but the restrictions are that W may equal Y and X may equal Z, but W may not equal X and Y may not equal Z. There is an important difference from the double-bond case: The



73

substituted carbons are sterogenic carbons. This means that there are not *only* two isomers. In the most general case, where W, X, Y, and Z are all different,

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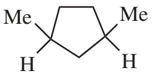
[229] Yamamoto, T.; Tomoda, S. *Chem. Lett.* ***1997***, 1069.

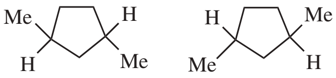
[230] For a discussion of why this is so, see Leonard, J.E.; Hammond, G.S.; Simmons, H.E. *J. Am. Chem. Soc.* ***1975***, *97*, 5052.

[231] Sorensen, T.S.; Sun, F. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 1053.

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, for example, **73**. In this case, the substituted carbons are *not* chiral carbons. Note also that 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

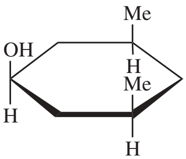


trans *dl* pair

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.[105] 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 **73**), 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 (**74**), *t*-3,*t*-5-dimethylcyclohexan-*r*-1-ol (**75**), and *c*-3,*t*-5-dimethylcyclohexan-*r*-1-ol (**76**). The last 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 (**77**).



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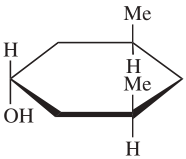

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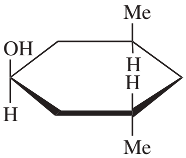

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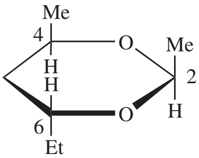
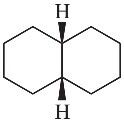


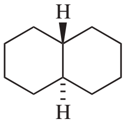
77

Cis–Trans Isomerism of Fused and Bridged Ring Systems

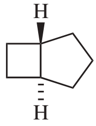
Fused bicyclic systems are those in which two rings share two and only two atoms. In such systems, there is no new principle. The fusion may be cis or trans, as illustrated by *cis*- and *trans*-decalin. However, when the rings are small enough, the trans configuration is impossible and the junction 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 (**78**) is known.[232] For the bicyclo[2.2.0] system (a four–four fusion), only cis compounds have been 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 **79**.[233] 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.[234]



cis-Decalin



trans-Decalin



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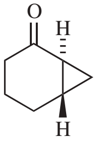

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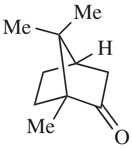
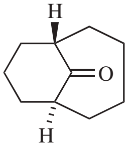


Camphor

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 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 **80** has been prepared.[235] In this case there



80

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[232] Meinwald, J.; Tufariello, J.J.; Hurst, J.J. *J. Org. Chem.* ***1964***, *29*, 2914.

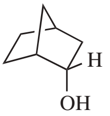
[233] Paukstelis, J.V.; Kao, J. *J. Am. Chem. Soc.* ***1972***, *94*, 4783. For references to other examples, see Dixon, D.A.; Gassman, P.G. *J. Am. Chem. Soc.* ***1988***, *110*, 2309.

[234] Corbally, R.P.; Perkins, M.J.; Carson, A.S.; Laye, P.G.; Steele, W.V. *J. Chem. Soc. Chem. Commun.* ***1978***, 778.

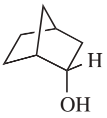
[235] Winkler, J.D.; Hey, J.P.; Williard, P.G. *Tetrahedron Lett.* ***1988***, *29*, 4691.

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 closer to the longer of the two unsubstituted bridges; the prefix exo- is used when the substituent is closer to the shorter bridge; for example,

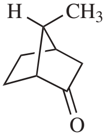


exo-2-Norborneol

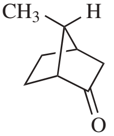


endo-2-Norborneol

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; for example, 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 (or *in–out*),[236] is found in salts of tricyclic diamines with nitrogen at the bridgeheads. In medium-sized bicyclic ring systems, *in–out* isomerisim is possible,[237] and the bridgehead nitrogen atoms adopt whichever arangement is more stable.[238] If we focus attention on the nitrogne lone pairs, 1,4-diazabicyclo[2.2.2]octane (**81**) favors the *out–out* isomer, 1,6-diazabicyclo[4.4.4]tetradecane (**82**) the *in,in*,[239] 1,5-diazabicyclo[3.3.3]undecane (**83**) has nearly planar nitrogen atoms,[240] and 1,9-diazabicyclo[7.3.1]tridecane (**84**) is *in,out*.[241] One can also focus on the NH unit in the case of ammonium salts.

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[236] See Alder, R. *Acc. Chem. Res.* ***1983***, *16*, 321.

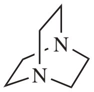
[237] Alder, R.W.; East, S.P. *Chem. Rev.* ***1996***, *96*, 2097.

[238] Alder, R.W. *Tetrahedron* ***1990***, *46*, 683.

[239] Alder, R.W.; Orpen, A.G.; Sessions, R.B. *J. Chem. Soc., Chem. Commun.* ***1983***, 999.

[240] Alder, R.W.; Goode, N.C.; King, T.J.; Mellor, J.M.; Miller, B.W. *J. Chem. Soc., Chem. Commun.* ***1976***, 173; Alder, R.W.; Arrowsmith, R.J.; Casson, A.; Sessions, R.B.; Heilbronner, E.; Kovac, B.; Huber, H.; Taagepera, M. *J. Am. Chem. Soc.* ***1981***, *103*, 6137.

[241] Alder, R.W.; Heilbronner, E.; Honegger, E.; McEwen, A.B.; Moss, R.E.; Olefirowicz, E.; Petillo, P.A.; Sessions, R.B.; Weisman, G.R.; White, J.M.; Yang, Z.-Z. *J. Am. Chem. Soc.* ***1993***, *115*, 6580.



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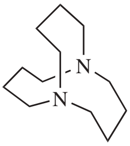

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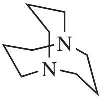

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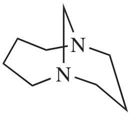
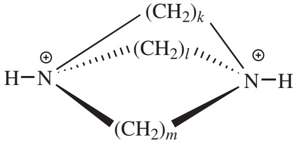


84

In the examples **85**–**87**, when *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[242] isolated several such isomers with *k*, *l*, and *m* varying from 6 to 10. In the 9,9,9 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. 119 in that there is a negative rather than a positive ion enclosed.[243] Even smaller ones (e.g., the 4,4,4 compound) have been shown to form mono-inside-protonated ions.[244] In compound **88**, which has four quaternary nitrogens, a halide ion has been encapsulated without a hydrogen being present on a nitrogen.[245] This ion does not display *in–out* isomerism. *Out–in* and *in–in* isomers have also been prepared in analogous all-carbon tricyclic systems.[246]

out–out isomer



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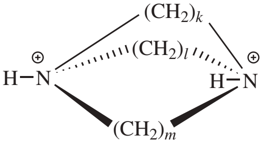
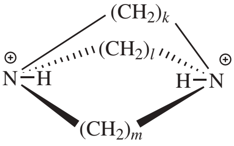
out–in isomer



86

in–in isomer



87

It is known that chiral phosphanes are more pyramidal and that inversion is more difficult, usually requiring temperatures well over 100°C for racemization.[247] Alder

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[242] Simmons, H.E.; Park, C.H. *J. Am. Chem. Soc.* ***1968***, *90*, 2428; Park, C.H.; Simmons, H.E. *J. Am. Chem. Soc.* ***1968***, *90*, 2429, 2431; Simmons, H.E.; Park, C.H.; Uyeda, R.T.; Habibi, M.F. *Trans. N.Y. Acad. Sci.* ***1970***, *32*, 521. See also, Dietrich, B.; Lehn, J.M.; Sauvage, J.P. *Tetrahedron* ***1973***, *29*, 1647; Dietrich, B.; Lehn, J.M.; Sauvage, J.P.; Blanzat, J.*Tetrahedron* ***1973***, *29*, 1629.

[243] For reviews, see Schmidtchen, F.P.; Gleich, A.; Schummer, A. *Pure. Appl. Chem.* ***1989***, *61*, 1535; Pierre, J.; Baret, P. *Bull. Soc. Chim. Fr.* ***1983***, II-367. See also, Hosseini, M.W.; Lehn, J. *Helv. Chim. Acta* ***1988***, *71*, 749.

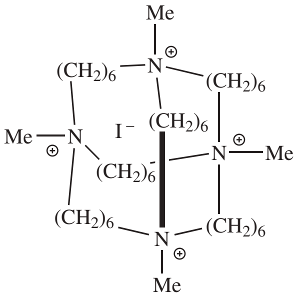
[244] Alder, R.W.; Moss, R.E.; Sessions, R.B. *J. Chem. Soc. Chem. Commun.* ***1983***, 997, 1000; Alder, R.W.; Orpen, A.G.; Sessions, R.B. *J. Chem. Soc. Chem. Commun.* ***1983***, 999; Dietrich, B.; Lehn, J.M.; Guilhem, J.; Pascard, C. *Tetrahedron Lett.* ***1989***, *30*, 4125; Wallon, A.; Peter-Katalinić, J.; Werner, U.; Müller, W.M.; Vögtle, F. *Chem. Ber.* ***1990***, *123*, 375.

[245] Schmidtchen, F.P.; Müller, G. *J. Chem. Soc. Chem. Commun.* ***1984***, 1115. See also, Schmidtchen, F.P. *J. Am. Chem. Soc.* ***1986***, *108*, 8249, *Top. Curr. Chem.* ***1986***, *132*, 101.

[246] Park, C.H.; Simmons, H.E. *J. Am. Chem. Soc.* ***1972***, *94*, 7184; Gassman, P.G.; Hoye, R.C. *J. Am. Chem. Soc.* ***1981***, *103*, 215; McMurry, J.E.; Hodge, C.N. *J. Am. Chem. Soc.* ***1984***, *106*, 6450; Winkler, J.D.; Hey, J.P.; Williard, P.G. *J. Am. Chem. Soc.* ***1986***, *108*, 6425.

[247] See Baechler, R.D.; Mislow, K. *J. Am. Chem. Soc.* ***1970***, *92*, 3090; Rauk, A.; Allen, L.C.; Mislow, K. *Angew. Chem. Int. Ed.* ***1970***, *9*, 400.

and Read found that deprotonation of bis(phosphorane) **89** (which is known to have an *in–out* structure with significant P—P bonding) leads to a rearrangement and the *out–out* diphosphane **90**.[248] Reprotonation gives **89**,[249] with inversion at the non-protonated phosphorus atom occurring at room temperature.



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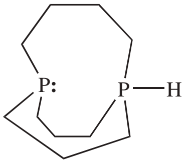
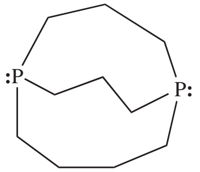


89



90

Enantiotopic and Diastereotopic Atoms, Groups, and Faces[250]

Many molecules contain atoms or groups that appear to be equivalent, but with 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 they are 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,[251] 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 (**91**), while replacement of the other hydrogen gives the *other* enantiomer (**92**). Since the

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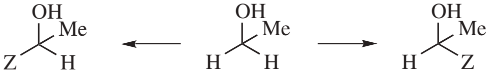
[248] Alder, R.W.; Read, D. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2879.

[249] Alder, R.W.; Ellis, D.D.; Gleiter, R.; Harris, C.J.; Lange, H.; Orpen, A.G.; Read, D.; Taylor, P.N. *J. Chem. Soc., Perkin Trans. 1* ***1998***, 1657.

[250] These terms were coined by Mislow. For lengthy discussions of this subject, see Eliel, E.L. *Top. Curr. Chem.* ***1982***, *105*, 1, *J. Chem. Educ.* ***1980***, *57*, 52; Mislow, K.; Raban, M. *Top. Stereochem.* ***1967***, *1*, 1. See also, Ault, A. *J. Chem. Educ.* ***1974***, *51*, 729; Kaloustian, S.A.; Kaloustian, M.K. *J. Chem. Educ.* ***1975***, *52*, 56; Jennings, W.B. *Chem. Rev.* ***1975***, *75*, 307.

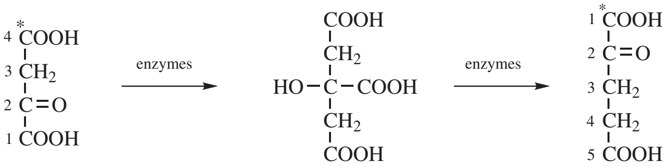
[251] In the case where Y is itself a chiral group, this statement is only true when the two Y groups have the same configuration.

two compounds that result upon replacement of H by Z (**91** and **92**) are not



91 **92**

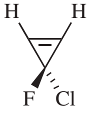
identical but enantiomeric, the hydrogens are *not* equivalent. We define as *enantiotopic* two atoms or groups that upon replacement with a third group give enantiomers. In any symmetrical environment the two hydrogens behave as equivalent, but in a dissymmetrical environment they may behave differently. 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,[252] 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 (**93**) is converted to α-oxoglutaric



$$\overset{*}{\mathrm{C}}\mathrm{OOH{-}CH_2{-}C{=}O{-}COOH} \xrightarrow{\text{enzymes}} \mathrm{HO{-}C(CH_2COOH)_2{-}COOH} \xrightarrow{\text{enzymes}} \overset{*}{\mathrm{C}}\mathrm{OOH{-}C{=}O{-}CH_2{-}CH_2{-}COOH}$$

93 **94** **95**

acid (**95**) by a sequence that includes citric acid (**94**) as an intermediate. When **93** is labeled with ^{14}C at the 4 position, the label is found only at C-1 of **95**, despite the fact that **94** is not chiral. The two CH_2COOH groups of **94** are enantiotopic and the enzyme easily discriminates between them.[253] 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, although enantiotopic atoms and groups may also be found in other molecules, for example, the hydrogen atoms in 3-fluoro-3-chlorocyclopropene (**96**). In this case, substitution of an H by a group Z makes the C-3 atom asymmetric and substitution at C-1 gives the opposite enantiomer from substitution at C-2.



96

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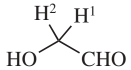
[252] For a review, see Benner, S.A.; Glasfeld, A.; Piccirilli, J.A. *Top. Stereochem.* ***1989***, *19*, 127. For a nonenzymatic example, see Job, R.C.; Bruice, T.C. *J. Am. Chem. Soc.* ***1974***, *96*, 809.

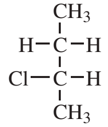
[253] The experiments were carried out by Evans, Jr., E.A.; Slotin, L. *J. Biol. Chem.* ***1941***, *141*, 439; Wood, H.G.; Werkman, C.H.; Hemingway, A.; Nier, A.O. *J. Biol. Chem.* ***1942***, *142*, 31. The correct interpretation was given by Ogston, A.G. *Nature (London)* ***1948***, *162*, 963. For discussion, see Hirschmann, H., in Florkin, M.; Stotz, E.H. *Comprehensive Biochemistry*, Vol. 12, pp. 236–260, Elsevier, NY, ***1964***; Cornforth, J.W. *Tetrahedron* ***1974***, *30*, 1515; Vennesland, B. *Top. Curr. Chem.* ***1974***, *48*, 39; Eliel, E.L. *Top. Curr. Chem.*, ***1982***, *105*, 1, pp. 5–7, 45–70.

The term *prochiral*[254] is used for a compound or group that has two enantiotopic atoms or groups, for example, 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*); for example,



H^2 = *pro*-(*S*)
H^1 = *pro*-(*R*)

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 (**97**), vinyl chloride (**98**), and chlorocyclopropane (**99**) and the two alkenyl hydrogens of **100**. Diastereotopic atoms and groups are different in any environment, chiral or achiral. These hydrogens react 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.[255] The term *isochronous* is used for hydrogens that are indistinguishable in the NMR.[256] 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. 181) or by changing the solvent or concentration. Note that X atoms or groups CX_2WY are diastereotopic if either W or Y is chiral.



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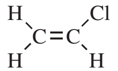

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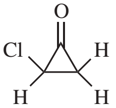

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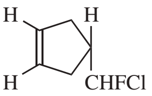

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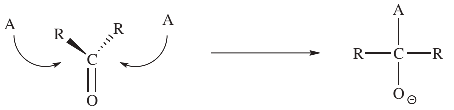

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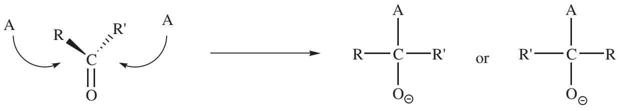

102

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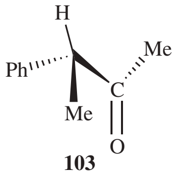
[254] Hirschmann, H.; Hanson, K.R. *Tetrahedron* ***1974***, *30*, 3649.

[255] Pirkle, W.H. *J. Am. Chem. Soc.* ***1966***, *88*, 1837; Burlingame, T.G.; Pirkle, W.H. *J. Am. Chem. Soc.* ***1966***, *88*, 4294; Pirkle, W.H.; Burlingame, T.G. *Tetrahedron Lett.* ***1967***, 4039.

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

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 (**101**), 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 (**102**), attack by an achiral A at one face gives a transition 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. 153), 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 **103**, the two faces are obviously not equivalent and are called diastereotopic. Enantiotopic and diastereotopic faces can be named by an extension of the Cahn–Ingold–Prelog system.[210] 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 **104**) is the *Re* face (from Latin *rectus*), whereas **105** shows the *Si* face (from Latin *sinister*).



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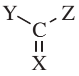

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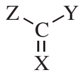

105

Note that new terminology has been proposed.[257] The concept of sphericity is used, and the terms homospheric, enantiospheric, and hemispheric have been coined to specify the nature of an orbit (an equivalent class) assigned to a coset representation.[258] Using these terms, prochirality can be defined: if a molecule has at least one enantiospheric orbit, the molecule is defined as being prochiral.[258]

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.[259] The same term is used when a mixture of two or more stereoisomers is exclusively or predominantly formed at

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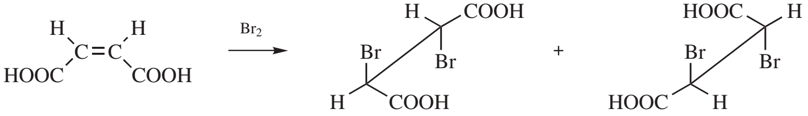
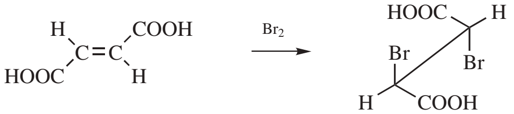
[257] Fujita, S. *J. Org. Chem.* ***2002***, *67*, 6055.

[258] Fujita, S. *J. Am. Chem. Soc.* ***1990***, *112*, 3390.

[259] For a further discussion of these terms and of stereoselective reactions in general, see Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 835–990.

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:





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 3D arrangements in space of the atoms in a molecule are interconvertible merely by free rotation about bonds, they are called *conformations*.[260] If they are not interconvertible, they are called *configurations*.[261] Configurations represent *isomers* that can be separated, as previously discussed in this chapter. Conformations represent *conformers*, which are rapidly interconvertible and thus

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[260] For related discussions see Bonchev, D.; Rouvray, D.H. *Chemical Topology*, Gordon and Breach, Australia, ***1999***.

[261] For books on conformational analysis see Dale, J. *Stereochemistry and Conformational Analysis*; Verlag Chemie: Deerfield Beach, FL, ***1978***; Chiurdoglu, G. *Conformational Analysis*; Academic Press, NY, ***1971***; Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*; Wiley, NY, ***1965***; Hanack, M. *Conformation Theory*; Academic Press, NY, ***1965***. For reviews, see Dale, J. *Top. Stereochem.* ***1976***, *9*, 199; Truax, D.R.; Wieser, H. *Chem. Soc. Rev.* ***1976***, *5*, 411; Eliel, E.L. *J. Chem. Educ.* ***1975***, *52*, 762; Bastiansen, O.; Seip, H.M.; Boggs, J.E. *Perspect. Struct. Chem.* ***1971***, *4*, 60; Bushweller, C.H.; Gianni, M.H., in Patai, S. *The Chemistry of Functional Groups, Supplement E*; Wiley, NY, ***1980***, pp. 215–278.

nonseparable. The terms "conformational isomer" and "rotamer"[262] are sometimes used instead of "conformer." A number of methods have been used to determine conformations.[263] These include X-ray and electron diffraction, IR, Raman, UV, NMR,[264] and microwave spectra,[265] photoelectron spectroscopy,[266] supersonic molecular jet spectroscopy,[267] and optical rotatory dispersion and CD measurements.[268] Ring current NMR anisotropy has been applied to conformational analysis,[269] as has chemical shift simulation.[270] 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.[271] Conformations can be *calculated* by a method called molecular mechanics (p. 213). A method was reported that characterized six-membered ring conformations as a linear combination of ideal basic conformations.[272] The term absolute conformation has been introduced for molecules for which one conformation is optically inactive but, by internal rotation about a C(sp^3)—C(sp^3) bond, optically active conformers are produced.[273]

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[262] Ōki, M. *The Chemistry of Rotational Isomers*, Springer-Verlag, Berlin, ***1993***.

[263] For a review, see Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*, Wiley, NY, ***1965***, pp. 129–188.

[264] For monographs on the use of NMR to study conformational questions, see Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***; Marshall, J.L. *Carbon–Carbon and Carbon–Proton NMR Couplings*, VCH, NY, ***1983***. For reviews, see Anet, F.A.L.; Anet, R., in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3, Academic Press, NY, ***1971***, pp. 343–420; Kessler, H. *Angew. Chem. Int. Ed.* ***1970***, *9*, 219; Ivanova, T.M.; Kugatova-Shemyakina, G.P. *Russ. Chem. Rev.* ***1970***, *39*, 510; Anderson, J.E. *Q. Rev. Chem. Soc.* ***1965***, *19*, 426; Franklin, N.C.; Feltkamp, H. *Angew. Chem. Int. Ed.* ***1965***, *4*, 774; Johnson, Jr., C.S. *Adv. Magn. Reson.* ***1965***, *1*, 33. See also, Whitesell, J.K.; Minton, M. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*, Chapman and Hall, NY, ***1987***.

[265] For a review see Wilson, E.B. *Chem. Soc. Rev.* ***1972***, *1*, 293.

[266] For a review, see Klessinger, M.; Rademacher, P. *Angew. Chem. Int. Ed.* ***1979***, *18*, 826.

[267] Breen, P.J.; Warren, J.A.; Bernstein, E.R.; Seeman, J.I. *J. Am. Chem. Soc.* ***1987***, *109*, 3453.

[268] For monographs, see Kagan, H.B. *Determination of Configurations by Dipole Moments, CD, or ORD* (Vol. 2 of Kagan, *Stereochemistry*), Georg Thieme Publishers, Stuttgart, ***1977***; Crabbé, P. *ORD and CD in Chemistry and Biochemistry*, Academic Press, NY, ***1972***, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Holden-Day, San Francisco, ***1965***; Snatzke, G. *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Sadtler Research Laboratories, Philadelphia, ***1967***; Velluz, L.; Legrand, M.; Grosjean, M. *Optical Circular Dichroism*, Academic Press, NY, ***1965***. For reviews, see Smith, H.E. *Chem. Rev.* ***1983***, *83*, 359; Håkansson, R., in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 67–120; Hudec, J.; Kirk, D.N. *Tetrahedron* ***1976***, *32*, 2475; Schellman, J.A. *Chem. Rev.* ***1975***, *75*, 323; Velluz, L.; Legrand, M. *Bull. Soc. Chim. Fr.* ***1970***, 1785; Barrett, G.C., in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1972***, pp. 515–610; Snatzke, G. *Angew. Chem. Int. Ed.* ***1968***, *7*, 14; Crabbé, P., in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3, Academic Press, NY, ***1971***, pp. 133–205; Crabbé, P.; Klyne, W. *Tetrahedron* ***1967***, *23*, 3449; Crabbé, P. *Top. Stereochem.* ***1967***, *1*, 93–198; Eyring, H.; Liu, H.; Caldwell, D. *Chem. Rev.* ***1968***, *68*, 525.

[269] Chen, J.; Cammers-Goodwin, A. *Eur. J. Org. Chem.* ***2003***, 3861.

[270] Iwamoto, H.; Yang, Y.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* ***2001***, *42*, 49.

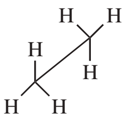
[271] See Kessler, H.; Zimmermann, G.; Förster, H.; Engel, J.; Oepen, G.; Sheldrick, W.S. *Angew. Chem. Int. Ed.* ***1981***, *20*, 1053.

[272] Bérces, A.; Whitfield, D.M.; Nukada, T. *Tetrahedron* ***2001***, *57*, 477.

[273] Ōki, M.; Toyota, S. *Eur. J. Org. Chem.* ***2004***, 255.

Conformation in Open-Chain Systems[274]

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. As a practical matter, the number of conformations is much less. If one ignores duplications due to symmetry, the number of conformations can be *estimated* as being greater than 3^n, where $n =$ the number of internal C—C bonds. *n*-Pentane, for example, has 11, *n*-hexane 35, *n*-heptane 109, *n*-octane 347, *n*-nonane 1101, and *n*-decane 3263.[275] For ethane there are two extremes, a conformation of highest and one of lowest potential energy, depicted in two ways as: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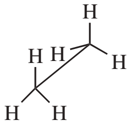
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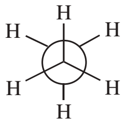
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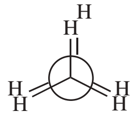
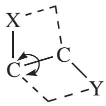

Eclipsed

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. Fig. 4.4 illustrates this. The *angle of torsion*, which is a dihedral angle, is the angle between the X—C—C and the C—C—Y planes, as shown:



For ethane, the difference in energy is ~2.9 kcal mol^{-1} (12 kJ mol^{-1}).[276] 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.[277] It

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[274] For a review, see Berg, U.; Sandström, J. *Adv. Phys. Org. Chem.* ***1989***, *25*, 1. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 597–664. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 32–37.

[275] Gotō, H.; Ō sawa, E.; Yamato, M. *Tetrahedron* ***1993***, *49*, 387.

[276] Lide, Jr., D.R. *J. Chem. Phys.* ***1958***, *29*, 1426; Weiss, S.; Leroi, G.E. *J. Chem. Phys.* ***1968***, *48*, 962; Hirota, E.; Saito, S.; Endo, Y. *J. Chem. Phys.* ***1979***, *71*, 1183.

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

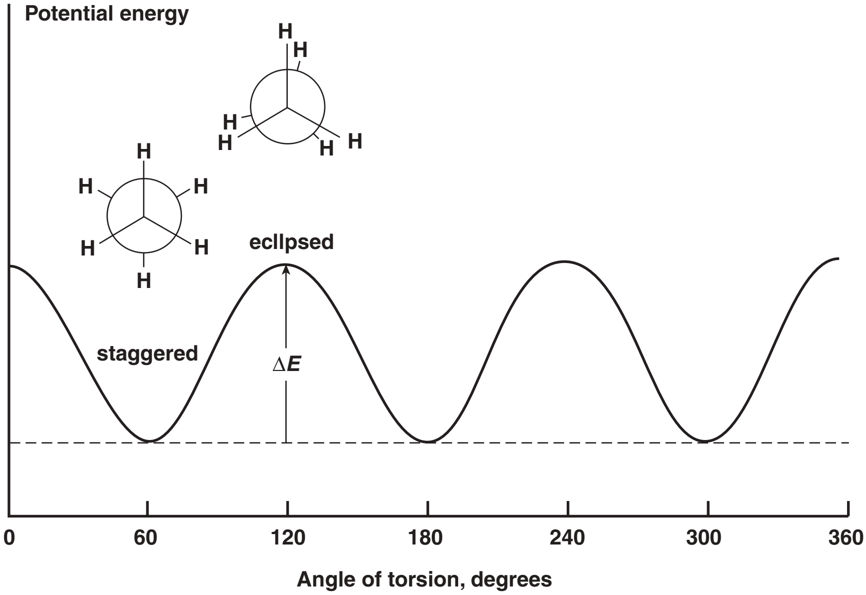

Fig. 4.4. Conformational energy diagram for ethane.

was concluded from molecular-orbital calculations that the barrier is caused by repulsion between overlapping filled molecular orbitals.[278] 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, although 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 in the case of suitably substituted biphenyls (p. 146) or the diadamantyl compound mentioned on p. 201, 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),[279] such as *n*-butane, for which there are four extremes: a fully staggered conformation, called anti, trans, or antiperiplanar; another

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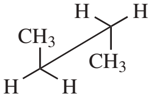
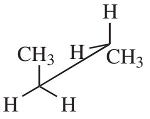
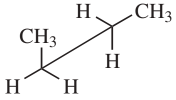
[278] See Pitzer, R.M. *Acc. Chem. Res.* ***1983***, *16*, 207. See, however, Bader, R.F.W.; Cheeseman, J.R.; Laidig, K.E.; Wiberg, K.B.; Breneman, C.*J. Am. Chem. Soc.* ***1990***, *112*, 6350.

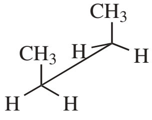
[279] For discussions of the conformational analysis of such systems, see Kingsbury, C.A. *J. Chem. Educ.* ***1979***, *56*, 431; Wiberg, K.B.; Murcko, M.A. *J. Am. Chem. Soc.* ***1988***, *110*, 8029; Allinger, N.L.; Grev, R.S.; Yates, B.F.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1990***, *112*, 114.

staggered conformation, called *gauche* or *synclinal*; and two types of eclipsed


anti, trans, or
antiperiplanar


anticlinal


gauche or
synclinal


synperiplanar

106

conformations, called synperiplanar and anticlinal. An energy diagram for this system is given in Fig. 4.5. 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 ~70% of the molecules are in the anti and ~30% in the gauche conformation.[280] The corresponding figures for 1,2-dibromoethane are 89% *anti* and 11% *gauche*.[281] The eclipsed conformations are unpopulated and serve only as pathways from one staggered conformation to another. Solids normally consist of a single conformer.

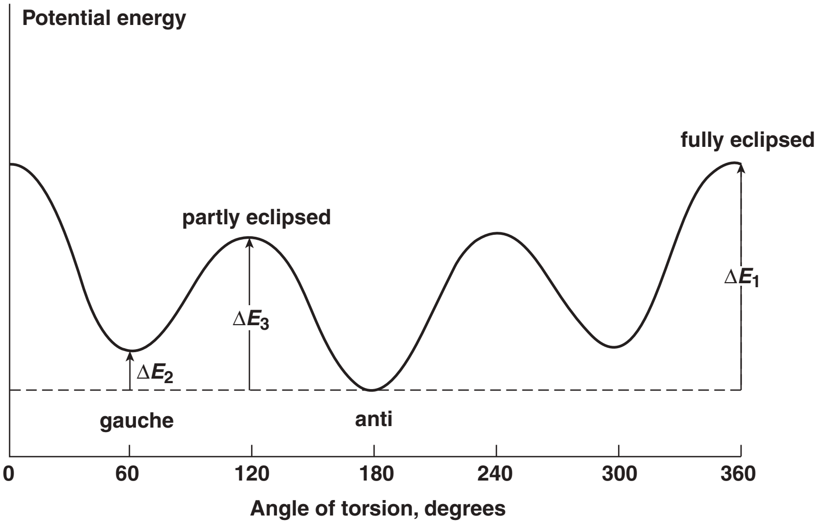


Fig. 4.5. Conformational energy for YCH_2—CH_2Y or YCH_2—CH_2X. For *n*-butane, $\Delta E_1 = 4$–6, $\Delta E_2 = 0.9$, and $\Delta E_3 = 3.4\,\text{kcal mol}^{-1}$ (17–25, 3.8, 14 kL mol^{-1}, respectively).

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[280] Aroney, M.; Izsak, D.; Le Fèvre, R.J.W. *J. Chem. Soc.* ***1962***, 1407; Le Fèvre, R.J.W.; Orr, B.J. *Aust. J. Chem.* ***1964***, *17*, 1098.

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

It may be observed that the *gauche* conformation of butane (**106**) or any other similar molecule is chiral. The lack of optical activity in such compounds arises from the fact that **106** 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,[282] 1,2-difluoroethane,[283] and 2-fluoroethyl trichloroacetate ($FCH_2CH_2OCOCCl_3$)[284] exist predominantly in the *gauche* form and compounds, such as 2-chloroethanol and 2-bromoethanol,[282] also prefer the *gauche* form. It has been proposed that the preference for the *gauche* conformation in these molecules is an example of a more general phenomenon, known as the *gauche effect*, that is, a tendency to adopt that structure that has the maximum number of *gauche* interactions between adjacent electron pairs or polar bonds.[285] It was believed that the favorable *gauche* conformation of 2-fluoroethanol was the result of intramolecular hydrogen bonding, but this explanation does not do for molecules like 2-fluoroethyl trichloroacetate and has in fact been ruled out for 2-fluoroethanol as well.[286] The effect of β-substituents in Y—C—C—OX systems, where Y = F or SiR_3 has been examined and there is a small bond shortening effect on C—OX that is greatest when OX is a good leaving group. Bond lengthening was also observed with the β-silyl substituent.[287] 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,[288] even although 1,1,2,2-tetrafluoroethane prefers the anti.[289] Also, both 2,3-dimethylpentane and 3,4-dimethylhexane prefer the *gauche* conformation,[290] and 2,3-dimethylbutane shows no preference for either.[291] Furthermore, the solvent can exert a powerful

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

[283] Klaboe, P.; Nielsen, J.R. *J. Chem. Phys.* ***1960***, *33*, 1764; Abraham, R.J.; Kemp, R.H. *J. Chem. Soc. B* ***1971***, 1240; Bulthuis, J.; van den Berg, J.; MacLean, C. *J. Mol. Struct.* ***1973***, *16*, 11; van Schaick, E.J.M.; Geise, H.J.; Mijlhoff, F.C.; Renes, G. *J. Mol. Struct.* ***1973***, *16*, 23; Friesen, D.; Hedberg, K. *J. Am. Chem. Soc.* ***1980***, *102*, 3987; Fernholt, L.; Kveseth, K. *Acta Chem. Scand. Ser. A* ***1980***, *34*, 163.

[284] Abraham, R.J.; Monasterios, J.R. *Org. Magn. Reson.* ***1973***, *5*, 305.

[285] This effect is ascribed to nuclear electron attactive forces between the groups or unshared pairs: Wolfe, S.; Rauk, A.; Tel, L.M.; Csizmadia, I.G. *J. Chem. Soc. B* ***1971***, 136; Wolfe, S. *Acc. Chem. Res.* ***1972***, *5*, 102. See also, Phillips, L.; Wray, V. *J. Chem. Soc. Chem. Commun.* ***1973***, 90; Radom, L.; Hehre, W.J.; Pople, J.A. *J. Am. Chem. Soc.* ***1972***, *94*, 2371; Zefirov, N.S. *J. Org. Chem. USSR* ***1974***, *10*, 1147; Juaristi, E. *J. Chem. Educ.* ***1979***, *56*, 438.

[286] Griffith, R.C.; Roberts, J.D. *Tetrahedron Lett.* ***1974***, 3499.

[287] Amos, R.D.; Handy, N.C.; Jones, P.G.; Kirby, A.J.; Parker, J.K.; Percy, J.M.; Su, M.D. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 549.

[288] Kagarise, R.E. *J. Chem. Phys.* ***1956***, *24*, 300.

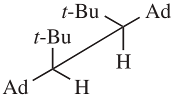
[289] Brown, D.E.; Beagley, B. *J. Mol. Struct.* ***1977***, *38*, 167.

[290] Ritter, W.; Hull, W.; Cantow, H. *Tetrahedron Lett.* ***1978***, 3093.

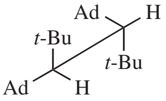
[291] Lunazzi, L.; Macciantelli, D.; Bernardi, F.; Ingold, K.U. *J. Am. Chem. Soc.* ***1977***, *99*, 4573.

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).[292] In many cases, there are differences in the conformation of these molecules between the gas and the liquid phase (as when $X = Y = OMe$) because of polar interactions with the solvent.[293]

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.[294] The two isomers **107** and **108** 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.)



107



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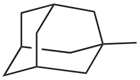

All the conformations so far discussed have involved rotation about sp^3–sp^3 bonds. Many studies were also made of compounds with sp^3–sp^2 bonds.[295] For example, propanal (or any similar molecule) has four extreme conformations, two of which are called *eclipsing* and the other two *bisecting*. For propanal the eclipsing conformations have lower energy than the other two, with **109** favored over **110** by ~1 kcal mol^{-1} (4 kJ mol^{-1}).[296] As has already been pointed out (p. 184), for a few of these compounds, rotation is slow enough to permit cis–trans isomerism, although for simple compounds rotation is rapid. The cis conformer of acetic acid was produced in solid Ar,[297] and it was reported that acetaldehyde has a lower rotational barrier (~1 kcal mol^{-1} or 4 kJ mol^{-1}) than ethane.[298] Calculations have examined the rotational barriers around the CO and CC bonds

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[292] Tan, B.; Chia, L.H.L.; Huang, H.; Kuok, M.; Tang, S. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1407.

[293] Smith, G.D.; Jaffe, R.L.; Yoon, D.Y. *J. Am. Chem. Soc.* ***1995***, *117*, 530. For an analysis of *N,N*-dimethylacetamide see Mack, H.-G.; Oberhammer, H. *J. Am. Chem. Soc.* ***1997***, *119*, 3567.

[294] Flamm-ter Meer; Beckhaus, H.; Peters, K.; von Schnering, H.; Fritz, H.; Rüchardt, C. *Chem. Ber.* ***1986***, *119*, 1492; Rüchardt, C.; Beckhaus, H. *Angew. Chem. Int. Ed.* ***1985***, *24*, 529.

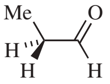
[295] For reviews, see Sinegovskaya, L.M.; Keiko, V.V.; Trofimov, B.A. *Sulfur Rep.* ***1987***, *7*, 337 (for enol ethers and thioethers); Karabatsos, G.J.; Fenoglio, D.J. *Top. Stereochem.* ***1970***, *5*, 167; Jones, G.I.L.; Owen, N.L. *J. Mol. Struct.* ***1973***, *18*, 1 (for carboxylic esters). See also, Schweizer, W.B.; Dunitz, J.D. *Helv. Chim. Acta* ***1982***, *65*, 1547; Chakrabarti, P.; Dunitz, J.D. *Helv. Chim. Acta* ***1982***, *65*, 1555; Cossé-Barbi, A.; Massat, A.; Dubois, J.E. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 919; Dorigo, A.E.; Pratt, D.W.; Houk, K.N. *J. Am. Chem. Soc.* ***1987***, *109*, 6591.

[296] Butcher, S.S.; Wilson Jr., E.B. *J. Chem. Phys.* ***1964***, *40*, 1671; Allinger, N.L.; Hickey, M.J. *J. Mol. Struct.* ***1973***, *17*, 233; Gupta, V.P. *Can. J. Chem.* ***1985***, *63*, 984.

[297] Macoas, E. M. S.; Khriachtchev, L.; Pettersson, M.; Fausto, R.; Rasanen, M. J. *Am. Chem. Soc.* ***2003***, *125*, 16188.

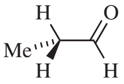
[298] Davidson, R.B.; Allen, L.C. *J. Chem. Phys.* ***1971***, *54*, 2828.

in formic acid, ethanedial and glycolaldedyde molecules.[299]



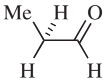
Eclipsing

109

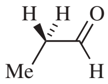


Eclipsing

110

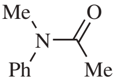


Bisecting

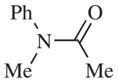


Bisecting

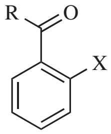
Other carbonyl compounds exhibit rotation about sp^3–sp^3 bonds, including amides.[300] In *N*-acetyl-*N*-methylaniline, the cis conformation (**111**) is more stable than the *trans*- (**112**) by 3.5 kcal mol^{-1} (14.6 kJ mol^{-1}).[301] This is due to destabilization of (*S*) due to steric hindrance between two methyl groups, and to electronic repulsion between the carbonyl lone-pair electrons and the phenyl π-electrons in the twisted phenyl orientation.[301]



111



112



113

A similar conformational analysis has been done with formamide derivatives,[302] with secondary amides,[303] and for hydroxamide acids.[304] It is known that thioformamide has a larger rotational barrier than formamide, which can be explained by a traditional picture of amide ‘‘resonance’ that is more appropriate for the thioformamide than formamide itself.[305] Torsional barriers in α-keto amides have been reported,[306] and the C—N bond of acetamides,[307] thioamides,[308] enamides[309] carbamates ($R_2N—CO_2R'$),[310,311] and enolate anions derived

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[299] Ratajczyk, T.; Pecul, M.; Sadlej, J. *Tetrahedron* ***2004***, *60*, 179.

[300] Avalos, M.; Babiano, R.; Barneto, J.L.; Bravo, J.L.; Cintas, P.; Jiménez, J.L.; Palcios, J.C. *J. Org. Chem.* ***2001***, *66*, 7275.

[301] Saito, S.; Toriumi, Y.; Tomioka, A.; Itai, A. *J. Org. Chem.* ***1995***, *60*, 4715.

[302] Axe, F.U.; Renugopalakrishnan, V.; Hagler, A.T. *J. Chem. Res.* ***1998***, 1. For an analysis of DMF see Wiberg, K.B.; Rablen, P.R.; Rush, D.J.; Keith, T.A. *J. Am. Chem. Soc.* ***1995***, *117*, 4261.

[303] Avalos, M.; Babiano, R.; Barneto, J.L.; Cintas, P.; Clemente, F.R.; Jiménez, J.L.; Palcios, J.C. *J. Org. Chem.* ***2003***, *68*, 1834.

[304] Kakkar, R.; Grover, R.; Chadha, P. *Org. Biomol. Chem.* ***2003***, *1*, 2200.

[305] Wiberg, K.B.; Rablen, P.R. *J. Am. Chem. Soc.* ***1995***, *117*, 2201.

[306] Bach, R.D.; Mintcheva, I.; Kronenberg, W.J.; Schlegel, H.B. *J. Org. Chem.* ***1993***, *58*, 6135.

[307] Ilieva, S.; Hadjieva, B.; Galabov, B. *J. Org. Chem.* ***2002***, *67*, 6210.

[308] Wiberg, K. B.; Rush, D. J. *J. Am. Chem. Soc.* **2001**, 123, 2038; *J. Org. Chem.* ***2002***, *67*, 826.

[309] Rablen, P.R.; Miller, D.A.; Bullock, V.R.; Hutchinson, P.H.; Gorman, J.A. *J. Am. Chem. Soc.* ***1999***, *121*, 218.

[310] Menger, F.M.; Mounier, C.E. *J. Org. Chem.* ***1993***, *58*, 1655.

[311] Deetz, M.J.; Forbes, C.C.; Jonas, M.; Malerich, J.P.; Smith, B.D.; Wiest, O. *J. Org. Chem.* ***2002***, *67*, 3949.

from amides[312] have been examined. It is known that substituents influence rotational barriers.[313]

On p. 146, atropisomerism was possible when ortho substituents on biphenyl derivatives and certain other aromatic compounds prevented rotation about the C*sp*^{3}—C*sp*^{3} bond. The presence of ortho substituents can also influence the conformation of certain groups. In **113**, R = alkyl the carbonyl unit is planar with the trans C=O•••F conformer more stable when X = F. When X = CF_3, the cis and trans are planar and the trans predominates.[314] When R = alkyl there is one orthogonal conformation, but there are two interconverting nonplanar conformations when R = O-alkyl.[314] In 1,2-diacylbenzenes, the carbonyl units tend to adopt a twisted conformation to minimize steric interactions.[315]

Conformation in Six-Membered Rings[316]

For cyclohexane there are two extreme conformations in which all the angles are tetrahedral.[317] 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[318] and can easily pass over to a somewhat more stable form known as the *twist* conformation. The twist form is ~1.5 kcal mol^{-1} (6.3 kJ mol^{-1}) more stable than the boat because it has less eclipsing interaction (see p. 224).[319] The chair form is more stable than the twist form by ~5 kcal mol^{-1} (21 kJ mol^{-1}).[320] In the vast majority of compounds containing a cyclohexane ring, the molecules exist almost entirely in the chair form.[321] Yet, it

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[312] Kim, Y.-J.; Streitwieser, A.; Chow, A.; Fraenkel, G. *Org. Lett.* ***1999***, *1*, 2069.

[313] Smith, B.D.; Goodenough-Lashua, D.M.; D'Souza, C.J.E.; Norton, K.J.; Schmidt, L.M.; Tung, J.C. *Tetrahedron Lett.* ***2004***, *45*, 2747.

[314] Abraham, R.J.; Angioloni, S.; Edgar, M.; Sancassan, F. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 41.

[315] Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* ***1997***, *62*, 7592.

[316] For reviews, see Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139; Robinson, D.L.; Theobald, D.W. *Q. Rev. Chem. Soc.* ***1967***, *21*, 314; Eliel, E.L. *Angew. Chem. Int. Ed.* ***1965***, *4*, 761. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 686–753. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 46–57.

[317] The C—C—C angles in cyclohexane are actually 111.5° [Davis, M.; Hassel, O. *Acta Chem. Scand.* ***1963***, *17*, 1181; Geise, H.J.; Buys, H.R.; Mijlhoff, F.C. *J. Mol. Struct.* ***1971***, *9*, 447; Bastiansen, O.; Fernholt, L.; Seip, H.M.; Kambara, H.; Kuchitsu, K. *J. Mol. Struct.* ***1973***, *18*, 163], but this is within the normal tetrahedral range (see p. 26).

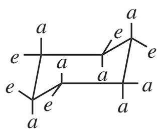
[318] See Dunitz, J.D. *J. Chem. Educ.* ***1970***, *47*, 488.

[319] For a review of nonchair forms, see Kellie, G.M.; Riddell, F.G. *Top. Stereochem.* ***1974***, *8*, 225.

[320] Margrave, J.L.; Frisch, M.A.; Bautista, R.G.; Clarke, R.L.; Johnson, W.S. *J. Am. Chem. Soc.* ***1963***, *85*, 546; Squillacote, M.; Sheridan, R.S.; Chapman, O.L.; Anet, F.A.L. *J. Am. Chem. Soc.* ***1975***, *97*, 3244.

[321] For a study of conformations in the cyclohexane series, see Wiberg, K. B.; Hammer, J. D.; Castejon, H.; Bailey, W. F.; DeLeon, E. L.; Jarret, R. M. *J. Org. Chem.* ***1999***, *64*, 2085; Wiberg, K.B.; Castejon, H.; Bailey, W.F.; Ochterski, J. *J. Org. Chem.* ***2000***, *65*, 1181.

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:



a = axial group
e = equatorial group

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 mono-substituted 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.[322] 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 $\sim$10 kcal mol^{-1} (42 kJ mol^{-1})[323] and is very rapid at room temperature.[324] However, by working at low temperatures, Jensen and Bushweller were able to obtain the pure equatorial conformers of chlorocyclohexane and trideuteriomethoxycyclohexane as solids and in solution.[325] Equatorial chlorocyclohexane has a half-life of 22 years in solution at -160°C.

In some molecules, the twist conformation is actually preferred.[326] Of course, in certain bicyclic compounds, the six-membered ring is forced to maintain a boat or twist conformation, as in norbornane or twistane.

Norbornane

Twistane

In mono-substituted cyclohexanes, the substituent normally prefers the equatorial position because in the axial position there is interaction between the substituent

[322] Wehle, D.; Fitjer, L. *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.

[323] Jensen, F.R.; Noyce, D.S.; Sederholm, C.H.; Berlin, A.J. *J. Am. Chem. Soc.* ***1962***, *84*, 386; Bovey, F.A.; Hood, F.P.; Anderson, E.W.; Kornegay, R.L. *J. Chem. Phys.* ***1964***, *41*, 2041; Anet, F.A.L.; Bourn, A.J.R. *J. Am. Chem. Soc.* ***1967***, *89*, 760. See also Strauss, H.L. *J. Chem. Educ.* ***1971***, *48*, 221.

[324] For reviews of chair–chair interconversions, see Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 287–307; Anderson, J.E. *Top. Curr. Chem.* ***1974***, *45*, 139.

[325] Jensen, F.R.; Bushweller, C.H. *J. Am. Chem. Soc.* ***1966***, *88*, 4279; Paquette, L.A.; Meehan, G.V.; Wise, L.D. ***1969***, *91*, 3223.

[326] Weiser, J.; Golan, O.; Fitjer, L.; Biali, S.E. *J. Org. Chem.* ***1996***, *61*, 8277.

and the axial hydrogens in the 3 and 5 positions, but the extent of this preference depends greatly on the nature of the group.[327] Alkyl groups have a greater preference for the equatorial postion than polar groups. For alkyl groups, the preference increases with size, although size seems to be unimportant for polar groups. Both the large HgBr[328] and HgCl[329] 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),[330] although it must be kept in mind that they vary somewhat with physical state, temperature, and solvent.[331]

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[332] and most *trans*-1,2-dihalocyclohexanes exist predominantly in the *aa* conformation.[333] Note that in the latter case the two halogen atoms are anti in the *aa* conformation, but *gauche* in the *ee* conformation.[334]

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 $\sim$2 kcal mol^{-1}

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[327] For a study of thioether, sulfoxide and sulfone substituents, see Juaristi, E.; Labastida, V.; Antúnez, S. *J. Org. Chem.* ***2000***, *65*, 969.

[328] Jensen, F.R.; Gale, L.H. *J. Am. Chem. Soc.* ***1959***, *81*, 6337.

[329] Anet, F.A.L.; Krane, J.; Kitching, W.; Dodderel, D.; Praeger, D. *Tetrahedron Lett.* ***1974***, 3255.

[330] Except where otherwise indicated, these values are from Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139. See also Schneider, H.; Hoppen, V. *Tetrahedron Lett.* ***1974***, 579 and see Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 46–57.

[331] See, for example, Ford, R.A.; Allinger, N.L. *J. Org. Chem.* ***1970***, *35*, 3178. For a critical review of the methods used to obtain these values, see Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139.

[332] Atkinson, V.A.; Hassel, O. *Acta Chem. Scand.* ***1959***, *13*, 1737; Abraham, R.J.; Rossetti, Z.L. *Tetrahedron Lett.* ***1972***, 4965, *J. Chem. Soc. Perkin Trans. 2* ***1973***, 582. See also, Hammarström, L.; Berg, U.; Liljefors, T. *Tetrahedron Lett.* ***1987***, *28*, 4883.

[333] Hageman, H.J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* ***1969***, *88*, 97; Klaeboe, P. *Acta Chem. Scand.* ***1971***, *25*, 695; Abraham, M.H.; Xodo, L.E.; Cook, M.J.; Cruz, R. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1503; Samoshin, V.V.; Svyatkin, V.A.; Zefirov, N.S. *J. Org. Chem. USSR* ***1988***, *24*, 1080, and references cited therein. *trans*-1,2-Difluorocyclohexane exists predominantly in the ee conformation: see Zefirov, N.S.; Samoshin, V.V.; Subbotin, O.A.; Sergeev, N.M. *J. Org. Chem. USSR* ***1981***, *17*, 1301.

[334] For a case of a preferential diaxial conformation in 1,3 isomers, see Ochiai, M.; Iwaki, S.; Ukita, T.; Matsuura, Y.; Shiro, M.; Nagao, Y. *J. Am. Chem. Soc.* ***1988***, *110*, 4606.

TABLE 4.3. Free-Energy Differences between Equatorial and Axial Substituents on a Cyclohexane Ring (*A* Values)[330]

	Approximate $-\Delta G^\circ$,			Approximate $-\Delta G^\circ$	
Group	kcal mol^{-1}	kJ mol^{-1}	Group	kcal mol^{-1}	kJ mol^{-1}
HgCl[330]	−0.25	−1.0	NO_2	1.1	4.6
HgBr	0	0	COOEt	1.1–1.2	4.6–5.0
D[335]	0.008	0.03	COOMe	1.27–1.31	5.3–5.5
CN	0.15–0.25	0.6–1.0	COOH	1.35–1.46	5.7–6.1
F	0.25	1.0	NH_2[336]	1.4	5.9
C≡CH	0.41	1.7	$CH{=}CH_2$[337]	1.7	7.1
I	0.46	1.9	CH_3[338]	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	*i*-Pr	~2.15	~9.0
Cl	0.52	2.2	C_6H_{11}[339]	2.15	9.0
OAc	0.71	3.0	$SiMe_3$[340]	2.4–2.6	10–11
OMe[341]	0.75	3.1	C_6H_5[342]	2.7	11
OH	0.92–0.97	3.8–4.1	*t*-Bu[343]	4.9	21

(8 kJ mol^{-1}). Similarly, *trans*-1,4 and *cis*-1,3 compounds are more stable than their stereoisomers.

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.[344] 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 although they are not planar (p. 186). In the case of both a *cis*-1,2-X,X-disubstituted and a *cis*-1,2-X,Y-disubstituted cyclohexane, the molecule is nonsuperimposable on its mirror image;

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[335] Anet, F.A.L.; O'Leary, D.J. *Tetrahedron Lett.* ***1989***, *30*, 1059.

[336] Buchanan, G.W.; Webb, V.L. *Tetrahedron Lett.* ***1983***, *24*, 4519.

[337] Eliel, E.L.; Manoharan, M. *J. Org. Chem.* ***1981***, *46*, 1959.

[338] Booth, H.; Everett, J.R. *J. Chem. Soc. Chem. Commun.* ***1976***, 278.

[339] Hirsch, J.A. *Top. Stereochem.* ***1967***, *1*, 199.

[340] Kitching, W.; Olszowy, H.A.; Drew, G.M.; Adcock, W. *J. Org. Chem.* ***1982***, *47*, 5153.

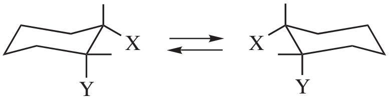
[341] Schneider, H.; Hoppen, V. *Tetrahedron Lett.* ***1974***, 579.

[342] Squillacote, M.E.; Neth, J.M. *J. Am. Chem. Soc.* ***1987***, *109*, 198. Values of 2.59–2.92 kcal mol^{-1} were determined for 4-X-C_6H_4- substituents (X = NO_2, Cl, MeO) - see Kirby, A.J.; Williams, N.H. *J. Chem. Soc. Chem. Commun.* ***1992***, 1285, 1286.

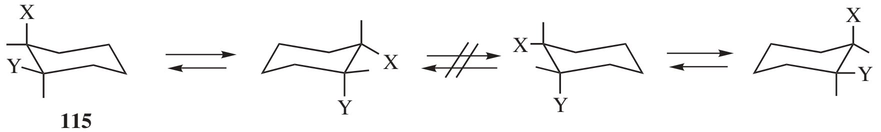
[343] Manoharan, M.; Eliel, E.L. *Tetrahedron Lett.* ***1984***, *25*, 3267.

[344] Golan, O.; Goren, Z.; Biali, S.E. *J. Am. Chem. Soc.* ***1990***, *112*, 9300.

neither has a plane of symmetry. However, in the former case (**114**) 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 (**115**) 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 **114** 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 X,X and X,Y) optical inactivity arises from a plane of symmetry in both conformations. All-trans-1,2- and trans-1,3-disubstituted cyclohexanes are chiral (whether X,X or X,Y), while trans-1,4 compounds (both X,X and X,Y) are achiral, since all conformations have a plane of symmetry. It has been shown that the equilibrium is very dependent on both the solvent and the concentration of the disubstituted cyclohexane.[345] A theoretical study of the 1,2-dihalides showed a preference for the diaxial form with $X = Cl$, but predicted that the energy difference between diaxial and diequatorial was small when $X = F$.[346]



114



115

The conformation of a group can be frozen into a desired position by putting into the ring a large alkyl group (most often *tert*-butyl), which greatly favors the equatorial position.[347] It is known that silylated derivatives of *trans*-1,4- and *trans*-1,2-dihydroxycyclohexane, some monosilyloxycyclohexanes and some silylated sugars have unusually large populations of chair conformations with axial substituents.[348] Adjacent silyl groups in the 1,2-disubstituted series show a stabilizing interaction in all conformations, and this leads generally to unusually large axial populations.

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[345] Abraham, R.J.; Chambers, E.J.; Thomas, W.A. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1061.

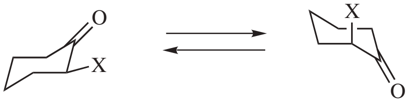
[346] Wiberg, K. B. *J. Org. Chem.* ***1999***, *64*, 6387.

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

[348] Marzabadi, C. H.; Anderson, J.E.; Gonzalez-Outeirino, J.; Gaffney, P.R.J.; White, C.G.H.; Tocher, D.A.; Todaro, L.J. *J. Am. Chem. Soc.* ***2003***, *125*, 15163.

The principles involved in the conformational analysis of six-membered rings containing one or two trigonal atoms, for example, cyclohexanone and cyclohexene, are similar.[349–351] The barrier to interconversion in cyclohexane has been calculated to be 8.4–12.1 kcal mol^{-1}.[352] Cyclohexanone derivatives also assume a chair-conformation. Substituents at C-2 can assume an axial or equatorial position depending on steric and electronic influences. The proportion of the conformation with an axial X group is shown in Table 4.4 for a variety of substituents (X) in 2-substituted cyclohexanones.[353]

TABLE 4.4. Proportion of Axial Conformation in 2-Substituted Cyclohexanones, in $CDCl_3$.[353]



X	% Axial Conformation
F	17 ± 3
Cl	45 ± 4
Br	71 ± 4
I	88 ± 5
MeO	28 ± 4
MeS	85 ± 7
MeSe	(92)
Me_2N	44 ± 3
Me	(26)

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[349] For a monograph, see Rabideau, P.W. *The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*, VCH, NY, ***1989***. For reviews, see Vereshchagin, A.N. *Russ. Chem. Rev.* ***1983***, *52*, 1081; Johnson, F. *Chem. Rev.* ***1968***, *68*, 375. See also, Lambert, J.B.; Clikeman, R.R.; Taba, K.M.; Marko, D.E.; Bosch, R.J.; Xue, L. *Acc. Chem. Res.* ***1987***, *20*, 454.

[350] For books on conformational analysis see Dale, J. *Stereochemistry and Conformational Analysis*, Verlag Chemie, Deerfield Beach, FL, ***1978***; Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, ***1971***; Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*, Wiley, NY, ***1965***; Hanack, M. *Conformation Theory*, Academic Press, NY, ***1965***. For reviews, see Dale, J. *Top. Stereochem.* ***1976***, *9*, 199; Truax, D.R.; Wieser, H. *Chem. Soc. Rev.* ***1976***, *5*, 411; Eliel, E.L. *J. Chem. Educ.* ***1975***, *52*, 762; Bastiansen, O.; Seip, H.M.; Boggs, J.E. *Perspect. Struct. Chem.* ***1971***, *4*, 60; Bushweller, C.H.; Gianni, M.H., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 215–278.

[351] For reviews, see Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139; Robinson, D.L.; Theobald, D.W. *Q. Rev. Chem. Soc.* ***1967***, *21*, 314; Eliel, E.L. *Angew. Chem. Int. Ed.* ***1965***, *4*, 761. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 686–753. Also see Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 53–55.

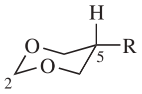
[352] Laane, J.; Choo, J. *J. Am. Chem. Soc.* ***1994***, *116*, 3889.

[353] Basso, E.A.; Kaiser, C.; Rittner, R.; Lambert, J.B. *J. Org. Chem.* ***1993***, *58*, 7865.

Conformation in Six-Membered Rings Containing Heteroatoms

In six-membered rings containing heteroatoms,[354] the basic principles are the same; that is, there are chair, twist, and boat forms, axial, and equatorial groups. The conformational equilibrium for tetrahydropyridines, for example, has been studied.[355] In certain compounds a number of new factors enter the picture. We deal with only two of these.[356]

1. In 5-alkyl-substituted 1,3-dioxanes, the 5-substituent has a much smaller preference for the equatorial position than in cyclohexane derivatives;[357] the *A* values are much lower. This indicates that the lone pairs on the oxygens have a smaller steric requirement than the C—H bonds in the corresponding cyclohexane derivatives. There is some evidence of an homoanomeric interaction in these systems.[358]



   Similar behavior is found in the 1,3-dithianes,[359] and 2,3-disubstituted-1,4-dithianes have also been examined.[360] With certain non-alkyl substituents (e.g., F, NO_2, SOMe,[361] NMe_3^+) the axial position is actually preferred.[362]

2. An alkyl group located on a carbon α to a heteroatom 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

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[354] For monographs, see Glass, R.S. *Conformational Analysis of Medium-Sized Heterocycles*, VCH, NY, ***1988***; Riddell, F.G. *The Conformational Analysis of Heterocyclic Compounds*, Academic Press, NY, ***1980***. For reviews, see Juaristi, E. *Acc. Chem. Res.* ***1989***, *22*, 357; Crabb, T.A.; Katritzky, A.R. *Adv. Heterocycl. Chem.* ***1984***, *36*, 1; Eliel, E.L. *Angew. Chem. Int. Ed.* ***1972***, *11*, 739; *Pure Appl. Chem.* ***1971***, *25*, 509; *Acc. Chem. Res.* ***1970***, *3*, 1; Lambert, J.B. *Acc. Chem. Res.* ***1971***, *4*, 87; Romers, C.; Altona, C.; Buys, H.R.; Havinga, E. *Top. Stereochem.* ***1969***, *4*, 39; Bushweller, C.H.; Gianni, M.H., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wley, NY, ***1980***, pp. 232–274.

[355] Bachrach, S.M.; Liu, M. *Tetrahedron Lett.* ***1992***, *33*, 6771.

[356] These factors are discussed by Eliel, E.L. *Angew. Chem. Int. Ed.* ***1972***, *11*, 739.

[357] Riddell, F.G.; Robinson, M.J.T. *Tetrahedron* ***1967***, *23*, 3417; Eliel, E.L.; Knoeber, M.C. *J. Am. Chem. Soc.* ***1968***, *90*, 3444. See also Eliel, E.L.; Alcudia, F. *J. Am. Chem. Soc.* ***1974***, *96*, 1939. See Cieplak, P.; Howard, A.E.; Powers, J.P.; Rychnovsky, S.D.; Kollman, P.A. *J. Org. Chem.* ***1996***, *61*, 3662 for conformational energy differences in 2,2,6-trimethyl-4-alkyl-1,3-dioxane.

[358] Cai, J.; Davies, A.G.; Schiesser, C.H. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 1151.

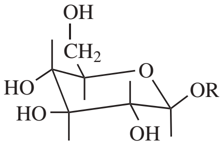
[359] Hutchins, R.O.; Eliel, E.L. *J. Am. Chem. Soc.* ***1969***, *91*, 2703. See also, Juaristi, E.; Cuevas, G. *Tetrahedron* ***1999***, *55*, 359.

[360] Strelenko, Y.A.; Samoshin, V.V.; Troyansky, E.I.; Demchuk, D.V.; Dmitriev, D.E.; Nikishin, G.I.; Zefirov, N.S. *Tetrahedron* ***1994***, *50*, 10107.

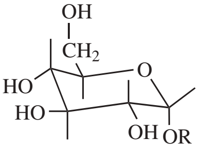
[361] Gordillo, B.; Juaristi, E.; Matínez, R.; Toscano, R.A.; White, P.S.; Eliel, E.L. *J. Am. Chem. Soc.* ***1992***, *114*, 2157.

[362] Kaloustian, M.K.; Dennis, N.; Mager, S.; Evans, S.A.; Alcudia, F.; Eliel, E.L. *J. Am. Chem. Soc.* ***1976***, *98*, 956. See also Eliel, E.L.; Kandasamy, D.; Sechrest, R.C. *J. Org. Chem.* ***1977***, *42*, 1533.

phenomenon, known as the *anomeric effect*,[363] is the greater stability of α-glucosides over β-glucosides. A number of explanations have been offered

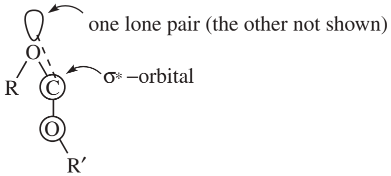


A β-glucoside
116

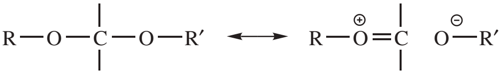


An α-glucoside
117

for the anomeric effect.[364] The one[365] that has received the most acceptance[366] is that one of the lone pairs of the polar atom connected to the carbon (an oxygen atom in the case of **117**) can be stabilized by overlapping with an antibonding orbital of the bond between the carbon and the other polar atom:



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"):



$$\mathrm{R{-}O{-}\overset{|}{\underset{|}{C}}{-}O{-}R'} \longleftrightarrow \mathrm{R{-}\overset{\oplus}{O}{=}\overset{|}{\underset{|}{C}}\quad \overset{\ominus}{O}{-}R'}$$

It is possible that simple repulsion between parallel dipoles in **116** also plays a part in the greater stability of **117**. It has been shown that aqueous solvation effects reduce anomeric stabilization in many systems, particularly for tetrahydropyranosyls.[367] In contrast to cyclic acetals, simple acyclic acetlas

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[363] For books on this subject, see Kirby, A.J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, NY, ***1983***; Szarek, W.A.; Horton, D. *Anomeric Effect*, American Chemical Society, Washington, ***1979***. For reviews see Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Elmsford, NY, ***1983***, pp. 4–26; Zefirov, N.S. *Tetrahedron* ***1977***, *33*, 3193; Zefirov, N.S.; Shekhtman, N.M. *Russ. Chem. Rev.* ***1971***, *40*, 315; Lemieux, R.U. *Pure Appl. Chem.* ***1971***, *27*, 527; Angyal, S.J. *Angew. Chem. Int. Ed.* ***1969***, *8*, 157; Martin, J. *Ann. Chim. (Paris) [14]*, ***1971***, *6*, 205.

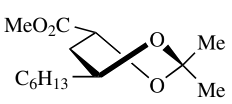
[364] Juaristi, E.; Cuevas, G. *Tetrahedron* ***1992***, *48*, 5019.

[365] See Romers, C.; Altona, C.; Buys, H.R.; Havinga, E. *Top. Stereochem.* ***1969***, *4*, 39, see pp. 73–77; Wolfe, S.; Whangbo, M.; Mitchell, D.J. *Carbohydr. Res.* ***1979***, *69*, 1.

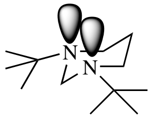
[366] For some evidence for this explanation, see Fuchs, B.; Ellencweig, A.; Tartakovsky, E.; Aped, P. *Angew. Chem. Int. Ed.* ***1986***, *25*, 287; Praly, J.; Lemieux, R.U. *Can. J. Chem.* ***1987***, *65*, 213; Booth, H.; Khedhair, K.A.; Readshaw, S.A. *Tetrahedron* ***1987***, *43*, 4699. For evidence against it, see Box, V.G.S. *Heterocycles* ***1990***, *31*, 1157.

[367] Cramer, C.J. *J. Org. Chem.* ***1992***, *57*, 7034; Booth, H.; Dixon, J.M.; Readshaw, S.A. *Tetrahedron* ***1992***, *48*, 6151.

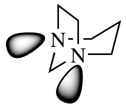
rarely adopt the anomeric conformation, apparently because the eclipsed conformation better accommodates steric interactions of groups linked by relatively short carbon–oxygen bonds.[368] In all-cis-2,5-di-*tert*-butyl-1,4-cyclohexanediol, hydrogen bonding stabilizes the otherwise high-energy form[369] and 1,3-dioxane (**118**) exists largely as the twist conformation shown.[370] The conformational preference of 1-methyl-1-silacyclohexane (**121**) has been studied.[371] A strongly decreased activation barrier in silacyclohexane was observed, as compared to that in the parent ring, and is explained by the longer endocyclic Si—C bonds.



118



119



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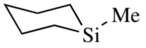

121

Second-row heteroatoms are known to show a substantial anomeric effect.[372] There appears to be evidence for a reverse anomeric effect in 2-aminotetrahydropyrans.[373] It has been called into question whether a reverse anomeric effect exists at all.[374] In **119**, the lone-pair electrons assume an axial conformation and there is an anomeric effect.[375] In **120**, however, the lone-pair electron orbitals are oriented gauche to both the axial and equatorial α-CH bond and there is no anomeric effect.[375]

Conformation in Other Rings[376]

Three-membered saturated rings are usually planar, but other three-membered rings can have some flexibility. Cyclobutane[377] is not planar but exists as in **122**, with an

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[368] Anderson, J.E. *J. Org. Chem.* ***2000***, *65*, 748.

[369] Stolow, R.D. *J. Am. Chem. Soc.* ***1964***, *86*, 2170; Stolow, R.D.; McDonagh, P.M.; Bonaventura, M.M. *J. Am. Chem. Soc.* ***1964***, *86*, 2165. For some other examples, see Camps, P.; Iglesias, C. *Tetrahedron Lett.* ***1985***, *26*, 5463; Fitjer, L.; Scheuermann, H.; Klages, U.; Wehle, D.; Stephenson, D.S.; Binsch, G. *Chem. Ber.* ***1986***, *119*, 1144.

[370] Rychnovsky, S.D.; Yang, G.; Powers, J.P. *J. Org. Chem.* ***1993***, *58*, 5251.

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[373] Salzner, U.; Schleyer, P.v.R. *J. Org. Chem.* ***1994***, *59*, 2138.

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[375] Anderson, J.E.; Cai, J.; Davies, A.G. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 2633. For some controversy concerning the anomeric effect a related system, see Perrin, C.L.; Armstrong, K.B.; Fabian, M.A. *J. Am. Chem.Soc.* ***1994***, *116*, 715 and Salzner, U. *J. Org. Chem.* ***1995***, *60*, 986.

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[377] For reviews of the stereochemistry of four-membered rings, see Legon, A.C. *Chem. Rev.* ***1980***, *80*, 231; Moriarty, R.M. *Top. Stereochem.* ***1974***, *8*, 271; Cotton, F.A.; Frenz, B.A. *Tetrahedron* ***1974***, *30*, 1587.

angle between the planes of ~35°.[378] The deviation from planarity is presumably caused by eclipsing in the planar form (see p. 219). Oxetane, in which eclipsing is

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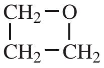
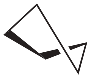


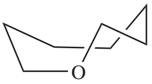
Oxetane

less, is closer to planarity, with an angle between the planes of ~10°.[379] 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.[380] 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.[381] Although in the envelope conformation one 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*.[382] In substituted cyclopentanes and five-membered rings in which at least one atom does not contain two substituents [e.g., tetrahydrofuran (THF), cyclopentanone, C_3 and C_7-mono- and disubstituted hexahydroazepin-2-ones (caprolactams),[383] and tetrahydrothiophene *S*-oxide[384]], one conformer may be more stable than the others. The barrier to planarity in cyclopentane has been reported to be 5.2 kcal mol^{-1} (22 kJ mol^{-1}).[385] Contrary to previous reports, there is only weak stabilization (<2 kcal mol^{-1}; <8 kJ mol^{-1}) of 3-, 4-, and 5-membered rings by *gem*–dialkoxycarbonyl substituents (e.g., COOR).[386]

Envelope



Half-chair



123

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[378] Dows, D.A.; Rich, N. *J. Chem. Phys.* ***1967***, *47*, 333; Stone, J.M.R.; Mills, I.M. *Mol. Phys.* ***1970***, *18*, 631; Miller, F.A.; Capwell, R.J.; Lord, R.C.; Rea, D.G. *Spectrochim. Acta Part A*, ***1972***, *28*, 603. However, some cyclobutane derivatives are planar, at least in the solid state: for example, see Margulis, T.N. *J. Am. Chem. Soc.* ***1971***, *93*, 2193.

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

[380] For reviews of the conformational analysis of five-membered rings, see Fuchs, B. *Top. Stereochem.* ***1978***, *10*, 1; Legon, A.C. *Chem. Rev.* ***1980***, *80*, 231.

[381] Willy, W.E.; Binsch, G.; Eliel, E.L. *J. Am. Chem. Soc.* ***1970***, *92*, 5394; Lipnick, R.L. *J. Mol. Struct.* ***1974***, *21*, 423.

[382] Kilpatrick, J.E.; Pitzer, K.S.; Spitzer, R. *J. Am. Chem. Soc.* ***1947***, *69*, 2438; Pitzer, K.S.; Donath, W.E. *J. Am. Chem. Soc.* ***1959***, *81*, 3213; Durig, J.R.; Wertz, D.W. *J. Chem. Phys.* ***1968***, *49*, 2118; Lipnick, R.L. *J. Mol. Struct.* ***1974***, *21*, 411; Poupko, R.; Luz, Z.; Zimmermann, H. *J. Am. Chem. Soc.* ***1982***, *104*, 5307; Riddell, F.G.; Cameron K.S.; Holmes, S.A.; Strange, J.H. *J. Am. Chem. Soc.* ***1997***, *119*, 7555.

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[384] Abraham, R.J.; Pollock, L.; Sancassan, F. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 2329.

[385] Carreira, L.A.; Jiang, G.J.; Person, W.B.; Willis, Jr., J.N. *J. Chem. Phys.* ***1972***, *56*, 1440.

[386] Verevkin, S.P.; Kümmerlin, M.; Beckhaus, H.-D.; Galli, C.; Rüchardt, C. *Eur. J. Org. Chem.* ***1998***, 579.

Rings larger than six-membered are always puckered[387] unless they contain a large number of *sp*^{2} atoms (see the section on strain in medium rings, p. 223). The energy and conformations of the alkane series cycloheptane to cyclodecane has been reported.[388] The conformation shown for oxacyclooctane (**123**), for example, appears to be the most abundant one.[389] The conformations of other large ring compounds have been studied, including 11-membered ring lactones,[390] 10- and 11-membered ring ketones,[391] and 11- and 14-membered ring lactams.[392] Dynamic NMR was used to determine the conformation large-ring cycloalkenes and lactones.[393] Note 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,[394] although in some cases the terms "pseudo-axial" and "pseudo-equatorial" have been used to classify hydrogens in rings of other sizes.[395]

Molecular Mechanics[396]

Molecular mechanics Molecular Mechanics[397] describes a molecule in terms of a collection of bonded atoms that have been distorted from some idealized geometry due to non-bonded van der Waals (steric) and coulombic (charge–charge)

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[387] For reviews of conformations in larger rings, see Arshinova, R.P. *Russ. Chem. Rev.* ***1988***, *57*, 1142; Ounsworth, J.P.; Weiler, L. *J. Chem. Educ.* ***1987***, *64*, 568; Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 307–321; Casanova, J.; Waegell, B. *Bull. Soc. Chim. Fr.* ***1975***, 911; Anet, F.A.L. *Top. Curr. Chem.* ***1974***, *45*, 169; Dunitz, J.D. *Pure Appl. Chem.* ***1971***, *25*, 495; *Perspect. Struct. Chem.* ***1968***, *2*, 1; Tochtermann, W. *Fortchr. Chem. Forsch.* ***1970***, *15*, 378; Dale, J. *Angew. Chem. Int. Ed.* ***1966***, *5*, 1000. For a monograph, see Glass, R.S. *Conformational Analysis of Medium-Sized Heterocycles*, VCH, NY, ***1988***. Also see the monographs by Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*; Wiley, NY, ***1965***; Hanack, M. *Conformation Theory*, Academic Press, NY, ***1965***.

[388] Wiberg, K.B. *J. Org. Chem* ***2003***, *68*, 9322.

[389] Meyer, W.L.; Taylor, P.W.; Reed, S.A.; Leister, M.C.; Schneider, H.-J.; Schmidt, G.; Evans, F.E.; Levine, R.A. *J. Org. Chem.* ***1992***, *57*, 291.

[390] Spracklin, D.K.; Weiler, L. *J. Chem. Soc. Chem. Commun.* ***1992***, 1347; Ogura, H.; Furuhata, K.; Harada, Y.; Iitaka, Y. *J. Am. Chem. Soc.* ***1978***, *100*, 6733; Ounsworth, J.P.; Weiler, L. *J. Chem. Ed.*, ***1987***, *64*, 568; Keller, T.H.; Neeland, E.G.; Rettig, S.; Trotter, J.; Weiler, L. *J. Am. Chem. Soc.* ***1988***, *110*, 7858.

[391] Pawar, D.M.; Smith, S.V.; Moody, E.M.; Noe, E.A. *J. Am. Chem. Soc.* ***1998***, *120*, 8241.

[392] Borgen, G.; Dale, J.; Gundersen, L.-L.; Krivokapic, A.; Rise, F.; Øverås, A.T. *Acta Chem. Scand. B*, ***1998***, *52*, 1110.

[393] Pawar, D.M.; Davids, K.L.; Brown, B.L.; Smith, S.V.; Noe, E.A. *J. Org. Chem.* ***1999***, *64*, 4580; Pawar, D.M.; Moody, E.M.; Noe, E.A. *J. Org. Chem.* ***1999***, *64*, 4586.

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

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

[396] Thanks to Dr. Warren Hehre, Wavefunction, Inc., Irvine, CA. Personal communication. See Hehre, W.J. *A Guide to Molecular Mechanics and Quantum Chemical Calculations*, Wavefunction, Inc., Irvine, CA, ***2003***, pp. 56–57.

[397] For a review, see Rappe, A.K.; Casewit, C.J. *Molecular Mechanics Across Chemistry*, University Science Books, Sausalito, CA, ***1997***.

interactions. This approach is fundamentally different from molecular-orbital theory that is based on quantum mechanics and that make no reference whatsoever to chemical bonding. The success of molecular mechanics depends on the ability to represent molecules in terms of unique valence structures, on the notion that bond lengths and angles may be transferred from one molecule to another and on a predictable dependence of geometrical parameters on the local atomic environment.

The molecular mechanics energy of a molecule is given as a sum of contributions arising from distortions from ideal bond distances (stretch contributions), bond angles (bend contributions) and torsion angles (torsion contributions), together with contributions from nonbonded interactions. This energy is commonly referred to as a strain energy, meaning that it reflects the inherent strain in a real molecule relative to a hypothetical idealized (strain-free) form.

$$\boldsymbol{E}^{\text{strain}} = \boldsymbol{E}_{\text{A}}^{\text{stretch}} + \boldsymbol{E}_{\text{A}}^{\text{bend}} + \boldsymbol{E}_{\text{A}}^{\text{torsion}} + \boldsymbol{E}_{\text{AB}}^{\text{nonbonded}} \tag{1}$$

Stretch and bend terms are most simply given in terms of quadratic (Hooke's law) forms:

$$\boldsymbol{E}^{\text{stretch}}\ (\text{r}) = \frac{1}{2}k^{\text{stretch}}\ (r - r^{\text{eq}})^2 \tag{2}$$

$$\boldsymbol{E}^{\text{bend}}\ (\alpha) = \frac{1}{2}k^{\text{bend}}\ (r - r^{\text{eq}})^2 \tag{3}$$

r and α are the bond distance and angle, respectively, and r^{eq} and α^{eq} are the ideal bond length and angle, respectively.

Torsion terms need to properly reflect the inherent periodicity of the particular bond involved in a rotation. For example, the threefold periodicity of the carbon-carbon bond in ethane may be represented by a simple cosine form.

$$\boldsymbol{E}^{\text{torsion}}(\omega) = k^{\text{torsion3}}[1 - \cos 3(\omega - \omega^{\text{eq}})] \tag{4}$$

Ω is the torsion angle, ω^{eq} is the ideal torsion angle and k^{torsion} is a parameter. Torsion contributions to the strain energy will also usually need to include contributions that are onefold and twofold periodic. These can be represented in the same manner as the threefold term.

$$\begin{aligned}\boldsymbol{E}^{\text{torsion}}(\omega) = {} & k^{\text{torsion1}}[1 - \cos\ (\omega - \omega^{\text{eq}})] + k^{\text{torsion2}}[1 - \cos 2\ (\omega - \omega^{\text{eq}})] \\ & + k^{\text{torsion3}}[1 - \cos 3\ (\omega - \omega^{\text{eq}})]\end{aligned} \tag{5}$$

Nonbonded interacations invovle a sum of van der Waals (VDW) interactions and coulombic interactions. The coulombic term accounts for charge–charge interactions.

$$\boldsymbol{E}^{\text{nonbonded}}\ (r) = E^{\text{VDW}}\ (r) + \boldsymbol{E}^{\text{coulombic}}\ (r) \tag{6}$$

The VDW is made up of two parts, the first to account for strong repulsion on nonbonded atoms as the closely approach, and the second to account for weak long-range attraction, *r* is the nonbonded distance.

Molecular mechanics methods differ both in the form of the terms that make up the strain energy and in their detailed parameterization. Older methods, such as SYBYL,[398] use very simple forms and relatively few parameters, while newer methods such as MM3,[399] MM4,[400] and MMFF[401] use more complex forms and many more parameters. In general, the more complex the form of the strain energy terms and the more extensive the parameterization, the better will be the results. Of course, more parameters mean that more (experimental) data will be needed in their construction. Because molecular mechanics is not based on "physical fundamentals," but rather is essentially an interpolation scheme, its success depends on the availability of either experimental or high-quality theoretical data for parameterization. A corollary is that molecular mechanics would not be expected to lead to good results for "new" molecules, that is, molecules outside the range of their parameterization.

The two most important applications of molecular mechanics are geometry calculations on very large molecules, for example, on proteins, and conformational analysis on molecules for which there may be hundreds, thousands, or even tens of thousands of distinct structures. It is here that methods based on quantum mechanics are simply not (yet) practical. It should be no surprise that equilibrium geometries obtained from molecular mechanics are generally in good accord with experimental values. There are ample data with which to parameterize and evaluate the methods. However, because there are very few experimental data relating to the equilibrium conformations of molecules and energy differences among different conformations, molecular mechanics calculations for these quantities need to be viewed with a very critical eye. In time, high-quality data from quantum mechanics will provide the needed data and allow more careful parameterization (and assessment) than now possible.

The most important limitation of molecular mechanics is its inability to provide thermochemical data. The reason for this is that the mechanics strain energy is specific to a given molecule (it provides a measure of how much this molecule deviates from an ideal arrangement), and different molecules have different ideal arrangements. For example, acetone and methyl vinyl ether have different bonds and would be referenced to different standards. The only exception occurs for conformational energy differences or, more generally, for energy comparisons among molecules with exactly the same bonding, for example, *cis*- and *trans*-2-butene.

Because a molecular mechanics calculation reveals nothing about the distribution of electrons or distribution of charge in molecules, and because mechanics

[398] Clark, M.; Cramer III, R.D.; van Opdenbosch, N. *J. Computational Chem.* ***1989***, *10*, 982.

[399] Allinger, N.L.; Li, F.; Yan, L. *J. Computational Chem.* ***1990***, *11*, 855, and later papers in this series.

[400] Allinger, N.L.; Chen, K.; Lii, J.-H. *J. Computational Chem.* ***1996***, *17*, 642, and later papers in this series.

[401] Halgren, T.A. *J. Computational Chem* ***1996***, *17*, 490, and later papers in this series.

methods have not (yet) been parameterized to reproduce transition state geometries, they are of limited value in describing either chemical reactivity or product selectivity. There are, however, situations where steric considerations associated with either the product or reactants are responsible for trends in reactivity and selectivity, and here molecular mechanics would be expected to be of some value.

Because of the different strengths and limitations of molecular mechanics and quantum chemical calculations, it is now common practice to combine the two, for example, to use molecular mechanics to establish conformation (or at least a set of reasonable conformations) and then to quantum calculations to evaluate energy differences.

In practical terms, molecular mechanics calculations may easily be performed on molecules comprising several thousand atoms. Additionally, molecular mechanics calculations are sufficiently rapid to permit extensive conformational searching on molecules containing upwards of a hundred atoms. Modern graphical based programs for desktop computers make the methods available to all chemists.

STRAIN

Steric strain[402] 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. It has been shown that there is a good correlation between the ^{13}C—H coupling constants in NMR and the bond angles and bond force angles in strained organic molecules.[403] There 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.[404] 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.[405] 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 (Fig. 4.6). As in the similar case of resonance energies (p. 36), 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

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[402] For a monograph, see Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***. For reviews, see Wiberg, K.B. *Angew. Chem. Int. Ed.* ***1986***, *25*, 312; Greenberg, A.; Stevenson, T.A. *Mol. Struct. Energ.*, ***1986***, *3*, 193; Liebman, J.F.; Greenberg, A. *Chem. Rev.* ***1976***, *76*, 311. For a review of the concept of strain, see Cremer, D.; Kraka, E. *Mol. Struct. Energ.* ***1988***, *7*, 65.

[403] Zhao, C.-Y.; Duan, W.-S.; Zhang, Y.; You, X.-Z. *J. Chem. Res. (S)* ***1998***, 156.

[404] Wiberg, K.B. *Accts. Chem. Res.* ***1996***, *29*, 229.

[405] For discussions, see Wiberg, K.B.; Bader, R.F.W.; Lau, C.D.H. *J. Am. Chem. Soc.* ***1987***, *109*, 985, 1001.

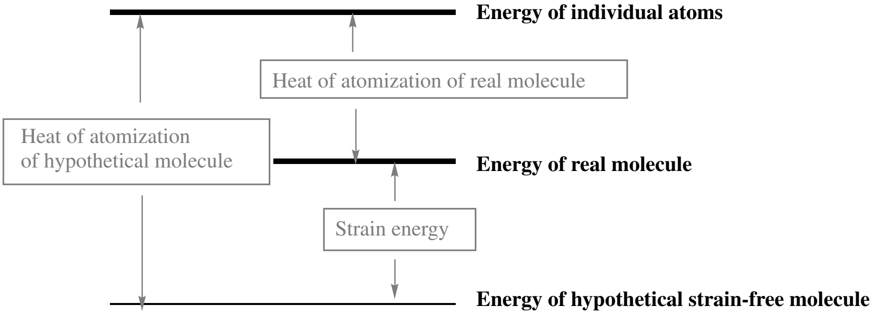

Fig. 4.6. Strain energy calculation.

to calculate strain energies by molecular mechanics, not only for real molecules, but also for those that cannot be made.[406]

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. 496). Ring opening, of course, relieves the strain.[407] Cyclopropane,[408] which is even more strained[409] than ethylene oxide, is also cleaved more easily than would be expected for an alkane.[410] Thus, pyrolysis at 450–500°C converts it to propene, bromination gives 1,3-dibromopropane,[411] and it can be hydrogenated to propane (though at high pressure).[412] Other three-membered rings are similarly reactive.[413] Alkyl substituents influence the strain energy of small ring compounds.[414] *gem*-Dimethyl substitution, for example, "lowers the strain energy of cyclopropanes,

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[406] For a review, see Rüchardt, C.; Beckhaus, K. *Angew. Chem. Int. Ed.* ***1985***, *24*, 529. See also Burkert, U.; Allinger, N.L. *Molecular Mechanisms*, American Chemical Society, Washington, ***1982***, pp. 169–194; Allinger, N.L. *Adv. Phys. Org. Chem.* ***1976***, *13*, 1, pp. 45–47.

[407] For reviews of reactions of cyclopropanes and cyclobutanes, see Trost, B.M. *Top. Curr. Chem.* ***1986***, *133*, 3; Wong, H.N.C.; Lau, C.D.H.; Tam, K. *Top. Curr. Chem.* ***1986***, *133*, 83.

[408] For a treatise, see Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, 2 pts., Wiley, NY, ***1987***.

[409] For reviews of strain in cyclopropanes, see, in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, 2 pts, Wiley, NY, ***1987***, the papers by Wiberg, K.B. pt. 1., pp. 1–26; Liebman, J.F.; Greenberg, A. pt. 2, pp. 1083–1119; Liebman, J.F.; Greenberg, A. *Chem. Rev.* ***1989***, *89*, 1225.

[410] For reviews of ring-opening reactions of cyclopropanes, see Wong, H.N.C.; Hon, M.; Ts, C.e; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165; Reissig, H., in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, ***1987***, pp. 375–443.

[411] Ogg Jr., R.A.; Priest, W.J. *J. Am. Chem. Soc.* ***1938***, *60*, 217.

[412] Shortridge, R.W.; Craig, R.A.; Greenlee, K.W.; Derfer, J.M.; Boord, C.E. *J. Am. Chem. Soc.* ***1948***, *70*, 946.

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

[414] Bach, R. D.; Dmitrenko, O. *J. Org. Chem.* ***2002***, *67*, 2588.

cyclobutanes, epoxides, and dimethyldioxirane by 6–10 kcal mol^{-1} (25.42 kJ mol^{-1}) relative to an unbranched acyclic reference molecule."[414] The C—H bond dissociation energy also tends to increase ring strain in small-ring alkenes.[415]

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.[416] For a normal carbon atom, one *s* and three *p* orbitals are hybridized to give four approximately equivalent sp^3 orbitals, each containing ~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 ~33% *s* character, so that they are $\sim sp^2$ orbitals, while the internal orbitals have ~17% *s* character, so that they may be called $\sim sp^5$ orbitals.[417] 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 *s* 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.[418] Fig. 4.7 shows the direction of orbital overlap.[419] For cyclopropane, the angle (marked θ) is 21°. Cyclobutane exhibits the same phenomenon but to a lesser extent, θ being 7°.[419,418] Molecular-orbital calculations also show that the

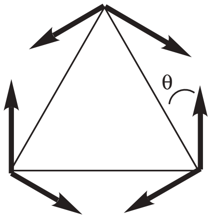

Fig. 4.7. Orbital overlap in cyclopropane. The arrows point toward the center of electron density.

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[415] Bach, R.D.; Dmitrenko, O. *J. Am. Chem. Soc.* ***2004***, *126*, 4444.

[416] For discussions of bonding in cyclopropanes, see Bernett, W.A. *J. Chem. Educ.* ***1967***, *44*, 17; de Meijere, A. *Angew. Chem. Int. Ed.* ***1979***, *18*, 809; Honegger, E.; Heilbronner, E.; Schmelzer, A. *Nouv. J. Chem.* ***1982***, *6*, 519; Cremer, D.; Kraka, E. *J. Am. Chem. Soc.* ***1985***, *107*, 3800, 3811; Slee, T.S. *Mol. Struct. Energ.* ***1988***, *5*, 63; Casaarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* ***1997***, *62*, 7592.

[417] Randić, M.; Maksić, Z. *Theor. Chim. Acta* ***1965***, *3*, 59; Foote, C.S. *Tetrahedron Lett.* ***1963***, 579; Weigert, F.J.; Roberts, J.D. *J. Am. Chem. Soc.* ***1967***, *89*, 5962.

[418] Wiberg, K.B. *Acc. Chem. Res.* ***1996***, *29*, 229.

[419] Coulson, C.A.; Goodwin, T.H. *J. Chem. Soc.* ***1962***, 2851; ***1963***, 3161; Peters, D. *Tetrahedron* ***1963***, *19*, 1539; Hoffmann, R.; Davidson, R.B. *J. Am. Chem. Soc.* ***1971***, *93*, 5699.

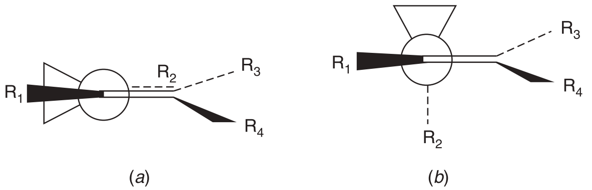

Fig. 4.8. Conformations of α-cyclopropylalkenes. Conformation (*a*) leads to maximum conjugation and conformation (*b*) to minimum conjugation.

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.[420] 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.[421] For one thing, there is much evidence, chiefly from UV spectra,[422] that a cyclopropane ring is conjugated with an adjacent double bond and that this conjugation is greatest for the conformation shown in *a* in Fig. 4.8 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.[423] For other examples of the similarities in behavior of a cyclopropane ring and a double bond (see p. 212).

Four-membered rings also exhibit angle strain, but much less, and are less easily opened. Cyclobutane is more resistant than cyclopropane to bromination, and although 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. 212), cyclobutane is not planar.

Many highly strained compounds containing small rings in fused systems have been prepared,[424] showing that organic molecules can exhibit much more

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[420] Wiberg, K.B.; Bader, R.F.W.; Lau, C.D.H. *J. Am. Chem. Soc.* ***1987***, *109*, 985, 1001; Cremer, D.; Kraka, E. *J. Am. Chem. Soc.* ***1985***, *107*, 3800, 1811.

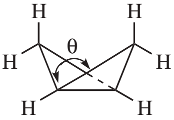
[421] For reviews, see Tidwell, T.T., in Rappoport, Z. *The Chemistry of the Cyclopropyl Groups*, pt. 1, Wiley, NY, ***1987***, pp. 565–632; Charton, M. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, pp. 511–610, Wiley, NY, ***1970***.

[422] See, for example, Cromwell, N.H.; Hudson, G.V. *J. Am. Chem. Soc.* ***1953***, *75*, 872; Kosower, E.M.; Ito, M. *Proc. Chem. Soc.* ***1962***, 25; Dauben, W.G.; Berezin, G.H. *J. Am. Chem. Soc.* ***1967***, *89*, 3449; Jorgenson, M.J.; Leung, T. *J. Am. Chem. Soc.* ***1968***, *90*, 3769; Heathcock, C.H.; Poulter, S.R. *J. Am. Chem. Soc.* ***1968***, *90*, 3766; Tsuji, T.; Shibata, T.; Hienuki, Y.; Nishida, S. *J. Am. Chem. Soc.* ***1978***, *100*, 1806; Drumright, R.E.; Mas, R.H.; Merola, J.S.; Tanko, J.M. *J. Org. Chem.* ***1990***, *55*, 4098.

[423] Staley, S.W. *J. Am. Chem. Soc.* ***1967***, *89*, 1532; Pews, R.G.; Ojha, N.D. *J. Am. Chem. Soc.* ***1969***, *91*, 5769. See, however, Noe, E.A.; Young, R.M. *J. Am. Chem. Soc.* ***1982***, *104*, 6218.

[424] For reviews discussing the properties of some of these as well as related compounds, see the reviews in *Chem. Rev.* ***1989***, *89*, 975, and the following: Jefford, C.W. *J. Chem. Educ.* ***1976***, *53*, 477; Seebach, D. *Angew. Chem. Int. Ed.* ***1965***, *4*, 121; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***, pp. 210–220. For a review of bicyclo[*n.m.0*]alkanes, see Wiberg, K.B. *Adv. Alicyclic Chem.* ***1968***, *2*, 185. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 771–811.

strain than simple cyclopropanes or cyclobutanes.[425] Table 4.5 shows a few of these compounds.[426] 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 is tetracyclo[2.2.0.0^{2},^{6}.0^{3},^{5}]hexane and many derivatives are known,[427] including bis(homohexaprismane) derivatives.[428] The bicyclobutane molecule is bent, with the angle θ between the planes equal to 126 ± 3°.[429] 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.[430] *Propellanes* are compounds in which two carbons, directly connected, are also connected by three other bridges. [1.1.1]Propellane is in the table and it is the smallest possible propellane,[431] 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.[432] The bicyclo[1.1.1]pentanes are obviously related to the propellanes except that the central connecting bond is missing, and several derivatives are known.[433] Even more complex systems are known.[434]

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

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

[427] Gleiter, R.; Treptow, B.; Irngartinger, H.; Oeser, T. *J. Org. Chem.* ***1994***, *59*, 2787; Gleiter, R.; Treptow, B. *J. Org. Chem.* ***1993***, *58*, 7740.

[428] Golobish, T.D.; Dailey, W.P. *Tetrahedron Lett.* ***1996***, *37*, 3239.

[429] Haller, I.; Srinivasan, R. *J. Chem. Phys.* ***1964***, *41*, 2745.

[430] Schulman, J.M.; Fisanick, G.J. *J. Am. Chem. Soc.* ***1970***, *92*, 6653; Newton, M.D.; Schulman, J.M. *J. Am. Chem. Soc.* ***1972***, *94*, 767.

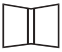
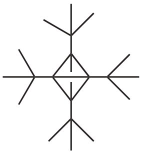
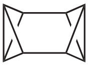
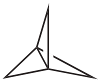
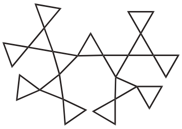
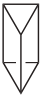
[431] Wiberg, K.B.; Waddell, S.T. *J. Am. Chem. Soc.* ***1990***, *112*, 2194; Seiler, S.T. *Helv. Chim. Acta* ***1990***, *73*, 1574; Bothe, H.; Schlüter, A. *Chem. Ber.* ***1991***, *124*, 587; Lynch, K.M.; Dailey, W.P. *J. Org. Chem.* ***1995***, *60*, 4666. For reviews of small-ring propellanes, see Wiberg, K.B. *Chem. Rev.* ***1989***, *89*, 975; Ginsburg, D., in Rappoport, Z *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 1193–1221. For a discussion of the formation of propellanes, see Ginsburg, D. *Top. Curr. Chem.* ***1987***, *137*, 1.

[432] Wiberg, K.B.; Walker, F.H.; Pratt, W.E.; Michl, J. *J. Am. Chem. Soc.* ***1983***, *105*, 3638.

[433] Della, E.W.; Taylor, D.K. *J. Org. Chem.* ***1994***, *59*, 2986.

[434] See Kuck, D.; Krause, R.A.; Gestmann, D.; Posteher, F.; Schuster, A. *Tetrahedron* ***1998***, *54*, 5247 for an example of a [5.5.5.5.5.5]centrohexacycline.

TABLE 4.5. Some Strained Small-Ring Compounds

Structural Formula of Compound Prepared	Systematic Name of Ring System	Common Name If Any	Reference
	Bicyclo[1.1.0]butane	Bicyclobutane	435
	$\Delta^{1,4}$-Bicyclo[2.2.0]hexene		436
	Tricyclo[1.1.0.0^{2,4}]butane	Tetrahedrane	437
	Pentacyclo[5.1.0.0^{2,4}.0^{3,5}.0^{6,8}]-octane	Octabisvalene	438
	Tricyclo[1.1.1.0^{1,3}]-pentane	a [1.1.1]propellane	364
	Tetradecaspiro[2.0.2.0.0.0.0.0.0.-2.0.2.0.0.0.2.0.2.0.0.1.0.0.2.0.2.-0.0.0]untriacontane	[15]-triangulane	439
	Tetracyclo[2.2.0.0^{2,6}.0^{3,5}]-hexane	Prismane	440

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[435] Lemal, D.M.; Menger, F.M.; Clark, G.W. *J. Am. Chem. Soc.* ***1963***, *85*, 2529; Wiberg, K.B.; Lampman, G.M. *Tetrahedron Lett.* ***1963***, 2173. For reviews of preparations and reactions of this system, see Hoz, S., in Rappoport, Z *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 1121–1192; Wiberg, K.B.; Lampman, G.M.; Ciula, R.P.; Connor, D.S.; Schertler, P.; Lavanish, J.M. *Tetrahedron* ***1965***, *21*, 2749; Wiberg, K.B. *Rec. Chem. Prog.*, ***1965***, *26*, 143; Wiberg, K.B. *Adv. Alicyclic Chem.* ***1968***, *2*, 185. For a review of [*n*.1.1] systems, see Meinwald, J.; Meinwald, Y.C. *Adv. Alicyclic Chem.* ***1966***, *1*, 1.

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

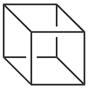
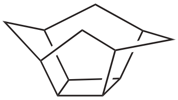
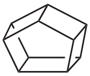
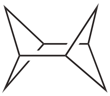
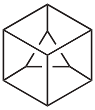
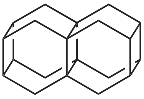
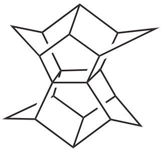
[437] Maier, G.; Pfriem, S.; Schäfer, U.; Malsch, K.; Matusch, R. *Chem. Ber.* ***1981***, *114*, 3965; Maier, G.; Pfriem, S.; Malsch, K.; Kalinowski, H.; Dehnicke, K. *Chem. Ber.* ***1981***, *114*, 3988; Irngartinger, H.; Goldmann, A.; Jahn, R.; Nixdorf, M.; Rodewald, H.; Maier, G.; Malsch, K.; Emrich, R. *Angew. Chem. Int. Ed.* ***1984***, *23*, 993; Maier, G.; Fleischer, F. *Tetrahedron Lett.* ***1991***, *32*, 57. For reviews of attempts to synthesize tetrahedrane, see Maier, G. *Angew. Chem. Int. Ed.* ***1988***, *27*, 309; Zefirov, N.S.; Koz'min, A.S.; Abramenkov, A.V. *Russ. Chem. Rev.* ***1978***, *47*, 163. For a review of tetrahedranes and other cage molecules stabilized by steric hindrance, see Maier, G.; Rang, H.; Born, D., in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, pp. 219–259. See also, Maier, G.; Born, D. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1050.

[438] Rücker, C.; Trupp, B. *J. Am. Chem. Soc.* ***1988***, *110*, 4828.

[439] Von Seebach, M.; Kozhushkov, S.I.; Boese, R.; Benet-Buchholz, J.; Yufit, D.S.; Howard, J.A.K.; de Meijere, A. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2495.

[440] Katz, T.J.; Acton, N. *J. Am. Chem. Soc.* ***1973***, *95*, 2738. See also Viehe, H.G.; Merényi, R.; Oth, J.F.M.; Senders, J.R.; Valange, P. *Angew. Chem. Int. Ed.* ***1964***, *3*, 755; Wilzbach, K.E.; Kaplan, L. *J. Am. Chem. Soc.* ***1965***, *87*, 4004.

TABLE 4.5 (*Continued*)

Structural Formula of Compound Prepared	Systematic Name of Ring System	Common Name If Any	Reference
	Pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$] octane	Cubane	441
	Pentacyclo[5.4.1.$0^{3,1}$.$0^{5.9}$.$0^{8,11}$] dodecane	4[Peristylane]	442
	Hexacyclo[5.3.0.$0^{2,6}$-.$0^{3,10}$.$0^{4,9}$.$0^{5,8}$]decane	Pentaprismane	443
	Tricyclo[3.1.1.$1^{2,4}$]octane	Diasterane	444
	Hexacyclo[4.4.0.$0^{2,4}$.$0^{3,9}$-.$0^{5,8}$.$0^{7,10}$]decane		445
	Nonacyclo[10.8.$0^{2,11}$.$0^{4,9}$-.$0^{4,19}$.$0^{6,17}$.$0^{7,16}$.$0^{9,14}$.$0^{14,19}$] eicosane	A double tetraesterane	446
	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	447

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[441] Barborak, J.C.; Watts, L.; Pettit, R. *J. Am. Chem. Soc.* ***1966***, *88*, 1328; Hedberg, L.; Hedberg, K.; Eaton, P.E.; Nodari, N.; Robiette, A.G. *J. Am. Chem. Soc.* ***1991***, *113*, 1514. For a review of cubanes, see Griffin, G.W.; Marchand, A.P. *Chem. Rev.* ***1989***, *89*, 997.

[442] Paquette, L.A.; Fischer, J.W.; Browne, A.R.; Doecke, C.W. *J. Am. Chem. Soc.* ***1985***, *105*, 686.

[443] Eaton, P.E.; Or, Y.S.; Branca, S.J.; Shankar, B.K.R. *Tetrahedron* ***1986***, *42*, 1621. See also Dauben, W.G.; Cunningham Jr., A.F. *J. Org. Chem.* ***1983***, *48*, 2842.

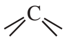
[444] Otterbach, A.; Musso, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 554.

[445] Allred, E.L.; Beck, B.R. *J. Am. Chem. Soc.* ***1973***, *95*, 2393.

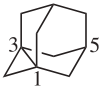
[446] Hoffmann, V.T.; Musso, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1006.

[447] Rihs, G. *Tetrahedron Lett.* ***1983***, *24*, 5857. See Mathew, T.; Keller, M.; Hunkler, D.; Prinzbach, H. *Tetrahedron Lett.* ***1996***, *37*, 4491 for the synthesis of azapagodanes (also called azadodecahedranes).

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 **124**.[448] An example is 1,3-dehydroadamantane, **125** (which is also a propellane).[449] X-ray crystallography of the 5-cyano derivative of ***125*** shows that the four carbon valences at C-1 and C-3 are all directed "into" the molecule and none point outside.[450] Compound ***125*** 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 **125**), the bond is very long (the C_1—C_3 bond length in the 5-cyano derivative of **125** 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 **125** 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.



124



125

Strain in Other Rings[451]

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, that is, interactions between the substituents on C-1 and C-3 or C-1 and C-4, and so on. These interactions occur because the internal space is not large enough for all the quasiaxial 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. 212), this means that the molecule is not planar. In rings larger than

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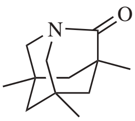
[448] For a review, see Wiberg, K.B. *Acc. Chem. Res.* ***1984***, *17*, 379.

[449] Scott, W.B.; Pincock, R.E. *J. Am. Chem. Soc.* ***1973***, *95*, 2040.

[450] Gibbons, C.S.; Trotter, J. *Can. J. Chem.* ***1973***, *51*, 87.

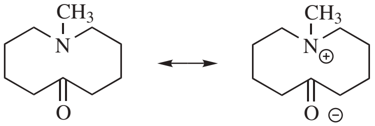
[451] For reviews, see Gol'dfarb, Ya.L.; Belen'kii, L.I. *Russ. Chem. Rev.* ***1960***, *29*, 214; Raphael, R.A. *Proc. Chem. Soc.* ***1962***, 97; Sicher, J. *Prog. Stereochem.* ***1962***, *3*, 202.

9-membered, Pitzer strain seems to disappear, but transannular strain is still present.[452] 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 115–120° have been found in X-ray diffraction of cyclononylamine hydrobromide and 1,6-diaminocyclodecane dihydrochloride.[453]

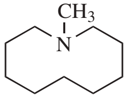


126

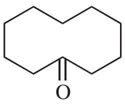
Strain can exert other influences on molecules. 1-Aza-2-adamantanone (**126**) is an extreme case of a twisted amide.[454] The overlap of the lone pair electrons on nitrogen with the π-system of the carbonyl is prevented.[454] In chemical reactions, **126** reacts more or less like a ketone, giving a Wittig reaction (**16-44**) and it can form a ketal (**16-7**). A twisted biadamantylidene compound has been reported.[455]



127a **127b**



128



129

The amount of strain in cycloalkanes is shown in Table 4.6,[456] 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.[457] Such interactions can be detected by dipole and spectral measurements. For example, that the carbonyl group in **127a** is affected by the nitrogen (**127b** is probably another canonical form) has been demonstrated by photoelectron spectroscopy, which shows that the ionization potentials of the nitrogen *n* and C=O π orbitals in **127** differ from those of the two comparison molecules **128** and **129**,[458] It is significant that when **127** accepts a proton, it goes to the

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[452] Huber-Buser, E.; Dunitz, J.D. *Helv. Chim. Acta* ***1960***, *43*, 760.

[453] Dunitz, J.D.; Venkatesan, K. *Helv. Chim. Acta* ***1961***, *44*, 2033.

[454] Kirby, A.J.; Komarov, I.V.; Wothers, P.D.; Feeder, N. *Angew. Chem. Int. Ed.*, ***1998***, *37*, 785. For other examples of twisted amides, see Duspara, P.A.; Matta, C.F.; Jenkins, S.I.; Harrison, P.H.M. *Org. Lett.* ***2001***, *3*, 495; Madder, R.D.; Kim, C.-Y.; Chandra, P.P.; Doyon, J.B.; Barid Jr., T.A.; Fierke, C.A.; Christianson, D.W.; Voet, J.G.; Jain, A. *J. Org. Chem.* ***2002***, *67*, 582.

[455] Okazaki, T.; Ogawa, K.; Kitagawa, T.; Takeuchi, K. *J. Org. Chem.* ***2002***, *67*, 5981.

[456] Gol'dfarb, Ya.L.; Belen'kii, L.I. *Russ. Chem. Rev.* ***1960***, *29*, 214, p. 218.

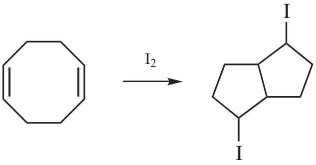
[457] For a review, see Cope, A.C.; Martin, M.M.; McKervey, M.A. *Q. Rev. Chem. Soc.* ***1966***, *20*, 119.

[458] Spanka, G.; Rademacher, P. *J. Org. Chem.* ***1986***, *51*, 592. See also, Spanka, G.; Rademacher, P.; Duddeck, H. *J. Chem. Soc. Perkin Trans. 2 1988*, 2119; Leonard, N.J.; Fox, R.C.; Ō ki, M. *J. Am. Chem. Soc.* ***1954***, *76*, 5708.

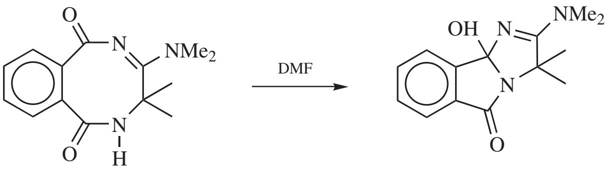
TABLE 4.6. Heats of Combustion in the Gas Phase for Cycloalkanes, per CH_2 Group[456]

	$-\Delta H_c$, (g)			$-\Delta H_c$, (g)	
Size of Ring	kcal mol^{-1}	kJ mol^{-1}	Size of Ring	kcal mol^{-1}	kJ mol^{-1}
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

oxygen rather than to the nitrogen. Many examples of transannular reactions are known, including:



Ref. 459



Ref. 460

In summary, we can divide saturated rings into four groups, of which the first and third are more strained than the other two.[461]

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.[462]

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[459] Uemura, S.; Fukuzawa, S.; Toshimitsu, A.; Okano, M.; Tezuka, H.; Sawada, S. *J. Org. Chem.* ***1983***, *48*, 270.

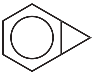
[460] Schläpfer-Dähler, M.; Prewo, R.; Bieri, J.H.; Germain, G.; Heimgartner, H. *Chimia* ***1988***, *42*, 25.

[461] For a review on the influence of ring size on the properties of cyclic systems, see Granik, V.G. *Russ. Chem. Rev.* ***1982***, *51*, 119.

[462] An example is the calculated strain of 1.4–3.2 kcal mol^{-1} in cyclotetradecane. See Chickos, J.S.; Hesse, D.G.; Panshin, S.Y.; Rogers, D.W.; Saunders, M.; Uffer, P.M.; Liebman, J.F. *J. Org. Chem.* ***1992***, *57*, 1897.

Unsaturated Rings[463]

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[464] because the ideal angle is greater. In cyclopropane, the bond angle is forced to be 60°, ~50° smaller than the tetrahedral angle; but in cyclopropene, the angle, also ~60°, is now ~60° smaller than the ideal angle of 120°. Thus, the angle is cyclopropene is ~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[465] and is stable at liquid-nitrogen temperatures, although on warming even to −80°C it rapidly polymerizes. Many other cyclopropenes are stable at room temperature and above.[464] The highly strained benzocyclopropene,[466] in which the cyclopropene ring is fused to a benzene ring, has been prepared[467] and is stable for weeks at room temperature, although 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[468] first appears in an eight-membered ring (*trans*-cyclooctene, p. 150), although the transient existence of *trans*-cyclohexene and cycloheptene has been demonstrated.[469] Above ~11 members, the trans isomer

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[463] For a review of strained double bonds, see Zefirov, N.S.; Sokolov, V.I. *Russ. Chem. Rev.* ***1967***, *36*, 87. For a review of double and triple bonds in rings, see Johnson, R.P. *Mol. Struct. Energ.* ***1986***, *3*, 85.

[464] For reviews of cyclopropenes, see Baird, M.S. *Top. Curr. Chem.* ***1988***, *144*, 137; Halton, B.; Banwell, M.G. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 2, pp. Wiley, NY, ***1987***, pp. 1223–1339; Closs, G.L. *Adv. Alicyclic Chem.* ***1966***, *1*, 53; For a discussion of the bonding and hybridization, see Allen, F.H. *Tetrahedron* ***1982***, *38*, 645.

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

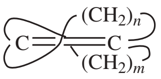
[466] For reviews of cycloproparenes, see Halton, B. *Chem. Rev.* ***1989***, *89*, 1161; ***1973***, *73*, 113; Billups, W.E.; Rodin, W.A.; Haley, M.M. *Tetrahedron* ***1988***, *44*, 1305; Halton, B.; Stang, P.J. *Acc. Chem. Res.* ***1987***, *20*, 443; Billups, W.E. *Acc. Chem. Res.* ***1978***, *11*, 245.

[467] Vogel, E.; Grimme, W.; Korte, S. *Tetrahedron Lett.* ***1965***, 3625. Also see Anet, R.; Anet, F.A.L. *J. Am. Chem. Soc.* ***1964***, *86*, 526; Müller, P.; Bernardinelli, G.; Thi, H.C.G. *Chimia* ***1988***, *42*, 261; Neidlein, R.; Christen, D.; Poignée, V.; Boese, R.; Bläser, D.; Gieren, A.; Ruiz-Pérez, C.; Hübner, T. *Angew. Chem. Int. Ed.* ***1988***, *27*, 294.

[468] For reviews of trans cycloalkenes, see Nakazaki, M.; Yamamoto, K.; Naemura, K. *Top. Curr. Chem.* ***1984***, *125*, 1; Marshall, J.A. *Acc. Chem. Res.* ***1980***, *13*, 213.

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

is more stable than the cis.[223] It has proved possible to prepare compounds in which a trans double bond is shared by two cycloalkene rings (e.g., **130**). Such compounds have been called *[m.n]betweenanenes*, and several have been prepared with *m* and *n* values from 8 to 26.[470] 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.



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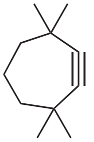

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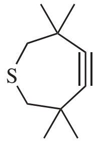

132

The smallest unstrained cyclic triple bond is found in cyclononyne.[471] Cyclooctyne has been isolated,[472] 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 (**131**) dimerizes within 1 h at room temperature,[473] but the thia derivative **132**, in which the C—S bonds are longer than the corresponding C—C bonds in **131**, is indefinitely stable even at 140°C.[474] Cycloheptyne itself has not been isolated, although its transient existence has been shown.[475] Cyclohexyne[476] and its 3,3,6,6-tetramethyl derivative[477] have been trapped at 77 K, and in an argon matrix at 12 K, respectively, and IR spectra

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[470] Nakazaki, M.; Yamamoto, K.; Yanagi, J. *J. Am. Chem. Soc.* ***1979***, *101*, 147; Ceré, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Chem. Soc. Chem. Commun.* ***1980***, 755; Marshall, J.A.; Flynn, K.E. *J. Am. Chem. Soc.* ***1983***, *105*, 3360. For reviews, see Nakazaki, M.; Yamamoto, K.; Naemura, K. *Top. Curr. Chem.* ***1984***, *125*, 1; Marshall, J.A. *Acc. Chem. Res.* ***1980***, *13*, 213. For a review of these and similar compounds, see Borden, W.T. *Chem. Rev.* ***1989***, *89*, 1095.

[471] For reviews of triple bonds in rings, see Meier, H. *Adv. Strain Org. Chem.* ***1991***, *1*, 215; Krebs, A.; Wilke, J. *Top. Curr. Chem.* ***1983***, *109*, 189; Nakagawa, M., in Patai, S. *The Chemistry of the* $C{\equiv}C$ *Triple Bond*, pt. 2; Wiley, NY, ***1978***, pp. 635–712; Krebs, A. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 987–1062. For a list of strained cycloalkynes that also have double bonds, see Meier, H.; Hanold, N.; Molz, T.; Bissinger, H.J.; Kolshorn, H.; Zountsas, J. *Tetrahedron* ***1986***, *42*, 1711.

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

[473] Krebs, A.; Kimling, H. *Angew. Chem. Int. Ed.* ***1971***, *10*, 509; Schmidt, H.; Schweig, A.; Krebs, A. *Tetrahedron Lett.* ***1974***, 1471.

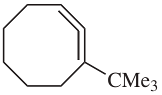
[474] Krebs, A.; Kimling, H. *Tetrahedron Lett. 1970*, 761.

[475] Wittig, G.; Meske-Schüller, J. *Liebigs Ann. Chem.* ***1968***, *711*, 65; Krebs, A.; Kimling, H. *Angew. Chem. Int. Ed.* ***1971***, *10*, 509; Bottini, A.T.; Frost II, K.A.; Anderson, B.R.; Dev, V. *Tetrahedron* ***1973***, *29*, 1975.

[476] Wentrup, C.; Blanch, R.; Briehl, H.; Gross, G. *J. Am. Chem. Soc.* ***1988***, *110*, 1874.

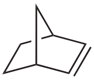
[477] See Sander, W.; Chapman, O.L. *Angew. Chem. Int. Ed.* ***1988***, *27*, 398; Krebs, A.; Colcha, W.; Müller, M.; Eicher, T.; Pielartzik, H.; Schnöckel, H. *Tetrahedron Lett.* ***1984***, *25*, 5027.

have been obtained. Transient six-and even five-membered rings containing triple bonds have also been demonstrated.[478]



133

A derivative of cyclopentyne has been trapped in a matrix.[479] Although cycloheptyne and cyclohexyne have not been isolated at room temperatures, Pt(0) complexes of these compounds have been prepared and are stable.[480] The smallest cyclic allene[481] so far isolated is 1-*tert*-butyl-1,2-cyclooctadiene **133**.[482] The parent 1,2-cyclooctadiene has not been isolated. It has been shown to exist transiently, but rapidly dimerizes.[483] The presence of the *tert*-butyl group apparently prevents this. The transient existence of 1,2-cycloheptadiene has also been shown,[484] and both 1,2-cyclooctadiene and 1,2-cycloheptadiene have been isolated in platinum complexes.[485] 1,2-Cyclohexadiene has been trapped at low temperatures, and its structure has been proved by spectral studies.[486] Cyclic allenes in general are less strained than their acetylenic isomers.[487] 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.[488]



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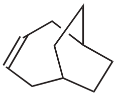

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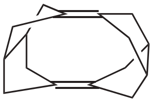

136

There are many examples of polycyclic molecules and bridged molecules that have one or more double bonds. There is flattening of the ring containing the C=C unit, and this can have a significant effect on the molecule. Norbornene (bicyclo[2.2.1]hept-2-ene; **134**) is a simple example and it has been calculated that it contains a distorted

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

[479] Chapman, O.L.; Gano, J.; West, P.R.; Regitz, M.; Maas, G. *J. Am. Chem. Soc.* ***1981***, *103*, 7033.

[480] Bennett, M.A.; Robertson, G.B.; Whimp, P.O.; Yoshida, T. *J. Am. Chem. Soc.* ***1971***, *93*, 3797.

[481] For reviews of cyclic allenes, see Johnson, R.P. *Adv. Theor. Interesting Mol.* ***1989***, *1*, 401; *Chem. Rev.* ***1989***, *89*, 1111; Thies, R.W. *Isr. J. Chem.* ***1985***, *26*, 191; Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*; Wiley, NY, ***1984***, pp. 38–56.

[482] Price, J.D.; Johnson, R.P. *Tetrahedron Lett.* ***1986***, *27*, 4679.

[483] See Marquis, E.T.; Gardner, P.D. *Tetrahedron Lett.* ***1966***, 2793.

[484] Wittig, G.; Dorsch, H.; Meske-Schüller, J. *Liebigs Ann. Chem.* ***1968***, *711*, 55.

[485] Visser, J.P.; Ramakers, J.E. *J. Chem. Soc. Chem. Commun.* ***1972***, 178.

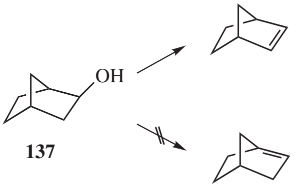
[486] Wentrup, C.; Gross, G.; Maquestiau, A.; Flammang, R. *Angew. Chem. Int. Ed.* ***1983***, *22*, 542. 1,2,3-Cyclohexatriene has also been trapped: Shakespeare, W.C.; Johnson, R.P. *J. Am. Chem. Soc.* ***1990***, *112*, 8578.

[487] Moore, W.R.; Ward, H.R. *J. Am. Chem. Soc.* ***1963***, *85*, 86.

[488] Angus Jr., R.O.; Johnson, R.P. *J. Org. Chem.* ***1984***, *49*, 2880.

π-face.[489] The double bond can appear away from the bridgehead carbon atoms, as in bicyclo[4.2.2]dec-3-ene (**135**) and that part of the molecule is flattened. In pentacyclo[8.2.1.1^{2,5}.1^{4,7}.1^{8,11}]hexadeca-1,7-diene (**136**), the C=C units are held in a position where there is significant π–π interactions across the molecule.[490]

Double bonds at the bridgehead of bridged bicyclic compounds are impossible in small systems. This is the basis of *Bredt's rule*,[491] which states that elimination to give a double bond in a bridged bicyclic system (e.g., **137**) always leads away from the bridgehead. This rule no longer applies when the rings are large enough. In determining whether a bicyclic 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.[492] Bicyclo[3.3.1]non-1-ene[493] (**138**) and bicyclo-[4.2.1]non-1(8)ene[494] (**139**) are stable compounds. Both can be looked upon as derivatives of *trans*-cyclooctene, which is of course a known compound. Compound **138** has been shown to have a strain energy of the same order of magnitude as that of *trans*-cyclooctene.[495] On the other hand, in bicyclo[3.2.2]non-1-ene (**140**), the largest ring that contains the double bond is *trans*-cycloheptene, which is as yet unknown. Compound **140** has been prepared, but dimerized before it could be isolated.[496] Even smaller systems ([3.2.1] and [2.2.2]), but with imine double



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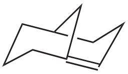

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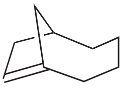

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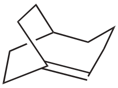

140

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[489] Ohwada, T. *Tetrahedron* ***1993***, *49*, 7649.

[490] Lange, H.; Schäfer, W.; Gleiter, R.; Camps, P.; Vázquez, S. *J. Org. Chem.* ***1998***, *63*, 3478.

[491] For reviews, see Shea, K.J. *Tetrahedron* ***1980***, *36*, 1683; Buchanan, G.L. *Chem. Soc. Rev.* ***1974***, *3*, 41; Köbrich, G. *Angew. Chem. Int. Ed.* ***1973***, *12*, 464. For reviews of bridgehead olefins, see Billups, W.E.; Haley, M.M.; Lee, G. *Chem. Rev.* ***1989***, *89*, 1147; Warner, P.M. *Chem. Rev.* ***1989***, *89*, 1067; Szeimies, G. *React. Intermed. (Plenum)* ***1983***, *3*, 299; Keese, R. *Angew. Chem. Int. Ed.* ***1975***, *14*, 528. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 502–504.

[492] For a discussion and predictions of stability in such compounds, see Maier, W.F.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1981***, *103*, 1891.

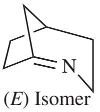
[493] Marshall, J.A.; Faubl, H. *J. Am. Chem. Soc.* ***1967***, *89*, 5965, ***1970***, *92*, 948; Wiseman, J.R.; Pletcher, W.A. *J. Am. Chem. Soc.* ***1970***, *92*, 956; Kim, M.; White, J.D. *J. Am. Chem. Soc.* ***1975***, *97*, 451; Becker, K.B. *Helv. Chim. Acta* ***1977***, *60*, 81. For the preparation of optically active **125**, see Nakazaki, M.; Naemura, K.; Nakahara, S. *J. Org. Chem.* ***1979***, *44*, 2438.

[494] Wiseman, J.R.; Chan, H.; Ahola, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 2812; Carruthers, W.; Qureshi, M.I. *Chem. Commun.* ***1969***, 832; Becker, K.B. *Tetrahedron Lett.* ***1975***, 2207.

[495] Lesko, P.M.; Turner, R.B. *J. Am. Chem. Soc.* ***1968***, *90*, 6888; Burkert, U. *Chem. Ber.* ***1977***, *110*, 773.

[496] Wiseman, J.R.; Chong, J.A. *J. Am. Chem. Soc.* ***1969***, *91*, 7775.

bonds (**141–143**), have been obtained in matrixes at low temperatures.[497] These compounds are destroyed on warming. Compounds **141** and **142** are the first reported example of (*E*–*Z*) isomerism at a strained bridgehead double bond.[498]

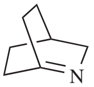


(*E*) Isomer

141

(*Z*) Isomer

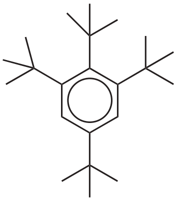
142



143

Strain Due to Unavoidable Crowding[499]

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*-*tert*-butyl groups. Two examples that have been prepared, of several, are 1,2,3-tri-*tert*-butyl compound **144**[500] and the 1,2,3,4-tetra-*tert*-butyl compound **145**.[501] That these molecules are strained is demonstrated by UV and IR spectra,



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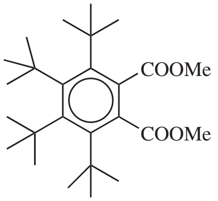

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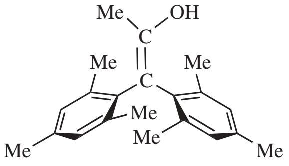

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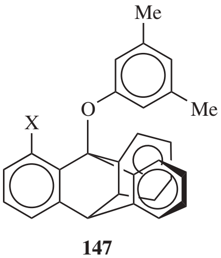

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[497] Sheridan, R.S.; Ganzer, G.A. *J. Am. Chem. Soc.* ***1983***, *105*, 6158; Radziszewski, J.G.; Downing, J.W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* ***1985***, *107*, 2799.

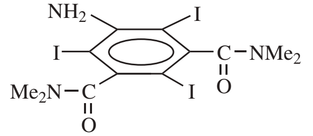
[498] Radziszewski, J.G.; Downing, J.W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* ***1985***, *107*, 2799.

[499] For reviews, see Tidwell, T.T. *Tetrahedron* ***1978***, *34*, 1855; Voronenkov, V.V.; Osokin, Yu.G. *Russ. Chem. Rev.* ***1972***, *41*, 616. For a review of early studies, see Mosher, H.S.; Tidwell, T.T. *J. Chem. Educ.* ***1990***, *67*, 9. For a review of van der Waals radii, see Zefirov, Yu.V.; Zorkii, P.M. *Russ. Chem. Rev.* ***1989***, *58*, 421.

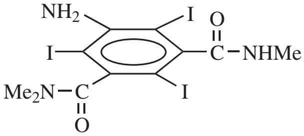
[500] Arnett, E.M.; Bollinger, J.M. *Tetrahedron Lett.* ***1964***, 3803.

[501] Maier, G.; Schneider, K. *Angew. Chem. Int. Ed.* ***1980***, *19*, 1022. For another example, see Krebs, A.; Franken, E.; Müller, S. *Tetrahedron Lett.* ***1981***, *22*, 1675.

which show that the ring is not planar in 1,2,4-tri-*tert*-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 $\sim$22 kcal mol^{-1} (92 kJ mol^{-1}) more strain energy than its isomer[502] (see also, p. 1642). Since $SiMe_3$ 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.[503] 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 the same direction.[504] This compound is an example of a *geared molecule*.[505] The isopropyl groups fit into each other in the same manner as interlocked gears. Another example



cis



trans

is **146** (which is a stable enol).[506] 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 **147**, a 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^{-1} (43.1 kJ mol^{-1}) for $X = F$ to 17.6 kcal mol^{-1} (73.6 kJ mol^{-1}) for X = *tert*-butyl.[507] 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.[508] The trans isomer is chiral and has been resolved, while the cis isomer is a meso form. Another

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[502] Arnett, E.M.; Sanda, J.C.; Bollinger, J.M.; Barber, M. *J. Am. Chem. Soc.* ***1967***, *89*, 5389; Krüerke, U.; Hoogzand, C.; Hübel, W. *Chem. Ber.* ***1961***, *94*, 2817; Dale, J. *Chem. Ber.* ***1961***, *94*, 2821. See also Barclay, L.R.C.; Brownstein, S.; Gabe, E.J.; Lee, F.L. *Can. J. Chem.* ***1984***, *62*, 1358.

[503] Sakurai, H.; Ebata, K.; Kabuto, C.; Sekiguchi, A. *J. Am. Chem. Soc.* ***1990***, *112*, 1799.

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

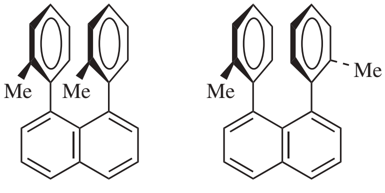
[505] For reviews, see Iwamura, H.; Mislow, K. *Acc. Chem. Res.* ***1988***, *21*, 175; Mislow, K. *Chemtracts: Org. Chem.* ***1989***, *2*, 151; *Chimia*, ***1986***, *40*, 395; Berg, U.; Liljefors, T.; Roussel, C.; Sandström, J. *Acc. Chem. Res.* ***1985***, *18*, 80.

[506] Nugiel, D.A.; Biali, S.E.; Rappoport, Z. *J. Am. Chem. Soc.* ***1984***, *106*, 3357.

[507] Yamamoto, G.; Ōki, M. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 3597. For reviews of similar cases, see Yamamoto, G. *Pure Appl. Chem.* ***1990***, *62*, 569; Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 269–284.

[508] Ackerman, J.H.; Laidlaw, G.M.; Snyder, G.A. *Tetrahedron Lett.* ***1969***, 3879; Ackerman, J.H.; Laidlaw, G.M. *Tetrahedron Lett.* ***1969***, 4487. See also Cuyegkeng, M.A.; Mannschreck, A. *Chem. Ber.* ***1987***, *120*, 803.

example of cis–trans isomerism resulting from restricted rotation about single bonds[509] is found in 1,8-di-*o*-tolylnapthalene[510] (see also, p. 182).



cis trans

There are many other cases of intramolecular crowding that result in the distortion of bond angles. We have already mentioned hexahelicene (p. 150) and bent benzene rings (p. 48). The compounds tri-*tert*-butylamine and tetra-*tert*-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-*tert*-butylamine the crowding can be eased somewhat if the three bulky groups assume a planar instead of the normal pyramidal configuration. In tri-*tert*-butylcarbinol, coplanarity of the three *tert*-butyl groups is prevented by the presence of the OH group, and yet this compound has been prepared.[511] Tri-*tert*-butylamine should have less steric strain than tri-*tert*-butylcarbinol and it should be possible to prepare it.[512] The tetra-*tert*-butylphosphonium cation $(t\text{-Bu})_4P^+$ has been prepared.[513] 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.[514] 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-*tert*-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

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[509] For a monograph on restricted rotation about single bonds, see Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***. For reviews, see Förster, H.; Vögtle, F. *Angew. Chem. Int. Ed.* ***1977***, *16*, 429; Ōki, M. *Angew. Chem. Int. Ed.* ***1976***, *15*, 87.

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

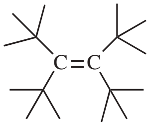
[511] Bartlett, P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1968***, *90*, 4421.

[512] For attempts to prepare tri-*tert*-butylamine, see Back, T.G.; Barton, D.H.R. *J. Chem. Soc. Perkin Trans 1*, ***1977***, 924. For the preparation of di-*tert*-butylmethylamine and other sterically hindered amines, see Kopka, I.E.; Fataftah, Z.A.; Rathke, M.W. *J. Org. Chem.* ***1980***, *45*, 4616; Audeh, C.A.; Fuller, S.E.; Hutchinson, R.J.; Lindsay Smith, J.R. *J. Chem. Res. (S)*, ***1979***, 270.

[513] Schmidbaur, H.; Blaschke, G.; Zimmer-Gasser, B.; Schubert, U. *Chem. Ber.* ***1980***, *113*, 1612.

[514] DeTar, D.F.; Binzet, S.; Darba, P. *J. Org. Chem.* ***1985***, *50*, 2826, 5298, 5304.

deviation from planarity can result.[515] The compound tetra-*tert*-butylethene (**148**) has not been prepared,[516] but the tetraaldehyde **149**, which should have about the same amount of strain, has been made. X-ray crystallography shows that **149** is twisted out of a planar shape by an angle of 28.6°.[517] 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(*tert*-butyldimethylsilyl)-1,2-bis(trimethylsilyl)ethene (**150**) 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.[518] A different kind of double bond strain is found in tricyclo$[4.2.2.2^{2,5}]$dodeca-1,5-diene (**151**),[519] cubene (**152**),[520] and homocub-4(5)-ene (**153**).[521] In these molecules, the four groups on the double bond are all forced to be on one side of the double-bond plane.[522] In **151**, the angle between 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). Compounds **152** and **153** have ***not*** been isolated, but have been generated as intermediates that were trapped by reaction with other compounds.[520,521]



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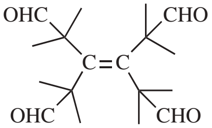

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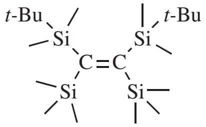

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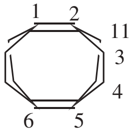

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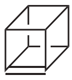

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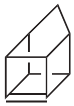

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[515] For reviews, see Luef, W.; Keese, R. *Top. Stereochem.* ***1991***, *20*, 231; Sandström, J. *Top. Stereochem.* ***1983***, *14*, 83, pp. 160–169.

[516] For a list of crowded alkenes that have been made, see Drake, C.A.; Rabjohn, N.; Tempesta, M.S.; Taylor, R.B. *J. Org. Chem.* ***1988***, *53*, 4555. See also, Garratt, P.J.; Payne, D.; Tocher, D.A. *J. Org. Chem.* ***1990***, *55*, 1909.

[517] Krebs, A.; Nickel, W.; Tikwe, L.; Kopf, J. *Tetrahedron Lett.* ***1985***, *26*, 1639.

[518] Sakurai, H.; Ebata, K.; Kabuto, C.; Nakadaira, Y. *Chem. Lett.* ***1987***, 301.

[519] Wiberg, K.B.; Matturo, M.G.; Okarma, P.J.; Jason, M.E. *J. Am. Chem. Soc.* ***1984***, *106*, 2194; Wiberg, K.B.; Adams, R.D.; Okarma, P.J.; Matturo, M.G.; Segmuller, B. *J. Am. Chem. Soc.* ***1984***, *106*, 2200.

[520] Eaton, P.E.; Maggini, M. *J. Am. Chem. Soc.* ***1988***, *110*, 7230.

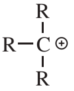
[521] Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***1988***, *110*, 7229.

[522] For a review of such molecules, see Borden, W.T. *Chem. Rev.* ***1989***, *89*, 1095. See also, Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***1988***, *110*, 4710.

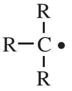
CHAPTER 5

Carbocations, Carbanions, Free Radicals, Carbenes, and Nitrenes

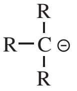
There are four types of organic species in which a carbon atom has a valence of only 2 or 3.[1] They are usually very short-lived, and most exist only as intermediates that are quickly converted to more stable molecules. However, some are more stable than others and fairly stable examples have been prepared of three of the four


$R-\underset{R}{\overset{R}{C}}\oplus$

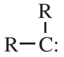
A


$R-\underset{R}{\overset{R}{C}}\bullet$

B


$R-\underset{R}{\overset{R}{C}}\ominus$

C


$R-\overset{R}{C}:$

D

$R-N:$

E

types. The four types of species are *carbocations* (**A**), *free radicals* (**B**), *carbanions* (**C**), and *carbenes* (**D**). Of the four, only carbanions have a complete octet around the carbon. There are many other organic ions and radicals with charges and unpaired electrons on atoms other than carbon, but we will discuss only *nitrenes* (**E**), the nitrogen analogs of carbenes. Each of the five types is discussed in a separate section, which in each case includes brief summaries of the ways in which the species form and react. These summaries are short and schematic. The generation and fate of the five types are more fully treated in appropriate places in Part 2 of this book.

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[1] For general references, see Isaacs, N.S. *Reactive Intermediates in Organic Chemistry*, Wiley, NY, ***1974***; McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***. Two serial publications devoted to review articles on this subject are *Reactive Intermediates (Wiley)* and *Reactive Intermediates (Plenum).*

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by Michael B. Smith and Jerry March

CARBOCATIONS[2]

Nomenclature

First, we must say a word about the naming of **A**. For many years these species were called "carbonium ions," although it was suggested[3] as long ago as 1902 that this was inappropriate because "-onium" usually refers to a covalency higher than that of the neutral atom. Nevertheless, the name "carbonium ion" was well established and created few problems[4] until some years ago, when George Olah and his co-workers found evidence for another type of intermediate in which there is a positive charge at a carbon atom, but in which the formal covalency of the carbon atom is five rather than three. The simplest example is the methanonium ion CH_5^+ (see p. 766). Olah proposed[5] that the name "carbonium ion" be reserved for pentacoordinated positive ions, and that **A** be called "carbenium ions." He also proposed the term "carbocation" to encompass both types. The International Union of Pure and Applied Chemistry (IUPAC) has accepted these definitions.[6] Although some authors still refer to **A** as carbonium ions and others call them carbenium ions, the general tendency is to refer to them simply as *carbocations*, and we will follow this practice. The pentavalent species are much rarer than **A**, and the use of the term "carbocation" for **A** causes little or no confusion.

Stability and Structure

Carbocations are intermediates in several kinds of reactions.[7] The more stable ones have been prepared in solution and in some cases even as solid salts, and X-ray crystallographic structures have been obtained in some cases.[8] The X-ray of the

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[2] For a treatise, see Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, 5 vols., Wiley, NY, ***1968–1976***. For monographs, see Vogel, P. *Carbocation Chemistry*, Elsevier, NY, ***1985***; Bethell, D.; Gold, V. *Carbonium Ions*, Academic Press, NY, ***1967***. For reviews, see Saunders, M.; Jiménez-Vázquez, H.A. *Chem. Rev.* ***1991***, *91*, 375; Arnett, E.M.; Hofelich, T.C.; Schriver, G.W. *React. Intermed. (Wiley)* ***1987***, *3*, 189; Bethell, D.; Whittaker, D. *React. Intermed. (Wiley)* ***1981***, *2*, 211; Bethell, D. *React. Intermed. (Wiley)* ***1978***, *1*, 117; Olah, G.A. *Chem. Scr.* ***1981***, *18*, 97, *Top. Curr. Chem.* ***1979***, *80*, 19, *Angew. Chem. Int. Ed.* ***1973***, *12*, 173 (this review has been reprinted as Olah, G.A. *Carbocations and Electrophilic Reactions*, Wiley, NY, ***1974***); Isaacs, N.S. *Reactive Intermediates in Organic Chemistry*, Wiley, NY, ***1974***, pp. 92–199; McManus, S.P.; Pittman, Jr., C.U., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 193–335; Buss, V.; Schleyer, P.v.R.; Allen, L.C. *Top. Stereochem.* ***1973***, *7*, 253; Olah, G.A.; Pittman Jr., C.U. *Adv. Phys. Org. Chem.* ***1966***, *4*, 305. For reviews of dicarbocations, see Lammertsma, K.; Schleyer, P.v.R.; Schwarz, H. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1321; Pagni, R.M. *Tetrahedron* ***1984***, *40*, 4161; Prakash, G.K.S.; Rawdah, T.N.; Olah, G.A. *Angew. Chem. Int. Ed.* ***1983***, *22*, 390. See also, the series *Advances in Carbocation Chemistry.*

[3] Gomberg, M. *Berchte* ***1902***, *35*, 2397.

[4] For a history of the term "carbonium ion," see Traynham, J.G. *J. Chem. Educ.* ***1986***, *63*, 930.

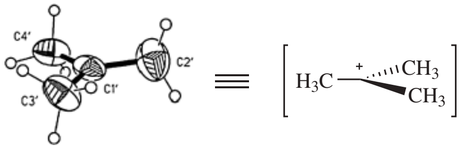
[5] Olah, G.A. *CHEMTECH* ***1971***, *1*, 566; *J. Am. Chem. Soc.* ***1972***, *94*, 808.

[6] Gold, V.; Loening, K.L.; McNaught, A.D.; Sehmi, P. *Compendium of Chemical Terminology: IUPAC Recommendations*, Blackwell Scientific Publications, Oxford, ***1987***.

[7] Olah, G.A. *J. Org. Chem.* ***2001***, *66*, 5943.

[8] See Laube, T. *J. Am. Chem.* ***2004***, 126, 10904 and references cited therein. For the X-ray of a vinyl carbocation, see Müller, T.; Juhasz, M.; Reed, C.A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 1543.

tert-butyl cation complexed with dichloromethane was reported,[9] for example, and is presented as **1** with the solvent molecules removed for clarity. An isolable dioxa-stabilized pentadienylium ion was isolated and its structure was determined by ^{1}H-, ^{13}C-NMR, mass spectrometry (MS), and IR.[10] A β-fluoro substituted 4-methoxyphenethyl cation has been observed directly by laser flash photolysis.[11] In solution, the carbocation may be free (this is more likely in polar solvents, in which it is solvated) or it may exist as an ion pair,[12] which means that it is closely associated with a negative ion, called a *counterion* or *gegenion*. Ion pairs are more likely in nonpolar solvents.



1

Among simple alkyl carbocations[13] the order of stability is tertiary > secondary > primary. There are many known examples of rearrangements of primary or secondary carbocations to tertiary, both in solution and in the gas phase. Since simple alkyl cations are not stable in ordinary strong-acid solutions (e.g., H_2SO_4), the study of these species was greatly facilitated by the discovery that many of them could be kept indefinitely in stable solutions in mixtures of fluorosulfuric acid and antimony pentafluoride. Such mixtures, usually dissolved in SO_2 or SO_2ClF, are among the strongest acidic solutions known and are often called *super acids*.[14] The original experiments involved the addition of alkyl fluorides to SbF_5.[15]

$$\mathrm{RF} \ + \ \mathrm{SbF_5} \longrightarrow \mathrm{R^+ \ SbF_6^-}$$

Subsequently, it was found that the same cations could also be generated from alcohols in super acid-SO_2 at −60°C[16] and from alkenes by the addition of a proton from super acid or HF—SbF_5 in SO_2 or SO_2ClF at low temperatures.[17] Even alkanes give carbocations in super acid by loss of H^-. For example,[18]

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[9] Kato, T.; Reed, C.A. *Angew. Chem. Int. Ed.* ***2004**, 43*, 2908.

[10] Lüning, U.; Baumstark, R. *Tetrahedron Lett.* ***1993***, *34*, 5059.

[11] McClelland, R.A.; Cozens, F.L.; Steenken, S.; Amyes, T.L.; Richard, J.P. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1717.

[12] For a treatise, see Szwarc, M. *Ions and Ion Pairs in Organic Reactions*, 2 vols., Wiley, NY, ***1972–1974***.

[13] For a review, see Olah, G.A.; Olah, J.A., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, WIley, NY, ***1969***, pp. 715–782. Also see Fărcaşiu, D.; Norton, S.H. *J. Org. Chem.* ***1997***, *62*, 5374.

[14] For a review of carbocations in super acid solutions, see Olah, G.A.; Prakash, G.K.S.; Sommer, J., in *Superacids*, Wiley, NY, ***1985***, pp. 65–175.

[15] Olah, G.A.; Baker, E.B.; Evans, J.C.; Tolgyesi, W.S.; McIntyre, J.S.; Bastien, I.J. *J. Am. Chem. Soc.* ***1964***, *86*, 1360; Brouwer, D.M.; Mackor, E.L. *Proc. Chem. Soc.* ***1964***, 147; Kramer, G.M. *J. Am. Chem. Soc.* ***1969***, *91*, 4819.

[16] Olah, G.A.; Sommer, J.; Namanworth, E. *J. Am. Chem. Soc.* ***1967***, *89*, 3576.

[17] Olah, G.A.; Halpern, Y. *J. Org. Chem.* ***1971***, *36*, 2354. See also, Herlem, M. *Pure Appl. Chem.* ***1977***, *49*, 107.

[18] Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* ***1967***, *89*, 4739.

isobutane gives the *tert*-butyl cation

$$\mathrm{Me_3CH} \xrightarrow{\mathrm{FSO_3H{-}SbF_6}} \mathrm{Me_3}\overset{\oplus}{\mathrm{C}}\ \ \mathrm{SbF_5FS}\overset{\ominus}{\mathrm{O}}\mathrm{_3} \quad + \quad \mathrm{H_2}$$

No matter how they are generated, study of the simple alkyl cations has provided dramatic evidence for the stability order.[19] Both propyl fluorides gave the isopropyl cation; all four butyl fluorides[20] gave the *tert*-butyl cation, and all seven of the pentyl fluorides tried gave the *tert*-pentyl cation. *n*-Butane, in super acid, gave only the *tert*-butyl cation. To date, no primary cation has survived long enough for detection. Neither methyl nor ethyl fluoride gave the corresponding cations when treated with SbF_5. At low temperatures, methyl fluoride gave chiefly the methylated sulfur dioxide salt $(CH_3OSO)^+\ SbF_6^-$,[21] while ethyl fluoride rapidly formed the *tert*-butyl and *tert*-hexyl cations by addition of the initially formed ethyl cation to ethylene molecules also formed.[22] At room temperature, methyl fluoride also gave the *tert*-butyl cation.[23] In accord with the stability order, hydride ion is abstracted from alkanes by super acid most readily from tertiary and least readily from primary positions.

The stability order can be explained by the polar effect and by hyperconjugation. In the polar effect, nonconjugated substituents exert an influence on stability through bonds (inductive effect) or through space (field effect). Since a tertiary carbocation has more carbon substituents on the positively charged carbon, relative to a primary, there is a greater polar effect that leads to great stability. In the hyperconjugation explanation,[24] we compare a primary carbocation with a tertiary. It should be made clear that "*the hyperconjugation concept arises solely from our model-building procedures*. When we ask whether hyperconjugation is important in a given situation, we are asking only whether the localized model is adequate for that situation at the particular level of precision we wish to use, or whether the model must be corrected by including some delocalization in order to get a good enough description."[25] Using the hyperconjugation model, is seen that the

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[19] See Amyes, T.L.; Stevens, I.W.; Richard, J.P. *J. Org. Chem.* ***1993***, *58*, 6057 for a recent study.

[20] The *sec*-butyl cation has been prepared by slow addition of *sec*-butyl chloride to SbF_5—SO_2ClF solution at −110°C [Saunders, M.; Hagen, E.L.; Rosenfeld, J. *J. Am. Chem. Soc.* ***1968***, *90*, 6882] and by allowing molecular beams of the reagents to impinge on a very cold surface [Saunders, M.; Cox, D.; Lloyd, J.R. *J. Am. Chem. Soc.* ***1979***, *101*, 6656; Myhre, P.C.; Yannoni, C.S. *J. Am. Chem. Soc.* ***1981***, *103*, 230].

[21] Peterson, P.E.; Brockington, R.; Vidrine, D.W. *J. Am. Chem. Soc.* ***1976***, *98*, 2660; Calves, J.; Gillespie, R.J. *J. Chem. Soc. Chem. Commun.* ***1976***, 506; Olah, G.A.; Donovan, D.J. *J. Am. Chem. Soc.* ***1978***, *100*, 5163.

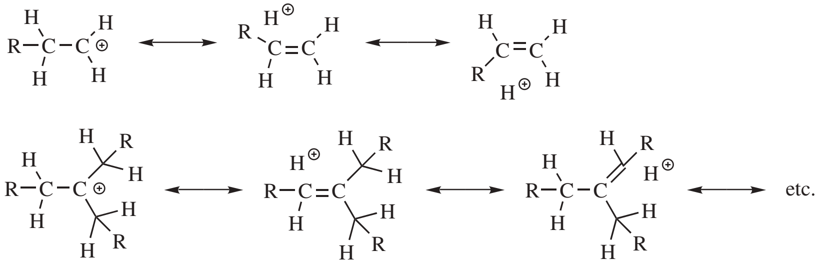
[22] Olah, G.A.; Olah, J.A., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1969***, p. 722.

[23] Olah, G.A.; DeMember, J.R.; Schlosberg, R.H. *J. Am. Chem. Soc.* ***1969***, *91*, 2112; Bacon, J.; Gillespie, R.J. *J. Am. Chem. Soc.* ***1971***, *91*, 6914.

[24] For a review of molecular-orbital theory as applied to carbocations, see Radom, L.; Poppinger, D.; Haddon, R.C., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2303–2426.

[25] Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry, 3rd ed.*, HarperCollins, NY, ***1987***, p. 68.

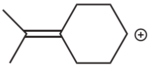
primary ion has only two hyperconjugative forms while the tertiary has six:



According to rule 6 for resonance contributors (p. 47), the greater the number of equivalent forms, the greater the resonance stability. Evidence used to support the hyperconjugation explanation is that the equilibrium constant for this reaction:

$$\underset{\mathbf{2}}{(CD_3)_3C^{\oplus}} + (CH_3)_3CH \rightleftharpoons \underset{\mathbf{3}}{(CH_3)_3C^{\oplus}} + (CD_3)_3CH \qquad K_{298} = 1.97 \pm 0.20$$

is 1.97, showing that **3** is more stable than **2**.[26] Due to a β secondary isotope effect, there is less hyperconjugation in **2** than in **3** (see p. 324 for isotope effects).[27]



4

There are several structural types of delocalization, summarized in Table 5.1.[28] The stabilization of dimethylalkylidine cation **4** is an example of double hyperconjugation.[28,29]

The field effect explanation is that the electron-donating effect of alkyl groups increases the electron density at the charge-bearing carbon, reducing the net charge on the carbon, and in effect spreading the charge over the α carbons. It is a general rule that the more concentrated any charge is, the less stable the species bearing it will be.

The most stable of the simple alkyl cations is the *tert*-butyl cation. Even the relatively stable *tert*-pentyl and *tert*-hexyl cations fragment at higher temperatures to

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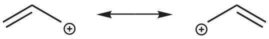
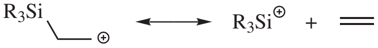
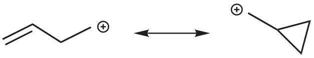
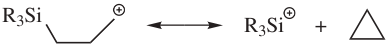
[26] Meot-Ner, M. *J. Am. Chem. Soc.* ***1987***, *109*, 7947.

[27] If only the field effect were operating, **2** would be more stable than **3**, since deuterium is electron-donating with respect to hydrogen (p. 23), assuming that the field effect of deuterium could be felt two bonds away.

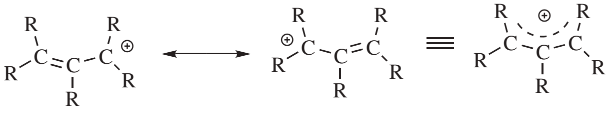
[28] Lambert, J.B.; Ciro, S.M. *J. Org. Chem.* ***1996***, *61*, 1940.

[29] Alabugin, I.V.; Manoharan, M. *J. Org. Chem.* ***2004***, *69*, 9011.

TABLE 5.1. Structural Types of Delocalization[25]

Valence Structures	Abbreviation	Name
	ππ	Simple conjugation
	σπ	Hyperconjugation
	πσ	Homoconjugation
	σσ	Homohyperconjugation
	σπ/ππ	Hyperconjugation/ conjugation
	σπ/σπ	Double hyperconjugation

produce the *tert*-butyl cation, as do all other alkyl cations with four or more carbons so far studied.[30] Methane,[31] ethane, and propane, treated with super acid, also yield *tert*-butyl cations as the main product (see reaction **12-20**). Even paraffin wax and polyethylene give *tert*-butyl cation. Solid salts of *tert*-butyl and *tert*-pentyl cations (e.g., $Me_3C^+\ SbF_6^-$) have been prepared from super acid solutions and are stable below −20°C.[32]



5

In carbocations where the positive carbon is in conjugation with a double bond, as in allylic cations (the allyl cation is **5**, R = H), the stability is greater because of increased delocalization due to resonance,[33] where the positive charge is spread over several atoms instead of being concentrated on one (see the molecular-orbital picture of this species on p. 41). Each of the terminal atoms has a charge of $\sim\frac{1}{2}$ (the charge is exactly $\frac{1}{2}$ if all of the R groups are the same). Stable cyclic and

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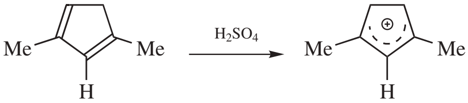
[30] Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* ***1967**, 89*, 4739; Olah, G.A.; Olah, J.A., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1969***, pp. 750–764.

[31] Olah, G.A.; Klopman, G.; Schlosberg, R.H. *J. Am. Chem. Soc.* ***1969***, *91*, 3261. See also, Hogeveen, H.; Gaasbeek, C.J. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 319.

[32] Olah, G.A.; Svoboda, J.J.; Ku, A.T. *Synthesis* ***1973***, 492; Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* ***1967**, 89*, 4739.

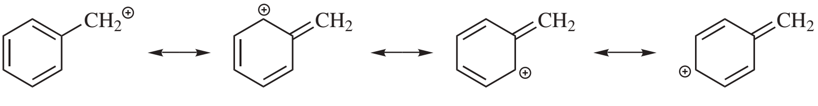
[33] See Barbour, J.B.; Karty, J.M. *J. Org. Chem.* ***2004***, *69*, 648; Mo, Y. *J. Org. Chem.* ***2004***, *69*, 5563 and references cited therein.

acyclic allylic-type cations[34] have been prepared by the solution of conjugated dienes in concentrated sulfuric acid, for example,[35]



Stable allylic cations have also been obtained by the reaction between alkyl halides, alcohols, or alkenes (by hydride extraction) and SbF_5 in SO_2 or SO_2ClF.[36] Bis(allylic) cations[37] are more stable than the simple allylic type, and some of these have been prepared in concentrated sulfuric acid.[38] Arenium ions (p. 658) are familiar examples of this type. Propargyl cations ($RC{\equiv}CR_2^+$) have also been prepared.[39]

Canonical forms can be drawn for benzylic cations,[40] similar to those shown above for allylic cations, for example,



A number of benzylic cations have been obtained in solution as SbF_6^- salts.[41] Diarylmethyl and triarylmethyl cations are still more stable. Triphenylchloromethane ionizes in polar solvents that do not, like water, react with the ion. In SO_2, the equilibrium

$$Ph_3CCl \rightleftharpoons Ph_3C^{\oplus} + Cl^{\ominus}$$

has been known for many years. Both triphenylmethyl and diphenylmethyl cations have been isolated as solid salts[42] and, in fact, $Ph_3C^+\ BF_4^-$ and related salts are available commercially. Arylmethyl cations are further stabilized if they have

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[34] For reviews, see Deno, N.C., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 783–806; Richey Jr., H.G., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 39–114.

[35] Deno, N.C.; Richey, Jr., H.G.; Friedman, N.; Hodge, J.D.; Houser, J.J.; Pittman, Jr., C.U. *J. Am. Chem. Soc.* ***1963***, *85*, 2991.

[36] Olah, G.A.; Spear, R.J. *J. Am. Chem. Soc.* ***1975***, *97*, 1539 and references cited therein.

[37] For a review of divinylmethyl and trivinylmethyl cations, see Sorensen, T.S., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 807–835.

[38] Deno, N.C.; Pittman, Jr., C.U. *J. Am. Chem. Soc.* ***1964***, *86*, 1871.

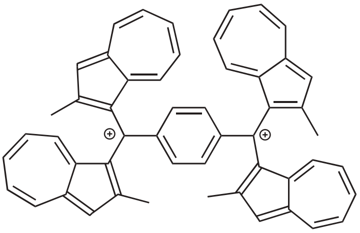
[39] Pittman, Jr., C.U.; Olah, G.A. *J. Am. Chem. Soc.* ***1965***, *87*, 5632; Olah, G.A.; Spear, R.J.; Westerman, P.W.; Denis, J. *J. Am. Chem. Soc.* ***1974***, *96*, 5855.

[40] For a review of benzylic, diarylmethyl, and triarymethyl cations, see Freedman, H.H., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1971***, pp. 1501–1578.

[41] Olah, G.A.; Porter, R.D.; Jeuell, C.L.; White, A.M. *J. Am. Chem. Soc.* ***1972***, *94*, 2044.

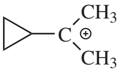
[42] Volz, H.; Schnell, H.W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 873.

electron-donating substituents in ortho or para positions.[43] Dications[44] and trications are also possible, including the particularly stable dication (**6**), where each positively charged benzylic carbon is stabilized by two azulene rings.[45] A related trication is known where each benzylic cationic center is also stabilized by two azulene rings.[46]

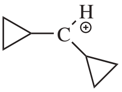


6

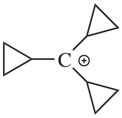
Cyclopropylmethyl cations[47] are even more stable than the benzyl type. Ion **9** has been prepared by solution of the corresponding alcohol in 96% sulfuric acid,[48] and **7**, **8**, and similar ions by solution of the alcohols in $FSO_3H—SO_2—SbF_5$.[49] This special stability, which increases with each additional cyclopropyl group, is a result of conjugation between the bent orbitals of the cyclopropyl rings (p. $$$) and the vacant *p* orbital of the cationic carbon (see **10**). Nuclear magnetic resonance and other studies have shown that the vacant *p* orbital lies parallel to the C-2,C-3 bond of the cyclopropane ring and not perpendicular to it.[50] In this respect, the



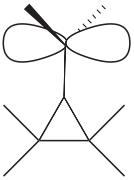
7



8



9



10

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[43] Goldacre, R.J.; Phillips, J.N. *J. Chem. Soc.* ***1949***, 1724; Deno, N.C.; Schriesheim, A. *J. Am. Chem. Soc.* ***1955***, *77*, 3051.

[44] Prakash, G.K.S. *Pure Appl. Chem.* ***1998***, *70*, 2001.

[45] Ito, S.; Morita, N.; Asao, T. *Tetrahedron Lett.* ***1992***, *33*, 3773.

[46] Ito, S.; Morita, N.; Asao, T. *Tetrahedron Lett.* ***1994***, *35*, 751.

[47] For reviews, see, in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***: Richey, Jr., H.G. pp. 1201–294; Wiberg, K.B.; Hess Jr., B.A.; Ashe III, A.H. pp. 1295–1345.

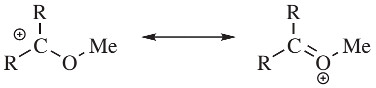
[48] Deno, N.C.; Richey, Jr., H.G.; Liu, J.S.; Hodge, J.D.; Houser, H.J.; Wisotsky, M.J. *J. Am. Chem. Soc.* ***1962***, *84*, 2016.

[49] Pittman Jr., C.U.; Olah, G.A. *J. Am. Chem. Soc.* ***1965***, *87*, 2998; Deno, N.C.; Liu, J.S.; Turner, J.O.; Lincoln, D.N.; Fruit, Jr., R.E. *J. Am. Chem. Soc.* ***1965***, *87*, 3000.

[50] For example, see Ree, B.; Martin, J.C. *J. Am. Chem. Soc.* ***1970***, *92*, 1660; Kabakoff, D.S.; Namanworth, E. *J. Am. Chem. Soc.* ***1970***, *92*, 3234; Buss, V.; Gleiter, R.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 3927; Poulter, C.D.; Spillner, C.J. *J. Am. Chem. Soc.* ***1974***, *96*, 7591; Childs, R.F.; Kostyk, M.D.; Lock, C.J.L.; Mahendran, M. *J. Am. Chem. Soc.* ***1990***, *112*, 8912; Deno, N.C.; Richey Jr., H.G.; Friedman, N.; Hodge, J.D.; Houser, J.J.; Pittman Jr., C.U. *J. Am. Chem. Soc.* ***1963***, *85*, 2991.

geometry is similar to that of a cyclopropane ring conjugated with a double bond (p. 218). Cyclopropylmethyl cations are further discussed on pp. 459–463. The stabilizing effect just discussed is unique to cyclopropyl groups. Cyclobutyl and larger cyclic groups are about as effective at stabilizing a carbocation as ordinary alkyl groups.[51]

Another structural feature that increases carbocation stability is the presence, adjacent to the cationic center, of a heteroatom bearing an unshared pair,[52] for example, oxygen,[53] nitrogen,[54] or halogen.[55] Such ions are stabilized by resonance:



The methoxymethyl cation can be obtained as a stable solid, $MeOCH_2^+ SbF_6^-$.[56] Carbocations containing either α, β, or γ silicon atom are also stabilized,[57] relative to similar ions without the silicon atom. In super acid solution, ions such as CX_3^+ (X = Cl, Br, I) have been prepared.[58] Vinyl-stabilized halonium ions are also known.[59]

Simple acyl cations RCO^+ have been prepared[60] in solution and the solid state.[61] The acetyl cation CH_3CO^+ is about as stable as the *tert*-butyl cation (see, e.g., Table 5.1). The 2,4,6-trimethylbenzoyl and 2,3,4,5,6-pentamethylbenzoyl cations are especially stable (for steric reasons) and are easily formed in 96% H_2SO_4.[62] These

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[51] Sorensen, T.S.; Miller, I.J.; Ranganayakulu, K. *Aust. J. Chem.* ***1973***, *26*, 311.

[52] For a review, see Hevesi, L. *Bull. Soc. Chim. Fr.* ***1990***, 697. For examples of stable solutions of such ions, see Kabus, S.S. *Angew. Chem. Int. Ed.* ***1966***, *5*, 675; Dimroth, K.; Heinrich, P. *Angew. Chem. Int. Ed.* ***1966***, *5*, 676; Tomalia, D.A.; Hart, H. *Tetrahedron Lett.* ***1966***, 3389; Ramsey, B.; Taft, R.W. *J. Am. Chem. Soc.* ***1966***, *88*, 3058; Olah, G.A.; Liang, G.; Mo, Y.M. *J. Org. Chem.* ***1974***, *39*, 2394; Borch, R.F. *J. Am. Chem. Soc.* ***1968***, *90*, 5303; Rabinovitz, M.; Bruck, D. *Tetrahedron Lett.* ***1971***, 245.

[53] For a review of ions of the form R_2C^+—OR′, see Rakhmankulov, D.L.; Akhmatdinov, R.T.; Kantor, E.A. *Russ. Chem. Rev.* ***1984***, *53*, 888. For a review of ions of the form $R'C^+(OR)_2$ and $C^+(OR)_3$, see Pindur, U.; Müller, J.; Flo, C.; Witzel, H. *Chem. Soc. Rev.* ***1987***, *16*, 75.

[54] For a review of such ions where nitrogen is the heteroatom, see Scott, F.L.; Butler, R.N., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1974***, pp. 1643–1696.

[55] See Allen, A.D.; Tidwell, T.T. *Adv. Carbocation Chem.* ***1989***, *1*, 1. See also, Teberekidis, V.I.; Sigalas, M.P. *Tetrahedron* ***2003***, *59*, 4749.

[56] Olah, G.A.; Svoboda, J.J. *Synthesis* ***1973***, 52.

[57] For a review and discussion of the causes, see Lambert, J.B. *Tetrahedron* ***1990***, *46*, 2677. See also, Lambert, J.B.; Chelius, E.C. *J. Am. Chem. Soc.* ***1990***, *112*, 8120.

[58] Olah, G.A.; Heiliger, L.; Prakash, G.K.S. *J. Am. Chem. Soc.* ***1989***, *111*, 8020.

[59] Haubenstock, H.; Sauers, R.R. *Tetrahedron* ***2004***, *60*, 1191.

[60] For reviews of acyl cations, see Al-Talib, M.; Tashtoush, H. *Org. Prep. Proced. Int.* ***1990***, *22*, 1; Olah, G.A.; Germain, A.; White, A.M., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2049–2133. For a review of the preparation of acyl cations from acyl halides and Lewis acids, see Lindner, E. *Angew. Chem. Int. Ed.* ***1970***, *9*, 114.

[61] See, for example, Deno, N.C.; Pittman, Jr., C.U.; Wisotsky, M.J. *J. Am. Chem. Soc.* ***1964***, *86*, 4370; Olah, G.A.; Dunne, K.; Mo, Y.K.; Szilagyi, P. *J. Am. Chem. Soc.* ***1972***, *94*, 4200; Olah, G.A.; Svoboda, J.J. *Synthesis* ***1972***, 306.

[62] Hammett, L.P.; Deyrup, A.J. *J. Am. Chem. Soc.* ***1933***, *55*, 1900; Newman, M.S.; Deno, N.C. *J. Am. Chem. Soc.* ***1951***, *73*, 3651.

ions are stabilized by a canonical form containing a triple bond (**12**), although the positive charge is principally located on the carbon,[63] so that **11** contributes more than **12**.

$$R-\overset{\oplus}{C}=O \longleftrightarrow R-C\equiv O^{\oplus}$$

11 **12**

The stabilities of most other stable carbocations can also be attributed to resonance. Among these are the tropylium, cyclopropenium,[64] and other aromatic cations discussed in Chapter 2. Where resonance stability is completely lacking, as in the phenyl ($C_6H_5^+$) or vinyl cations,[65] the ion, if formed at all, is usually very short lived.[66] Neither vinyl[67] nor phenyl cation has as yet been prepared as a stable species in solution.[68] However, stable alkenyl carbocations have been generated on Zeolite Y.[69]

Various quantitative methods have been developed to express the relative stabilities of carbocations.[70] One of the most common of these, although useful only for relatively stable cations that are formed by ionization of alcohols in acidic solutions, is based on the equation[71]

$$H_R = pK_{R^+} - \log \frac{C_{R^+}}{C_{ROH}}$$

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[63] Boer, F.P. *J. Am. Chem. Soc.* ***1968***, *90*, 6706; Le Carpentier, J.; Weiss, R. *Acta Crystallogr. Sect. B*, ***1972***, 1430. See also, Olah, G.A.; Westerman, P.W. *J. Am. Chem. Soc.* ***1973***, *95*, 3706.

[64] See Komatsu, K.; Kitagawa, T. *Chem. Rev.* ***2003***, *103*, 1371. Also see, Gilbertson, R.D.; Weakley, T.J.R.; Haley, M.M. *J. Org. Chem.* ***2000***, *65*, 1422.

[65] For the preparation and reactivity of a primary vinyl carbocation see Gronheid, R.; Lodder, G.; Okuyama, T. *J. Org. Chem.* ***2002***, *67*, 693.

[66] For a review of destabilized carbocations, see Tidwell, T.T. *Angew. Chem. Int. Ed.* ***1984***, *23*, 20.

[67] Solutions of aryl-substituted vinyl cations have been reported to be stable for at least a short time at low temperatures. The NMR spectra was obtained: Abram, T.S.; Watts, W.E. *J. Chem. Soc. Chem. Commun.* ***1974***, 857; Siehl, H.; Carnahan, Jr., J.C.; Eckes, L.; Hanack, M. *Angew. Chem. Int. Ed.* ***1974***, *13*, 675. The l-cyclobutenyl cation has been reported to be stable in the gas phase: Franke, W.; Schwarz, H.; Stahl, D. *J. Org. Chem.* ***1980***, *45*, 3493. See also, Siehl, H.; Koch, E. *J. Org. Chem.* ***1984***, *49*, 575.

[68] For a monograph, see Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, 1979. For reviews of aryl and/or vinyl cations, see Hanack, M. *Pure Appl. Chem.* ***1984***, *56*, 1819, *Angew. Chem. Int. Ed.* ***1978***, *17*, 333; *Acc. Chem. Res.* ***1976***, *9*, 364; Rappoport, Z. *Reactiv. Intermed. (Plenum)* ***1983***, *3*, 427; Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* ***1979***, *8*, 353; Richey Jr., H.G.; Richey, J.M., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 899–957; Richey Jr., H.G., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 42–49; Modena, G.; Tonellato, U. *Adv. Phys. Org. Chem.* ***1971***, *9*, 185; Stang, P.J. *Prog. Phys. Org. Chem.* ***1973***, *10*, 205. See also, Charton, M. *Mol. Struct. Energ.* ***1987***, *4*, 271. For a computational study, see Glaser, R.; Horan, C. J.; Lewis, M.; Zollinger, H. *J. Org. Chem.* ***1999***, *64,* 902.

[69] Yang, S.; Kondo, J.N.; Domen, K. *Chem. Commun.* ***2001***, 2008.

[70] For reviews, see Bagno, A.; Scorrano, G.; More O'Ferrall, R.A. *Rev. Chem. Intermed.* ***1987***, *7*, 313; Bethell, D.; Gold, V. *Carbonium Ions*, Academic Press, NY, ***1967***, pp. 59–87.

[71] Deno, N.C.; Berkheimer, H.E.; Evans, W.L.; Peterson, H.J. *J. Am. Chem. Soc.* ***1959***, *81*, 2344.

pK_{R^+} is the pK value for the reaction $R^+ + 2\ H_2O \rightleftharpoons ROH + H_3O^+$ and is a measure of the stability of the carbocation. The H_R parameter is an early obtainable measurement of the stability of a solvent (see p. 371) and approaches pH at low concentrations of acid. In order to obtain pK_{R^+}, for a cation R^+, one dissolves the alcohol ROH in an acidic solution of known H_R. Then the concentration of R^+ and ROH are obtained, generally from spectra, and pK_{R^+} is easily calculated.[72] A measure of carbocation stability that applies to less-stable ions is the dissociation energy $D(R^+–H^-)$ for the cleavage reaction $R - H \rightarrow R^+ + H^-$, which can be obtained from photoelectron spectroscopy and other measurements. Some values of $D(R^+—H^-)$ are shown in Table 5.2.[75] Within a given class of ion (primary, secondary, allylic, aryl, etc.), $D(R^+—H^-)$ has been shown to be a linear function of the logarithm of the number of atoms in R^+, with larger ions being more stable.[74]

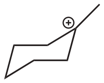
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TABLE 5.2. R–H → $R^+ + H^-$ Dissociation Energies in the Gas Phase

	$D(R^+–H^-)$		
Ion	kcal mol^{-1}	kJ mol^{-1}	Reference
CH_3^+	314.6	1316	73
$C_2H_5^+$	276.7	1158	73
$(CH_3)_2CH^+$	249.2	1043	73
$(CH_3)_3C^+$	231.9	970.3	73
$C_6H_5^+$	294	1230	74
$H_2C{=}CH^+$	287	1200	74
$H_2C{=}CH{-}CH_2^+$	256	1070	74
Cyclopentyl	246	1030	74
$C_6H_5CH_2^+$	238	996	74
CH_3CHO	230	962	74

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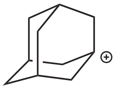
[72] For a list of stabilities of 39 typical carbocations, see Arnett, E.M.; Hofelich, T.C. *J. Am. Chem. Soc.* ***1983***, *105*, 2889. See also, Schade, C.; Mayr, H.; Arnett, E.M. *J. Am. Chem. Soc.* ***1988***, *110*, 567; Schade, C.; Mayr, H. *Tetrahedron* ***1988***, *44*, 5761.

[73] Schultz, J.C.; Houle, F.A.; Beauchamp, J.L. *J. Am. Chem. Soc.* ***1984***, *106*, 3917.

[74] Lossing, F.P.; Holmes, J.L. *J. Am. Chem. Soc.* ***1984***, *106*, 6917.

[75] Hammett, L.P.; Deyrup, A.J. *J. Am. Chem. Soc.* ***1933***, *55*, 1900; Newman, M.S.; Deno, N.C. *J. Am. Chem. Soc.* ***1951***, *73*, 3651; Boer, F.P. *J. Am. Chem. Soc.* ***1968***, *90*, 6706; Le Carpentier, J.; Weiss, R. *Acta Crystallogr. Sect. B*, ***1972***, 1430. See also, Olah, G.A.; Westerman, P.W. *J. Am. Chem. Soc.* ***1973***, *95*, 3706. See also, Staley, R.H.; Wieting, R.D.; Beauchamp, J.L. *J. Am. Chem. Soc.* ***1977***, *99*, 5964; Arnett, E.M.; Petro, C. *J. Am. Chem. Soc.* ***1978***, *100*, 5408; Arnett, E.M.; Pienta, N.J. *J. Am. Chem. Soc.* ***1980***, *102*, 3329.

Since the central carbon of tricoordinated carbocations has only three bonds and no other valence electrons, the bonds are *sp*^{2} and should be planar.[76] Raman, IR, and NMR spectroscopic data on simple alkyl cations show this to be so.[77] In methylcycohexyl cations, there are two chair conformations where the carbon bearing the positive charge is planar (**13** and **14**), and there is evidence that **14** is more stable due to a difference in hyperconjugation.[78] Other evidence is that carbocations are difficult to form at bridgehead atoms in [2.2.1] systems,[79] where they cannot be planar (see p. 435).[80] Bridgehead carbocations are known, however, as in [2.1.1]hexanes[81] and cubyl carbocations.[82] However, larger bridgehead ions can exist. For example, the adamantyl cation (**15**) has been synthesized, as the SF_6^- salt.[83] The relative stability of 1-adamantyl cations is influenced by the number and nature of substituents. For example, the stability of the 1-adamantyl cation increases with the number of isopropyl substituents at C-3, C-5 and C-7.[84] Among other bridgehead cations that have been prepared in super acid solution at −78°C are the dodecahydryl cation (**16**)[85] and the 1-trishomobarrelyl cation (**17**).[86] In the latter



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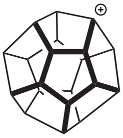

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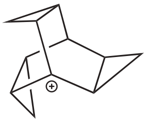

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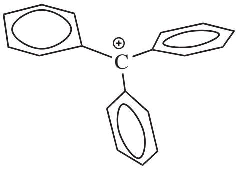

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[76] For discussions of the stereochemistry of carbocations, see Henderson, J.W. *Chem. Soc. Rev.* ***1973***, *2*, 397; Buss, V.; Schleyer, P.v.R.; Allen, L.C. *Top. Stereochem.* ***1973***, *7*, 253; Schleyer, P.v.R., in Chiurdoglu, G. *Conformational Analysis*; Academic Press, NY, ***1971***, p. 241; Hehre, W.J. *Acc. Chem. Res.* ***1975***, *8*, 369; Freedman, H.H., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1974***, pp. 1561–574.

[77] Olah, G.A.; DeMember, J.R.; Commeyras, A.; Bribes, J.L. *J. Am. Chem. Soc.* ***1971***, *93*, 459; Yannoni, C.S.; Kendrick, R.D.; Myhre, P.C.; Bebout, D.C.; Petersen, B.L. *J. Am. Chem. Soc.* ***1989***, *111*, 6440.

[78] Rauk, A.; Sorensen, T.S.; Maerker, C.; de M. Carneiro, J.W.; Sieber, S.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1996***, *118*, 3761.

[79] For a review of bridgehead carbocations, see Fort, Jr., R.C., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1974***, pp. 1783–1835.

[80] Della, E.W.; Schiesser, C.H. *J. Chem. Soc. Chem. Commun.* ***1994***, 417.

[81] Åhman, J.; Somfai, P.; Tanner, D. *J. Chem. Soc. Chem. Commun.* ***1994***, 2785.

[82] Della, E.W.; Head, N.J.; Janowski, W.K.; Schiesser, C.H. *J. Org. Chem.* ***1993***, *58*, 7876.

[83] Schleyer, P.v.R.; Fort, Jr., R.C.; Watts, W.E.; Comisarow, M.B.; Olah, G.A. *J. Am. Chem. Soc.* ***1964***, *86*, 4195; Olah, G.A.; Prakash, G.K.S.; Shih, J.G.; Krishnamurthy, V.V.; Mateescu, G.D.; Liang, G.; Sipos, G.; Buss, V.; Gund, T.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1985***, *107*, 2764. See also, Kruppa, G.H.; Beauchamp, J.L. *J. Am. Chem. Soc.* ***1986***, *108*, 2162; Laube, T. *Angew. Chem. Int. Ed.* ***1986***, *25*, 349.

[84] Takeuchi, K.; Okazaki, T.; Kitagawa, T.; Ushino, T.; Ueda, K.; Endo, T.; Notario, R. *J. Org. Chem.* ***2001***, *66*, 2034.

[85] Olah, G.A.; Prakash, G.K.S.; Fessner, W.; Kobayashi, T.; Paquette, L.A. *J. Am. Chem. Soc.* ***1988***, *110*, 8599.

[86] de Meijere, A.; Schallner, O. *Angew. Chem. Int. Ed.* ***1973***, *12*, 399.

TABLE 5.3. The ^{13}C Chemical Shift Values, in Parts Per Million from $^{13}CS_2$ for the Charged Carbon Atom of Some Carbocations in SO_2ClF–SbF_5, SO_2–FSO_3H–SbF_6, or SO_2–SbF_5[90]

Ion	Chemical Shift	Temperature, °C	Ion	Chemical Shift	Temperature, °C
Et_2MeC^+	−139.4	−20	$C(OH)_3^+$	+28.0	−50
Me_2EtC^+	−139.2	−60	$PhMe_2C^+$	−61.1	−60
Me_3C^+	−135.4	−20	$PhMeCH^+$	−40[91]	
Me_2CH^+	−125.0	−20	Ph_2CH^+	−5.6	−60
Me_2COH^+	−55.7	−50	Ph_3C^+	−18.1	−60
$MeC(OH)_2^+$	−1.6	−30	Me_2(cyclopropyl)C^+	−86.8	−60
$HC(OH)_2^+$	+17.0	−30			

case, the instability of the bridgehead position is balanced by the extra stability gained from the conjugation with the three cyclopropyl groups.

Triarylmethyl cations (**18**)[87] are propeller shaped, although the central carbon and the three ring carbons connected to it are in a plane:[88] The three benzene rings cannot be all in the same plane because of steric hindrance, although increased resonance energy would be gained if they could.

An important tool for the investigation of carbocation structure is measurement of the ^{13}C NMR chemical shift of the carbon atom bearing the positive charge.[89] This shift approximately correlates with electron density on the carbon. The ^{13}C chemical shifts for a number of ions are given in Table 5.3.[90] As shown in this table, the substitution of an ethyl for a methyl or a methyl for a hydrogen causes a downfield shift, indicating that the central carbon becomes somewhat more positive. On the other hand, the presence of hydroxy or phenyl groups decreases the positive character of the central carbon. The ^{13}C chemical shifts are not always in exact order of carbocation stabilities as determined in other ways. Thus the chemical shift shows that the triphenylmethyl cation has a more positive central carbon than diphenylmethyl cation, although the former is more stable. Also, the 2-cyclopropylpropyl and 2-phenylpropyl cations have shifts of −86.8 and −61.1, respectively, although we have seen that according to other criteria a cyclopropyl group is better

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[87] For a review of crystal-structure determinations of triarylmethyl cations and other carbocations that can be isolated in stable solids, see Sundaralingam, M.; Chwang, A.K., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2427–2476.

[88] Sharp, D.W.A.; Sheppard, N. *J. Chem. Soc.* ***1957***, 674; Gomes de Mesquita, A.H.; MacGillavry, C.H.; Eriks, K. *Acta Crystallogr.* ***1965***, *18*, 437; Schuster, I.I.; Colter, A.K.; Kurland, R.J. *J. Am. Chem. Soc.* ***1968***, *90*, 4679.

[89] For reviews of the nmr spectra of carbocations, see Young, R.N. *Prog. Nucl. Magn. Reson. Spectrosc.* ***1979***, *12*, 261; Farnum, D.G. *Adv. Phys. Org. Chem.* ***1975***, *11*, 123.

[90] Olah, G.A.; White, A.M. *J. Am. Chem. Soc.* ***1968***, *90*, 1884; ***1969***, *91*, 5801. For ^{13}C NMR data for additional ions, see Olah, G.A.; Donovan, D.J. *J. Am. Chem. Soc.* ***1977***, *99*, 5026; Olah, G.A.; Prakash, G.K.S.; Liang, G. *J. Org. Chem.* ***1977***, *42*, 2666.

than a phenyl group at stabilizing a carbocation.[91] The reasons for this discrepancy are not fully understood.[88,92]

Nonclassical Carbocations

These carbocations are discussed at pp. 450–455.

The Generation and Fate of Carbocations

A number of methods are available to generate carbocations, stable or unstable.

1. A direct ionization, in which a leaving group attached to a carbon atom leaves with its pair of electrons, as in solvolysis reactions of alkyl halides (see p. 480) or sulfonate esters (see p. 522):

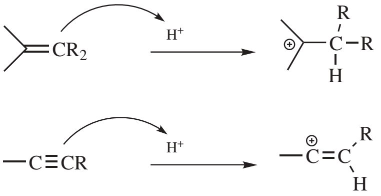
$$\mathrm{R{-}X} \longrightarrow \mathrm{R}^{\oplus} + \mathrm{X}^{\ominus} \quad \text{(may be reversible)}$$

2. Ionization after an initial reaction that converts one functional group into a leaving group, as in protonation of an alcohol to give an oxonium ion or conversion of a primary amine to a diazonium salt, both of which ionize to the corresponding carbocation:

$$\mathrm{R{-}OH} \xrightarrow{\mathrm{H}^+} \mathrm{R{-}OH_2} \longrightarrow \mathrm{R}^{\oplus} + \mathrm{H_2O} \quad \text{(may be reversible)}$$

$$\mathrm{R{-}NH_2} \xrightarrow{\mathrm{HONO}} \mathrm{R{-}N_2} \longrightarrow \mathrm{R}^{\oplus} + \mathrm{N_2}$$

3. A proton or other positive species adds to one atom of an alkene or alkyne, leaving the adjacent carbon atom with a positive charge (see Chapters 11, 15).



4. A proton or other positive species adds to one atom of an C=X bond, where X = O, S, N in most cases, leaving the adjacent carbon atom with a positive charge (see Chapter 16). When X = O, S this ion is resonance stabilized, as shown. When X = NR, protonation leads to an iminium ion, with the charge localized on the

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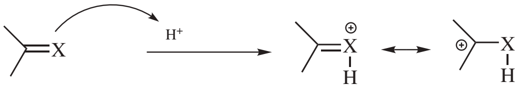
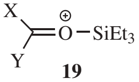
[91] Olah, G.A.; Porter, R.D.; Kelly, D.P. *J. Am. Chem. Soc.* ***1971***, *93*, 464.

[92] For discussions, see Brown, H.C.; Peters, E.N. *J. Am. Chem. Soc.* ***1973***, *95*, 2400; ***1977***, *99*, 1712; Olah, G.A.; Westerman, P.W.; Nishimura, J. *J. Am. Chem. Soc.* ***1974***, *96*, 3548; Wolf, J.F.; Harch, P.G.; Taft, R.W.; Hehre, W.J. *J. Am. Chem. Soc.* ***1975***, *97*, 2902; Fliszár, S. *Can. J. Chem.* ***1976***, *54*, 2839; Kitching, W.; Adcock, W.; Aldous, G. *J. Org. Chem.* ***1979***, *44*, 2652. See also, Larsen, J.W.; Bouis, P.A. *J. Am. Chem. Soc.* ***1975***, *97*, 4418; Volz, H.; Shin, J.; Streicher, H. *Tetrahedron Lett.* ***1975***, 1297; Larsen, J.W. *J. Am. Chem. Soc.* ***1978***, *100*, 330.

nitrogen. A silylated carboxonium ion, such as **19**, has been reported.[93]





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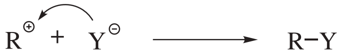
Formed by either process, carbocations are most often short-lived transient species and react further without being isolated. The intrinsic barriers to formation and reaction of carbocations has been studied.[94] Carbocations have been generated in zeolites.[95]

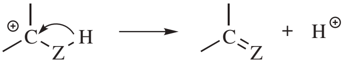
The two chief pathways by which carbocations react to give stable products are the reverse of the two pathways just described.

1. *The Carbocation May Combine with a Species Possessing an Electron Pair* (a Lewis acid–base reaction, see Chapter 8):



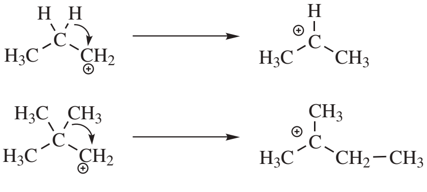
This species may be $^{-}$OH, halide ion, or any other negative ion, or it may be a neutral species with a pair to donate, in which case, of course, the immediate product must bear a positive charge (see Chapters 10, 13, 15, 16). These reactions are very fast. A recent study measured k_s (the rate constant for reaction of a simple tertiary carbocation) to be 3.5×10^{12} s^{-1}.[96]

2. *The Carbocation May Lose a Proton* (or much less often, another positive ion) from the adjacent atom (see Chapters 11, 17):



Carbocations can also adopt two other pathways that lead not to stable products, but to other carbocations:

3. *Rearrangement*. An alkyl or aryl group or a hydrogen (sometimes another group) migrates with its electron pair to the positive center, leaving another positive charge behind (see Chapter 18):



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[93] Prakash, G.K.S.; Bae, C.; Rasul, G.; Olah, G.A. *J. Org. Chem.* ***2002***, *67*, 1297.

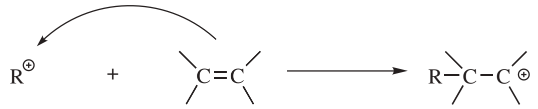
[94] Richard, J.P.; Amyes, T.L.; Williams, K.B. *Pure. Appl. Chem.* ***1998***, *70*, 2007.

[95] Song, W.; Nicholas, J. B.; Haw, J. F. *J. Am. Chem. Soc.* ***2001***, *123*, 121.

[96] Toteva, M.M.; Richard, J.P. *J. Am. Chem. Soc.* ***1996***, *118*, 11434.

A novel rearrangement has been observed. The 2-methyl-2-butyl-1-^{13}C cation (^{13}C-labeled *tert*-amyl cation) shows an interchange of the inside and outside carbons with a barrier of 19.5 (±2.0 kcal mol^{-1}).[97] Another unusual migratory process has been observed for the nonamethylcyclopentyl cation. It has been shown that "four methyl groups undergo rapid circumambulatory migration with a barrier <2 kcal mol^{-1} while five methyl groups are fixed to ring carbons, and the process that equalizes the two sets of methyls has a barrier of 7.0 kcal mol^{-1}."[98]

4. *Addition*. A carbocation may add to a double bond, generating a positive charge at a new position (see Chapters 11, 15):



20

Whether formed by pathway 3 or 4, the new carbocation normally reacts further in an effort to stabilize itself, usually by pathway 1 or 2. However, **20** can add to another alkene molecule, and this product can add to still another, and so on. This is one of the mechanisms for vinyl polymerization.

CARBANIONS

Stability and Structure[99]

An *organometallic compound* is a compound that contains a bond between a carbon atom and a metal atom. Many such compounds are known, and organometallic chemistry is a very large area, occupying a borderline region between organic and inorganic chemistry. Many carbon–metal bonds (e.g., carbon–mercury bonds)

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[97] Vrcek, V.; Saunders, M.; Kronja, O. *J. Am. Chem. Soc.* ***2004***, *126*, 13703.

[98] Kronja, O.; Kohli, T.-P.; Mayr, H.; Saunders, M. *J. Am. Chem. Soc.* ***2000***, *122*, 8067.

[99] For monographs, see Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pts. A, B, and C; Elsevier, NY, ***1980***, ***1984***, ***1987***; Bates, R.B.; Ogle, C.A. *Carbanion Chemistry*, Springer, NY, ***1983***; Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, ***1979***; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***. For reviews, see Staley, S.W. *React. Intermed. (Wiley)* ***1985***, *3*, 19; Staley, S.W.; Dustman, C.K. *React. Intermed. (Wiley)* ***1981***, *2*, 15; le Noble, W.J. *React. Intermed. (Wiley)* ***1978***, *1*, 27; Solov'yanov, A.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1978***, *47*, 425; Isaacs, N.S. *Reactive Intermediates in Organic Chemistry*, Wiley, NY, ***1974***, pp. 234–293; Kaiser, E.M.; Slocum, D.W., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 337–422; Ebel, H.F. *Fortchr. Chem. Forsch.* ***1969***, *12*, 387; Cram, D.J. *Surv. Prog. Chem.* ***1968***, *4*, 45; Reutov, O.A.; Beletskaya, I.P. *Reaction Mechanisms of Organometallic Compounds*, North Holland Publishing Co, Amsterdam, The Netherlands, ***1968***, pp. 1–64; Streitwieser Jr., A.; Hammons, J.H. *Prog. Phys. Org. Chem.* ***1965***, *3*, 41. For reviews of nmr spectra of carbanions, see Young, R.N. *Prog. Nucl. Magn. Reson. Spectrosc.* ***1979***, *12*, 261. For a review of dicarbanions, see Thompson, C.M.; Green, D.L.C. *Tetrahedron* ***1991***, *47*, 4223.

are undoubtedly covalent, but in bonds between carbon and the more active metals the electrons are closer to the carbon. Whether the position of the electrons in a given bond is close enough to the carbon to justify calling the bond ionic and the carbon moiety a carbanion depends on the metal, on the structure of the carbon moiety, and on the solvent and in some cases is a matter of speculation. In this section, we discuss carbanions with little reference to the metal. In the next section, we will deal with the structures of organometallic compounds.

By definition, every carbanion possesses an unshared pair of electrons and is therefore a base. When a carbanion accepts a proton, it is converted to its conjugate acid (see Chapter 8). The stability of the carbanion is directly related to the strength of the conjugate acid. The weaker the acid, the greater the base strength and the lower the stability of the carbanion.[100] By stability here we mean stability toward a proton donor; the lower the stability, the more willing the carbanion is to accept a proton from any available source, and hence to end its existence as a carbanion. Thus the determination of the order of stability of a series of carbanions is equivalent to a determination of the order of strengths of the conjugate acids, and one can obtain information about relative carbanion stability from a table of acid strengths like Table 8.1.

Unfortunately, it is not easy to measure acid strengths of very weak acids like the conjugate acids of simple unsubstituted carbanions. There is little doubt that these carbanions are very unstable in solution, and in contrast to the situation with carbocations, efforts to prepare solutions in which carbanions, such as ethyl or isopropyl, exist in a relatively free state have not yet been successful. Nor has it been possible to form these carbanions in the gas phase. Indeed, there is evidence that simple carbanions, such as ethyl and isopropyl, are unstable toward loss of an electron, which converts them to radicals.[101] Nevertheless, there have been several approaches to the problem. Applequist and O'Brien[102] studied the position of equilibrium for the reaction

$$\mathrm{RLi} + \mathrm{R'I} \rightleftharpoons \mathrm{RI} + \mathrm{R'Li}$$

in ether and ether–pentane. The reasoning in these experiments was that the R group that forms the more stable carbanion would be more likely to be bonded to lithium than to iodine. Carbanion stability was found to be in this order: vinyl > phenyl > cyclopropyl > ethyl > *n*-propyl > isobutyl > neopentyl > cyclobutyl > cyclopentyl. In a somewhat similar approach, Dessy and co-workers[103] treated a

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[100] For a monograph on hydrocarbon acidity, see Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*; Pergamon: Elmsford, NY, ***1978***. For a review, see Fischer, H.; Rewicki, D. *Prog. Org. Chem.* ***1968***, *7*, 116.

[101] See Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* ***1988***, *110*, 607; Schleyer, P.v.R.; Spitznagel, G.W.; Chandrasekhar, J. *Tetrahedron Lett.* ***1986***, *27*, 4411.

[102] Applequist, D.E.; O'Brien, D.F. *J. Am. Chem. Soc.* ***1963***, *85*, 743.

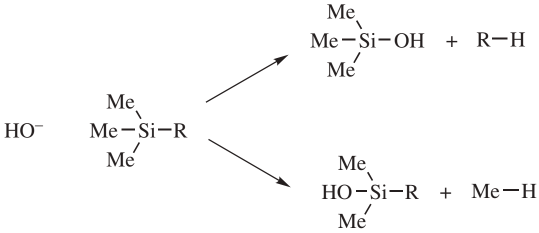
[103] Dessy, R.E.; Kitching, W.; Psarras, T.; Salinger, R.; Chen, A.; Chivers, T. *J. Am. Chem. Soc.* ***1966***, *88*, 460.

number of alkylmagnesium compounds with a number of alkylmercury compounds in tetrahydrofuran (THF), setting up the equilibrium

$$R_2Mg + R'_2Hg \rightleftharpoons R_2Hg + R'_2Mg$$

where the group of greater carbanion stability is linked to magnesium. The carbanion stability determined this way was in the order phenyl > vinyl > cyclopropyl > methyl > ethyl > isopropyl. The two stability orders are in fairly good agreement, and they show that stability of simple carbanions decreases in the order methyl > primary > secondary. It was not possible by the experiments of Dessy and co-workers to determine the position of *tert*-butyl, but there seems little doubt that it is still less stable. We can interpret this stability order solely as a consequence of the field effect since resonance is absent. The electron-donating alkyl groups of isopropyl result in a greater negative charge density at the central carbon atom (compared with methyl), thus decreasing its stability. The results of Applequist and O'Brien show that β branching also decreases carbanion stability. Cyclopropyl occupies an apparently anomalous position, but this is probably due to the large amount of *s* character in the carbanionic carbon (see p. 254).

A different approach to the problem of hydrocarbon acidity, and hence carbanion stability is that of Shatenshtein and co-workers, who treated hydrocarbons with deuterated potassium amide and measured the rates of hydrogen exchange.[104] The experiments did not measure *thermodynamic* acidity, since rates were measured, not positions of equilibria. They measured *kinetic* acidity, that is, which compounds gave up protons most rapidly (see p. 307 for the distinction between thermodynamic and kinetic control of product). Measurements of rates of hydrogen exchange enable one to compare acidities of a series of acids against a given base even where the positions of the equilibria cannot be measured because they lie too far to the side of the starting materials, that is, where the acids are too weak to be converted to their conjugate bases in measurable amounts. Although the correlation between thermodynamic and kinetic acidity is far from perfect,[105] the results of the rate measurements, too, indicated that the order of carbanion stability is methyl > primary > secondary > tertiary.[104]



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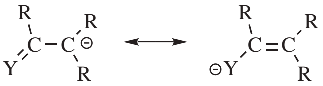
[104] For reviews, see Jones, J.R. *Surv. Prog. Chem.* ***1973***, *6*, 83; Shatenshtein, A.I.; Shapiro, I.O. *Russ. Chem. Rev.* ***1968***, *37*, 845.

[105] For example, see Bordwell, F.G.; Matthews, W.S.; Vanier, N.R. *J. Am. Chem. Soc.* ***1975***, *97*, 442.

However, experiments in the gas phase gave different results. In reactions of $^{-}$OH with alkyltrimethylsilanes, it is possible for either R or Me to cleave. Since the R or Me comes off as a carbanion or incipient carbanion, the product ratio RH/MeH can be used to establish the relative stabilities of various R groups. From these experiments a stability order of neopentyl > cyclopropyl > *tert*-butyl > *n*-propyl > methyl > isopropyl > ethyl was found.[106] On the other hand, in a different kind of gas-phase experiment, Graul and Squires were able to observe CH_3^- ions, but not the ethyl, isopropyl, or *tert*-butyl ions.[107]

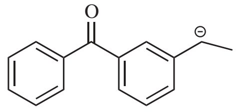
Many carbanions are far more stable than the simple kind mentioned above. The increased stability is due to certain structural features:

1. *Conjugation of the Unshared Pair with an Unsaturated Bond*:



In cases where a double or triple bond is located a to the carbanionic carbon, the ion is stabilized by resonance in which the unshared pair overlaps with the π electrons of the double bond. This factor is responsible for the stability of the allylic[108] and benzylic[109] types of carbanions:

$$R-CH=CH-\overset{\ominus}{C}H_2 \longleftrightarrow R-\overset{\ominus}{C}H-CH=CH_2$$



21

Diphenylmethyl and triphenylmethyl anions are still more stable and can be kept in solution indefinitely if water is rigidly excluded.[110]

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[106] DePuy, C.H.; Gronert, S.; Barlow, S.E.; Bierbaum, V.M.; Damrauer, R. *J. Am. Chem. Soc.* ***1989***, *111*, 1968. The same order (for *t*-Bu, Me, *i*Pr, and Et) was found in gas-phase cleavages of alkoxides (**12-41**): Tumas, W.; Foster, R.F.; Brauman, J.I. *J. Am. Chem. Soc.* ***1984***, *106*, 4053.

[107] Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* ***1988***, *110*, 607.

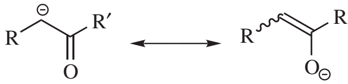
[108] For a review of allylic anions, see Richey, Jr., H.G., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 67–77.

[109] Although benzylic carbanions are more stable than the simple alkyl type, they have not proved stable enough for isolation so far. The benzyl carbanion has been formed and studied in submicrosecond times; Bockrath, B.; Dorfman, L.M. *J. Am. Chem. Soc.* ***1974***, *96*, 5708.

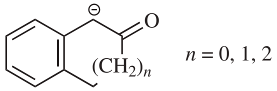
[110] For a review of spectrophotometric investigations of this type of carbanion, see Buncel, E.; Menon, B., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pts. A, B, and C, Elsevier, NY, ***1980***, ***1984***, ***1987***, pp. 97–124.

Condensed aromatic rings fused to a cyclopentadienyl anion are known to stabilize the carbanion.[111] X-ray crystallographic structures have been obtained for Ph_2CH^- and Ph_3C^- enclosed in crown ethers.[112] Carbanion **21** has a lifetime of several minutes (hours in a freezer at −20 °C) in dry THF.[113]

Where the carbanionic carbon is conjugated with a carbon–oxygen or carbon–nitrogen multiple bond (Y = O or N), the stability of the ion is greater than that of the triarylmethyl anions, since these electronegative atoms are better capable of bearing a negative charge than carbon. However, it is questionable whether ions of this type should be called carbanions at all, since in the case of enolate ions, for example, **23** contributes more to the hybrid than **22** although such ions react more often at the carbon than at the oxygen. In benzylic enolate anions such as **24**, the conformation of the enolate can be coplanar with the aromatic ring or bent out of plane if the strain is too great.[114] Enolate ions can also be kept in stable solutions. In the case of carbanions at a carbon α- to a nitrile, the "enolate" resonance form would be a ketene imine nitranion, but the existence of this species has been called into question.[115] A nitro group is particularly effective in stabilizing a negative charge on an adjacent carbon, and the anions of simple nitro alkanes can exist in water. Thus pK_a for nitromethane is 10.2. Dinitromethane is even more acidic (pK_a = 3.6).



22 **23**



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In contrast to the stability of cyclopropylmethyl cations (p. 241), the cyclopropyl group exerts only a weak stabilizing effect on an adjacent carbanionic carbon.[116]

By combining a very stable carbanion with a very stable carbocation, Okamoto and co-workers[117] were able to isolate the salt **25**, as well as several

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[111] Kinoshita, T.; Fujita, M.; Kaneko, H.; Takeuchi, K-i.; Yoshizawa, K.; Yamabe, T. *Bull. Chem. Soc. Jpn.* ***1998***, *71*, 1145.

[112] Olmstead, M.M.; Power, P.P. *J. Am. Chem. Soc.* ***1985***, *107*, 2174.

[113] Laferriere, M.; Sanrame, C.N.; Scaiano, J.C. *Org. Lett.* ***2004***, *6*, 873.

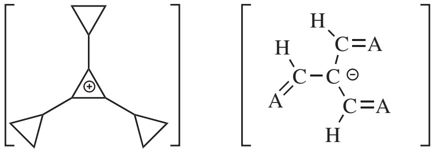
[114] Eldin, S.; Whalen, D.L.; Pollack, R.M. *J. Org. Chem.* ***1993***, *58*, 3490.

[115] Abbotto, A.; Bradamanti, S.; Pagani, G.A. *J. Org. Chem.* ***1993***, *58*, 449.

[116] Perkins, M.J.; Peynircioglu, N.B. *Tetrahedron* ***1985***, *41*, 225.

[117] Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Kinoshita, T.; Aonuma, S.; Nagai, M.; Miyabo, A. *J. Org. Chem.* ***1990***, *55*, 996. See also, Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Miyabo, A. *J. Chem. Soc. Chem. Commun.* ***1988***, 923.

similar salts, as stable solids. These are salts that consist entirely of carbon and hydrogen.



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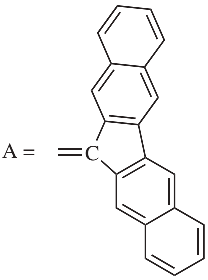
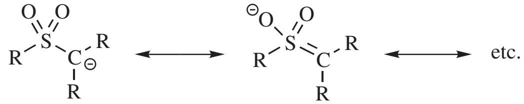


2. *Carbanions Increase in Stability with an Increase in the Amount of s Character at the Carbanionic Carbon.* Thus the order of stability is

$$RC{\equiv}C^- > R_2C{=}CH^- \sim Ar^- > R_3C{-}CH_2^-$$

Acetylene, where the carbon is *sp* hybridized with 50% *s* character, is much more acidic than ethylene[118] (sp^2, 33% *s*), which in turn is more acidic than ethane, with 25% *s* character. Increased *s* character means that the electrons are closer to the nucleus and hence of lower energy. As previously mentioned, cyclopropyl carbanions are more stable than methyl, owing to the larger amount of *s* character as a result of strain (see p. 218).

3. *Stabilization by Sulfur*[119] *or Phosphorus.* Attachment to the carbanionic carbon of a sulfur or phosphorus atom causes an increase in carbanion stability, although the reasons for this are in dispute. One theory is that there is overlap of the unshared pair with an empty *d* orbital[120] ($p\pi$–$d\pi$ bonding, see p. 52). For example, a carbanion containing the SO_2R group would be written



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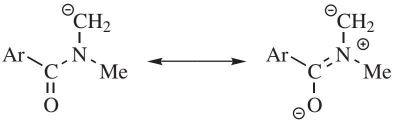
[118] For a review of vinylic anions, see Richey, Jr., H.G., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 49–56.

[119] For reviews of sulfur-containing carbanions, see Oae, S.; Uchida, Y., in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 583–664; Wolfe, S., in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***, pp. 133–190; Block, E. *Reactions of Organosulfur Compounds*; Academic Press, NY, ***1978***, pp. 42–56; Durst, T.; Viau, R. *Intra-Sci. Chem. Rep.* ***1973***, *7* (3), 63. For a review of selenium-stabilized carbanions, see Reich, H.J., in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 243–276.

[120] For support for this theory, see Wolfe, S.; LaJohn, L.A.; Bernardi, F.; Mangini, A.; Tonachini, G. *Tetrahedron Lett.* ***1983***, *24*, 3789; Wolfe, S.; Stolow, A.; LaJohn, L.A. *Tetrahedron Lett.* ***1983***, *24*, 4071.

However, there is evidence against *d*-orbital overlap; and the stabilizing effects have been attributed to other causes.[121] In the case of a PhS substituent, carbanion stabilization is thought to be due to a combination of the inductive and polarizability effects of the group, and *d*–*p*π resonance and negative hyperconjugation play a minor role, if any.[122] An α silicon atom also stabilizes carbanions.[123]

4. *Field Effects.* Most of the groups that stabilize carbanions by resonance effects (either the kind discussed in 1 above or the kind discussed in paragraph 3) have electron-withdrawing field effects and thereby stabilize the carbanion further by spreading the negative charge, although it is difficult to separate the field effect from the resonance effect. However, in a nitrogen ylid $R_3N^+{-}^-CR_2$ (see p. 54), where a positive nitrogen is adjacent to the negatively charged carbon, only the field effect operates. Ylids are more stable than the corresponding simple carbanions. Carbanions are stabilized by a field effect if there is any heteroatom (O, N, or S) connected to the carbanionic carbon, provided that the heteroatom bears a positive charge in at least one important canonical form,[124] for example,



5. *Certain Carbanions are Stable because they are Aromatic* (see the cyclopentadienyl anion p. 63, and other aromatic anions in Chapter 2).
6. *Stabilization by a Nonadjacent* π *Bond.*[125] In contrast to the situation with carbocations (see pp. 450–455), there have been fewer reports of carbanions stabilized by interaction with a nonadjacent π bond. One that may be mentioned is **17**, formed when optically active camphenilone (**15**) was treated with a strong base (potassium *tert*-butoxide).[126] That **17** was truly formed was

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[121] Bernardi, F.; Csizmadia, I.G.; Mangini, A.; Schlegel, H.B.; Whangbo, M.; Wolfe, S. *J. Am. Chem. Soc.* ***1975***, *97*, 2209; Lehn, J.M.; Wipff, G. *J. Am. Chem. Soc.* ***1976***, *98*, 7498; Borden, W.T.; Davidson, E.R.; Andersen, N.H.; Denniston, A.D.; Epiotis, N.D. *J. Am. Chem. Soc.* ***1978***, *100*, 1604; Bernardi, F.; Bottoni, A.; Venturini, A.; Mangini, A. *J. Am. Chem. Soc.* ***1986***, *108*, 8171.

[122] Bernasconi, C.F.; Kittredge, K.W. *J. Org. Chem.* ***1998***, *63*, 1944.

[123] Wetzel, D.M.; Brauman, J.I. *J. Am. Chem. Soc.* ***1988***, *110*, 8333.

[124] For a review of such carbanions, see Beak, P.; Reitz, D.B. *Chem. Rev.* ***1978***, *78*, 275. See also, Rondan, N.G.; Houk, K.N.; Beak, P.; Zajdel, W.J.; Chandrasekhar, J.; Schleyer, P.v.R. *J. Org. Chem.* ***1981***, *46*, 4108.

[125] For reviews, see Werstiuk, N.H. *Tetrahedron* ***1983***, *39*, 205; Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 410–437.

[126] Nickon, A.; Lambert, J.L. *J. Am. Chem. Soc.* ***1966***, *88*, 1905. Also see, Brown, J.M.; Occolowitz, J.L. *Chem. Commun.* ***1965***, 376; Grutzner, J.B.; Winstein, S. *J. Am. Chem. Soc.* ***1968***, *90*, 6562; Staley, S.W.; Reichard, D.W. *J. Am. Chem. Soc.* ***1969***, *91*, 3998; Miller, B. *J. Am. Chem. Soc.* ***1969***, *91*, 751; Werstiuk, N.H.; Yeroushalmi, S.; Timmins, G. *Can. J. Chem.* ***1983***, *61*, 1945; Lee, R.E.; Squires, R.R. *J. Am. Chem. Soc.* ***1986***, *108*, 5078; Peiris, S.; Ragauskas, A.J.; Stothers, J.B. *Can. J. Chem.* ***1987***, *65*, 789; Shiner, C.S.; Berks, A.H.; Fisher, A.M. *J. Am. Chem. Soc.* ***1988***, *110*, 957.

> shown by the following facts: (*1*) A proton was abstracted: ordinary
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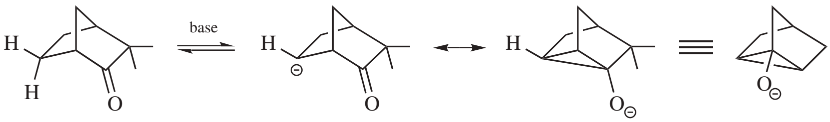
> 
>
>
> **26** **27** **28**
>
> CH_2 groups are not acidic enough for this base; (*2*) recovered **26** was racemized: **28** is symmetrical and can be attacked equally well from either side; (*3*) when the experiment was performed in deuterated solvent, the rate of deuterium uptake was equal to the rate of racemization; and (*4*) recovered **26** contained up to three atoms of deuterium per molecule, although if **27** were the only ion, no more than two could be taken up. Ions of this type, in which a negatively charged carbon is stabilized by a carbonyl group two carbons away, are called *homoenolate ions*.

Overall, functional groups in the a position stabilize carbanions in the following order: $NO_2 > RCO > COOR > SO_2 > CN \sim CONH_2 > Hal > H > R$.

It is unlikely that free carbanions exist in solution. Like carbocations, they usually exist as either ion pairs or they are solvated.[127] Among experiments that demonstrated this was the treatment of $PhCOCHMe^- M^+$ with ethyl iodide, where M^+ was Li^+, Na^+, or K^+. The half-lives of the reaction were[128] for Li, 31×10^{-6}; Na, 0.39×10^{-6}; and K, 0.0045×10^{-6}, demonstrating that the species involved were not identical. Similar results[129] were obtained with Li, Na, and Cs triphenylmethides $Ph_3C^- M^+$.[130] Where ion pairs are unimportant, carbanions are solvated. Cram[99] has demonstrated solvation of carbanions in many solvents. There may be a difference in the structure of a carbanion depending on whether it is free (e.g., in the gas phase) or in solution. The negative charge may be more

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[127] For reviews of carbanion pairs, see Hogen-Esch, T.E. *Adv. Phys. Org. Chem.* ***1977***, *15*, 153; Jackman, L.M.; Lange, B.C. *Tetrahedron* ***1977***, *33*, 2737. See also, Laube, T. *Acc. Chem. Res.* ***1995***, *28*, 399.

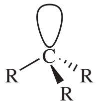
[128] Zook, H.D.; Gumby, W.L. *J. Am. Chem. Soc.* ***1960***, *82*, 1386.

[129] Solov'yanov, A.A.; Karpyuk, A.D.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1981***, *17*, 381. See also, Solov'yanov, A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1983***, *19*, 1964.

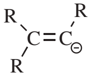
[130] For other evidence for the existence of carbanionic pairs, see Hogen-Esch, T.E.; Smid, J. *J. Am. Chem. Soc.* ***1966***, *88*, 307, 318; ***1969***, *91*, 4580; Abatjoglou, A.G.; Eliel, E.L.; Kuyper, L.F. *J. Am. Chem. Soc.* ***1977***, *99*, 8262; Solov'yanov, A.A.; Karpyuk, A.D.; Beletskaya, I.P.; Reutov, V.M. *Doklad. Chem.* ***1977***, *237*, 668; DePalma, V.M.; Arnett, E.M. *J. Am. Chem. Soc.* ***1978***, *100*, 3514; Buncel, E.; Menon, B. *J. Org. Chem.* ***1979***, *44*, 317; O'Brien, D.H.; Russell, C.R.; Hart, A.J. *J. Am. Chem. Soc.* ***1979***, *101*, 633; Streitwieser, Jr., A.; Shen, C.C.C. *Tetrahedron Lett.* ***1979***, 327; Streitwieser, Jr., A. *Acc. Chem. Res.* ***1984***, *17*, 353.

localized in solution in order to maximize the electrostatic attraction to the counterion.[131]

The structure of simple unsubstituted carbanions is not known with certainty since they have not been isolated, but it seems likely that the central carbon is *sp*^{3} hybridized, with the unshared pair occupying one apex of the tetrahedron. Carbanions would thus have pyramidal structures similar to those of amines.



The methyl anion CH_3^- has been observed in the gas phase and reported to have a pyramidal structure.[132] If this is a general structure for carbanions, then any carbanion in which the three R groups are different should be chiral and reactions in which it is an intermediate should give retention of configuration. Attempts have been made to demonstrate this, but without success.[133] A possible explanation is that pyramidal inversion takes place here, as in amines, so that the unshared pair and the central carbon rapidly oscillate from one side of the plane to the other. There is, however, other evidence for the *sp*^{3} nature of the central carbon and for its tetrahedral structure. Carbons at bridgeheads, although extremely reluctant to undergo reactions in which they must be converted to carbocations, undergo with ease reactions in which they must be carbanions and stable bridgehead carbanions are known.[134] Also, reactions at vinylic carbons proceed with retention,[135] indicating that the intermediate **29** has *sp*^{2} hybridization and not the *sp* hybridization that would be expected in the analogous carbocation. A cyclopropyl anion can also hold its configuration.[136]



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[131] See Schade, C.; Schleyer, P.v.R.; Geissler, M.; Weiss, E. *Angew. Chem. Int. Ed.* ***1986***, *21*, 902.

[132] Ellison, G.B.; Engelking, P.C.; Lineberger, W.C. *J. Am. Chem. Soc.* ***1978***, *100*, 2556.

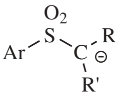
[133] Retention of configuration has never been observed with simple carbanions. Cram has obtained retention with carbanions stabilized by resonance. However, these carbanions are known to be planar or nearly planar, and retention was caused by asymmetric solvation of the planar carbanions (see p. $$$).

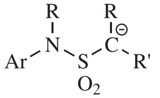
[134] For other evidence that carbanions are pyramidal, see Streitwieser, Jr., A.; Young, W.R. *J. Am. Chem. Soc.* ***1969***, *91*, 529; Peoples, P.R.; Grutzner, J.B. *J. Am. Chem. Soc.* ***1980***, *102*, 4709.

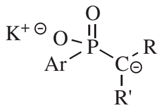
[135] Curtin, D.Y.; Harris, E.E. *J. Am. Chem. Soc.* ***1951***, *73*, 2716, 4519; Braude, E.A.; Coles, J.A. *J. Chem. Soc.* ***1951***, 2078; Nesmeyanov, A.N.; Borisov, A.E. *Tetrahedron* ***1957***, *1*, 158. Also see, Miller, S.I.; Lee, W.G. *J. Am. Chem. Soc.* ***1959***, *81*, 6313; Hunter, D.H.; Cram, D.J. *J. Am. Chem. Soc.* ***1964***, *86*, 5478; Walborsky, H.M.; Turner, L.M. *J. Am. Chem. Soc.* ***1972***, *94*, 2273; Arnett, J.F.; Walborsky, H.M. *J. Org. Chem.* ***1972***, *37*, 3678; Feit, B.; Melamed, U.; Speer, H.; Schmidt, R.R. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 775; Chou, P.K.; Kass, S.R. *J. Am. Chem. Soc.* ***1991***, *113*, 4357.

[136] Walborsky, H.M.; Motes, J.M. *J. Am. Chem. Soc.* ***1970***, *92*, 2445; Motes, J.M.; Walborsky, H.M. *J. Am. Chem. Soc.* ***1970***, *92*, 3697; Boche, G.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* ***1988***, *110*, 6925. For a monograph on cyclopropyl anions, cations, and radicals, see Boche, G.; Walborsky, H.M. *Cyclopropane Derived Reactive Intermediates*, Wiley, NY, ***1990***. For a review, see Boche, G.; Walborsky, H.M., in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, ***1987***, pp. 701–808 (the monograph includes and updates the review).

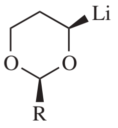
Carbanions in which the negative charge is stabilized by resonance involving overlap of the unshared-pair orbital with the π electrons of a multiple bond are essentially planar, as would be expected by the necessity for planarity in resonance, although unsymmetrical solvation or ion-pairing effects may cause the structure to deviate somewhat from true planarity.[137] Cram and co-workers showed that where chiral carbanions possessing this type of resonance are generated, retention, inversion, or racemization can result, depending on the solvent (see p. 759). This result is explained by unsymmetrical solvation of planar or near-planar carbanions. However, some carbanions that are stabilized by adjacent sulfur or phosphorus, for example,







are inherently chiral, since retention of configuration is observed where they are generated, even in solvents that cause racemization or inversion with other carbanions.[138] It is known that in THF, PhCH(Li)Me behaves as a prochiral entity,[139] and **30** has been prepared as an optically pure α-alkoxylithium reagent.[140] Cyclohexyllithium **31** shows some configurationally stability, and it is known that isomerization is slowed by an increase in the strength of lithium coordination and by an increase in solvent polarity.[141] It is known that a vinyl anion is configurationally stable whereas a vinyl radical is not. This is due to the instability of the radical anion that must be an intermediate for conversion of one isomer of vinyllithium to the other.[142] The configuration about the carbanionic carbon, at least for some of the α-sulfonyl carbanions, seems to be planar,[143] and the inherent chirality is caused by lack of rotation about the C—S bond.[144]



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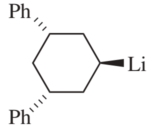

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[137] See the discussion, in Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 85–105.

[138] Cram, D.J.; Wingrove, A.S. *J. Am. Chem. Soc.* ***1962***, *84*, 1496; Goering, H.L.; Towns, D.L.; Dittmer, B. *J. Org. Chem.* ***1962***, *27*, 736; Corey, E.J.; Lowry, T.H. *Tetrahedron Lett.* ***1965***, 803; Bordwell, F.G.; Phillips, D.D.; Williams, Jr., J.M. *J. Am. Chem. Soc.* ***1968***, *90*, 426; Annunziata, R.; Cinquini, M.; Colonna, S.; Cozzi, F. *J. Chem. Soc. Chem. Commun.* ***1981***, 1005; Chassaing, G.; Marquet, A.; Corset, J.; Froment, F. *J. Organomet. Chem.* ***1982***, *232*, 293. For a discussion, see Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 105–113. Also see Hirsch, R.; Hoffmann, R.W. *Chem. Ber.* ***1992***, *125*, 975.

[139] Hoffmann, R.W.; Rühl, T.; Chemla, F.; Zahneisen, T. *Liebigs Ann. Chem.* ***1992***, 719.

[140] Rychnovsky, S.D.; Plzak, K.; Pickering, D. *Tetrahedron Lett.* ***1994***, *35*, 6799.

[141] Reich, H.J.; Medina, M.A.; Bowe, M.D. *J. Am. Chem. Soc.* ***1992***, *114*, 11003.

[142] Jenkins, P.R.; Symons, M.C.R.; Booth, S.E.; Swain, C.J. *Tetrahedron Lett.* ***1992***, *33*, 3543.

[143] Boche, G.; Marsch, M.; Harms, K.; Sheldrick, G.M. *Angew. Chem. Int. Ed.* ***1985***, *24*, 573; Gais, H.; Müller, J.; Vollhardt, J.; Lindner, H.J. *J. Am. Chem. Soc.* ***1991***, *113*, 4002. For a contrary view, see Trost, B.M.; Schmuff, N.R. *J. Am. Chem. Soc.* ***1985***, *107*, 396.

[144] Grossert, J.S.; Hoyle, J.; Cameron, T.S.; Roe, S.P.; Vincent, B.R. *Can. J. Chem.* ***1987***, *65*, 1407.

The Structure of Organometallic Compounds[145]

Whether a carbon–metal bond is ionic or polar-covalent is determined chiefly by the electronegativity of the metal and the structure of the organic part of the molecule. Ionic bonds become more likely as the negative charge on the metal-bearing carbon is decreased by resonance or field effects. Thus the sodium salt of acetoacetic ester has a more ionic carbon–sodium bond than methylsodium.

Most organometallic bonds are polar-covalent. Only the alkali metals have electronegativities low enough to form ionic bonds with carbon, and even here the behavior of lithium alkyls shows considerable covalent character. The simple alkyls and aryls of sodium, potassium, rubidium, and cesium[146] are nonvolatile solids[147] insoluble in benzene or other organic solvents, while alkyllithium reagents are soluble, although they too are generally nonvolatile solids. Alkyllithium reagents do not exist as monomeric species in hydrocarbon solvents or ether.[148] In benzene and cyclohexane, freezing-point-depression studies have shown that alkyllithium reagents are normally hexameric unless steric interactions favor tetrameric aggregates.[149] The NMR studies, especially measurements of ^{13}C–^{6}Li coupling, have also shown aggregation in hydrocarbon solvents.[150] Boiling-point-elevation studies have been performed in ether solutions, where alkyllithium reagents exist in two- to fivefold aggregates.[151] Even in the gas phase[152] and in

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[145] For a monograph, see Elschenbroich, C.; Salzer, A. *Organometallics*, VCH, NY, ***1989***. For reviews, see Oliver, J.P., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 789–826; Coates, G.E.; Green, M.L.H.; Wade, K. *Organometallic Compounds*, 3rd ed., Vol. 1; Methuen: London, ***1967***. For a review of the structures of organodialkali compounds, see Grovenstein, Jr., E., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. C, Elsevier, NY, ***1987***, pp. 175–221.

[146] For a review of X-ray crystallographic studies of organic compounds of the alkali metals, see Schade, C.; Schleyer, P.v.R. *Adv. Organomet. Chem.* ***1987***, *27*, 169.

[147] X-ray crystallography of potassium, rubidium, and cesium methyls shows completely ionic crystal lattices: Weiss, E.; Sauermann, G. *Chem. Ber.* ***1970***, *103*, 265; Weiss, E.; Köster, H. *Chem. Ber.* ***1977***, *110*, 717.

[148] For reviews of the structure of alkyllithium compounds, see Setzer, W.N.; Schleyer, P.v.R. *Adv. Organomet. Chem.* ***1985***, *24*, 353; Schleyer, P.v.R. *Pure Appl. Chem.* ***1984***, *56*, 151; Brown, T.L. *Pure Appl. Chem.* ***1970***, *23*, 447, *Adv. Organomet. Chem.* ***1965***, *3*, 365; Kovrizhnykh, E.A.; Shatenshtein, A.I. *Russ. Chem. Rev.* ***1969***, *38*, 840. For reviews of the structures of lithium enolates and related compounds, see Boche, G. *Angew. Chem. Int. Ed.* ***1989***, *28*, 277; Seebach, D. *Angew. Chem. Int. Ed.* ***1988***, *27*, 1624. For a review of the use of nmr to study these structures, see Günther, H.; Moskau, D.; Bast, P.; Schmalz, D. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1212. For monographs on organolithium compounds, see Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, *The Chemistry of Organolithium Compounds*, Pergamon, Elmsford, NY, ***1974***.

[149] Lewis, H.L.; Brown, T.L. *J. Am. Chem. Soc.* ***1970***, *92*, 4664; Brown, T.L.; Rogers, M.T. *J. Am. Chem. Soc.* ***1957***, *79*, 1859; Weiner, M.A.; Vogel, G.; West, R. *Inorg. Chem.* ***1962***, *1*, 654.

[150] Fraenkel, G.; Henrichs, M.; Hewitt, M.; Su, B.M. *J. Am. Chem. Soc.* ***1984***, *106*, 255; Thomas, R.D.; Jensen, R.M.; Young, T.C. *Organometallics* ***1987***, *6*, 565. See also, Kaufman, M.J.; Gronert, S.; Streitwieser, Jr., A. *J. Am. Chem. Soc.* ***1988***, *110*, 2829.

[151] Wittig, G.; Meyer, F.J.; Lange, G. *Liebigs Ann. Chem.* ***1951***, *571*, 167. See also, McGarrity, J.F.; Ogle, C.A. *J. Am. Chem. Soc.* ***1985***, *107*, 1805; Bates, T.F.; Clarke, M.T.; Thomas, R.D. *J. Am. Chem. Soc.* ***1988***, *110*, 5109.

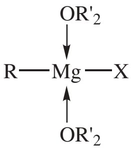
[152] Brown, T.L.; Dickerhoof, D.W.; Bafus, D.A. *J. Am. Chem. Soc.* ***1962***, *84*, 1371; Chinn, Jr., J.W.; Lagow, R.L. *Organometallics* ***1984***, *3*, 75; Plavšić, D.; Srzić, D.; Klasinc, L. *J. Phys. Chem.* ***1986***, *90*, 2075.

the solid state,[153] alkyllithium reagents exist as aggregates. X-ray crystallography has shown that methyllithium has the same tetrahedral structure in the solid state as in ether solution.[153] However, *tert*-butyllithium is monomeric in THF, although dimeric in ether and tetrameric in hydrocarbon solvents.[154] Neopentyllithium exists as a mixture of monomers and dimers in THF.[155]

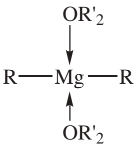
The C—Mg bond in Grignard reagents is covalent and not ionic. The actual structure of Grignard reagents in solution has been a matter of much controversy over the years.[156] In 1929, it was discovered[157] that the addition of dioxane to an ethereal Grignard solution precipitates all the magnesium halide and leaves a solution of R_2Mg in ether; that is, there can be no RMgX in the solution since there is no halide. The following equilibrium, now called the *Schlenk equilibrium*, was proposed as the composition of the Grignard solution:

$$2\,RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons \underset{\mathbf{32}}{R_2Mg{\bullet}MgX_2}$$

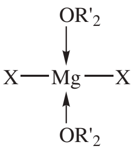
in which **32** is a complex of some type. Much work has demonstrated that the Schlenk equilibrium actually exists and that the position of the equilibrium is dependent on the identity of R, X, the solvent, the concentration, and the temperature.[158] It has been known for many years that the magnesium in a Grignard solution, no matter whether it is RMgX, R_2Mg, or MgX_2, can coordinate with two molecules of ether in addition to the two covalent bonds:



$$R{-}\overset{OR'_2\downarrow}{\underset{\uparrow OR'_2}{Mg}}{-}X$$



$$R{-}\overset{OR'_2\downarrow}{\underset{\uparrow OR'_2}{Mg}}{-}R$$



$$X{-}\overset{OR'_2\downarrow}{\underset{\uparrow OR'_2}{Mg}}{-}X$$

Rundle and co-workers[159] performed X-ray diffraction studies on solid phenylmagnesium bromide dietherate and on ethylmagnesium bromide dietherate, which they obtained by cooling ordinary ethereal Grignard solutions until the

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[153] Dietrich, H. *Acta Crystallogr.* ***1963***, *16*, 681; Weiss, E.; Lucken, E.A.C. *J. Organomet. Chem.* ***1964***, *2*, 197; Weiss, E.; Sauermann, G.; Thirase, G. *Chem. Ber.* ***1983***, *116*, 74.

[154] Bauer, W.; Winchester, W.R.; Schleyer, P.v.R. *Organometallics* ***1987***, *6*, 2371.

[155] Fraenkel, G.; Chow, A.; Winchester, W.R. *J. Am. Chem. Soc.* ***1990***, *112*, 6190.

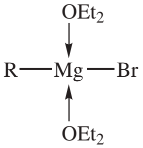
[156] For reviews, see Ashby, E.C. *Bull. Soc. Chim. Fr.* ***1972***, 2133; *Q. Rev. Chem. Soc.* ***1967***, *21*, 259; Wakefield, B.J. *Organomet. Chem. Rev.* ***1966***, *1*, 131; Bell, N.A. *Educ. Chem.* ***1973***, 143.

[157] Schlenk, W.; Schlenk Jr., W. *Ber.* ***1929***, *62B*, 920.

[158] See Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* ***1971***, *93*, 1206; Salinger, R.M.; Mosher, H.S. *J. Am. Chem. Soc.* ***1964***, *86*, 1782; Kirrmann, A.; Hamelin, R.; Hayes, S. *Bull. Soc. Chim. Fr.* ***1963***, 1395.

[159] Guggenberger, L.J.; Rundle, R.E. *J. Am. Chem. Soc.* ***1968***, *90*, 5375; Stucky, G.; Rundle, R.E. *J. Am. Chem. Soc.* ***1964***, *86*, 4825.

solids crystallized. They found that the structures were monomeric:



$$\mathrm{R-\underset{\underset{OEt_2}{\uparrow}}{\overset{\overset{OEt_2}{\downarrow}}{Mg}}-Br}$$

R = ethyl, phenyl

These solids still contained ether. When ordinary ethereal Grignard solutions[160] prepared from bromomethane, chloromethane, bromoethane, and chloroethane were evaporated at ~100°C under vacuum so that the solid remaining contained no ether, X-ray diffraction showed *no* RMgX, but a mixture of R_2Mg and MgX_2.[161] These results indicate that in the presence of ether $RMgX{\bullet}2Et_2O$ is the preferred structure, while the loss of ether drives the Schlenk equilibrium to $R_2Mg + MgX_2$. However, conclusions drawn from a study of the solid materials do not necessarily apply to the structures in solution.

Boiling-point-elevation and freezing-point-depression measurements have demonstrated that in THF at all concentrations and in ether at low concentrations (up to ~0.1 *M*) Grignard reagents prepared from alkyl bromides and iodides are monomeric, that is, there are few or no molecules with two magnesium atoms.[162] Thus, part of the Schlenk equilibrium is operating but not the other

$$2\,\mathrm{RMgX} \rightleftharpoons \mathrm{R_2Mg} + \mathrm{MgX_2}$$

part; that is, **32** is not present in measurable amounts. This was substantiated by ^{25}Mg NMR spectra of the ethyl Grignard reagent in THF, which showed the presence of three peaks, corresponding to EtMgBr, Et_2Mg, and $MgBr_2$.[163] That the equilibrium between RMgX and R_2Mg lies far to the left for "ethylmagnesium bromide" in ether was shown by Smith and Becker, who mixed 0.1 *M* ethereal solutions of Et_2Mg and $MgBr_2$ and found that a reaction occurred with a heat evolution of 3.6 kcal mol^{-1} (15 kJ mol^{-1}) of Et_2Mg, and that the product was *monomeric* (by boiling-point-elevation measurements).[164] When either solution was added little by little to the other, there was a linear output of heat until almost a 1:1 molar ratio was reached. Addition of an excess of either reagent gave no further heat output. These results show that at least under some conditions the Grignard reagent is largely RMgX (coordinated with solvent) but that the equilibrium can be driven to R_2Mg by evaporation of all the ether or by addition of dioxane.

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[160] The constitution of alkylmagnesium chloride reagents in THF has been determined. See Sakamoto, S.; Imamoto, T.; Yamaguchi, K. *Org. Lett.* ***2001***, *3*, 1793.

[161] Weiss, E. *Chem. Ber.* ***1965***, *98*, 2805.

[162] Ashby, E.C.; Smith, M.B. *J. Am. Chem. Soc.* ***1964***, *86*, 4363; Vreugdenhil, A.D.; Blomberg, C. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 453, 461.

[163] Benn, R.; Lehmkuhl, H.; Mehler, K.; Rufińska, A. *Angew. Chem. Int. Ed.* ***1984***, *23*, 534.

[164] Smith, M.B.; Becker, W.E. *Tetrahedron* ***1966***, *22*, 3027.

For some aryl Grignard reagents it has proved possible to distinguish separate NMR chemical shifts for ArMgX and Ar_2Mg.[165] From the area under the peaks it is possible to calculate the concentrations of the two species, and from them, equilibrium constants for the Schlenk equilibrium. These data show[165] that the position of the equilibrium depends very markedly on the aryl group and the solvent but that conventional aryl Grignard reagents in ether are largely ArMgX, while in THF the predominance of ArMgX is less, and with some aryl groups there is actually more Ar_2Mg present. Separate nmr chemical shifts have also been found for alkyl RMgBr and R_2Mg in HMPA[166] and in ether at low temperatures.[167] When Grignard reagents from alkyl bromides or chlorides are prepared in triethylamine the predominant species is RMgX.[168] Thus the most important factor determining the position of the Schlenk equilibrium is the solvent. For primary alkyl groups the equilibrium constant for the reaction as written above is lowest in Et_3N, higher in ether, and still higher in THF.[169]

However, Grignard reagents prepared from alkyl bromides or iodides in ether at higher concentrations (0.5–1 *M*) contain dimers, trimers, and higher polymers, and those prepared from alkyl chlorides in ether at all concentrations are dimeric,[170] so that **32** is in solution, probably in equilibrium with RMgX and R_2Mg; that is, the complete Schlenk equilibrium seems to be present.

The Grignard reagent prepared from 1-chloro-3,3-dimethylpentane in ether undergoes rapid inversion of configuration at the magnesium-containing carbon (demonstrated by NMR; this compound is not chiral).[171] The mechanism of this inversion is not completely known. Therefore, in almost all cases, it is not possible to retain the configuration of a stereogenic carbon while forming a Grignard reagent.

Organolithium reagents (RLi) are tremendously important reagents in organic chemistry. In recent years, a great deal has been learned about their structure[172] in both the solid state and in solution. X-ray analysis of complexes of *n*-butyllithium with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), THF, and 1,2-dimethoxyethane (DME) shows them to be dimers and tetramers [e.g., $(BuLi{\bullet}DME)_4$].[173] X-ray analysis of isopropyllithium shows it to be a hexamer,

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[165] Evans, D.F.; Fazakerley, V. *Chem. Commun.* ***1968***, 974.

[166] Ducom, J. *Bull. Chem. Soc. Fr.* ***1971***, 3518, 3523, 3529.

[167] Ashby, E.C.; Parris, G.; Walker, F. *Chem. Commun.* ***1969***, 1464; Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* ***1971***, *93*, 1206.

[168] Ashby, E.C.; Walker, F. *J. Org. Chem.* ***1968***, *33*, 3821.

[169] Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* ***1971***, *93*, 1206.

[170] Ashby, E.C.; Smith, M.B. *J. Am. Chem. Soc.* ***1964***, *86*, 4363.

[171] Whitesides, G.M.; Witanowski, M.; Roberts, J.D. *J. Am. Chem. Soc.* ***1965***, *87*, 2854; Whitesides, G.M.; Roberts, J.D. *J. Am. Chem. Soc.* ***1965***, *87*, 4878. Also see, Witanowski, M.; Roberts, J.D. *J. Am. Chem. Soc.* ***1966***, *88*, 737; Fraenkel, G.; Cottrell, C.E.; Dix, D.T. *J. Am. Chem. Soc.* ***1971***, *93*, 1704; Pechhold, E.; Adams, D.G.; Fraenkel, G. *J. Org. Chem.* ***1971***, *36*, 1368; Maercker, A.; Geuss, R. *Angew. Chem. Int. Ed.* ***1971***, *10*, 270.

[172] For a computational study of acidities, electron affinities, and bond dissociation energies of selected organolithium reagents, see Pratt, L.M.; Kass, S.R. *J. Org. Chem.* ***2004***, *69*, 2123.

[173] Nichols, M.A.; Williard, P.G. *J. Am. Chem. Soc.* ***1993***, *115*, 1568.

(iPrLi)$_6$],[174] and unsolvated lithium aryls are tetramers.[175] α-Ethoxyvinyllithium [$CH_2{=}C(OEt)Li$] shows a polymeric structure with tetrameric subunits.[176] Aminomethyl aryllithium reagents have been shown to be chelated and dimeric in solvents such as THF.[177]

The dimeric, tetrameric, and hexameric structures of organolithium reagents[178] in the solid state is often retained in solution, but this is dependent on the solvent and complexing additives, if any. A tetrahedral organolithium compound is known,[179] and the X-ray of an α,α-dilithio hydrocarbon has been reported.[180] Phenyllithium is a mixture of tetramers and dimers in diethyl ether, but stoichiometric addition of THF, dimethoxyethane, or TMEDA leads to the dimer.[181] The solution structures of mixed aggregates of butyllithium and amino-alkaloids has been determined,[182] and also the solution structure of sulfur-stabilized allyllithium compounds.[183] Vinyllithium is an 8:1 mixture of tetramer:dimer in THF at −90°C, but addition of TMEDA changes the ratio of tetramer:dimer to 1:13 at −80°C.[184] Internally solvated allylic lithium compounds have been studied, showing the coordinated lithium to be closer to one of the terminal allyl carbons.[185] A relative scale of organolithium stability has been established,[186] and the issue of configurational stability of enantio-enriched organolithium reagents has been examined.[187]

Enolate anions are an important class of carbanions that appear in a variety of important reactions, including alkylation α- to a carbonyl group and the aldol (reaction **16-34**) and Claisen condensation (reaction **16-85**) reactions. Metal enolate anions of aldehydes, ketones, esters, and other acid derivatives exist as aggregates in ether solvents,[188] and there is evidence that the lithium enolate of

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[174] Siemeling, U.; Redecker, T.; Neumann, B.; Stammler, H.-G. *J. Am. Chem. Soc.* ***1994***, *116*, 5507.

[175] Ruhlandt-Senge, K.; Ellison, J.J.; Wehmschulte, R.J.; Pauer, F.; Power, P.P. *J. Am. Chem. Soc.* ***1993***, *115*, 11353. For the X-ray structure of 1-methoxy-8-naphthyllithium see Betz, J.; Hampel, F.; Bauer, W. *Org. Lett.* ***2000***, *2*, 3805.

[176] Sorger, K.; Bauer, W.; Schleyer, P.v.R.; Stalke, D. *Angew. Chem. Int. Ed.* ***1995***, *34*, 1594.

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[178] For an *ab initio* correlation of structure with NMR, see Parisel, O.; Fressigne, C.; Maddaluno, J.; Giessner-Prettre, C. *J. Org. Chem.* ***2003***, *68*, 1290.

[179] Sekiguchi, A.; Tanaka, M. *J. Am. Chem. Soc.* ***2003***, *125*, 12684.

[180] Linti, G.; Rodig, A.; Pritzkow, H. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4503.

[181] Reich, H.J.; Green, D.P.; Medina, M.A.; Goldenberg, W.S.; Gudmundsson, B.Ö.; Dykstra, R.R.; Phillips. N.H. *J. Am. Chem. Soc.* ***1998***, *120*, 7201.

[182] Sun, X.; Winemiller, M.D.; Xiang, B.; Collum, D.B. *J. Am. Chem. Soc.* ***2001***, *123*, 8039. See also, Rutherford, J.L.; Hoffmann, D.; Collum, D.B. *J. Am. Chem. Soc.* ***2002***, *124*, 264.

[183] Piffl, M.; Weston, J.; Günther, W.; Anders, E. *J. Org. Chem.* ***2000***, *65*, 5942.

[184] Bauer, W.; Griesinger, C. *J. Am. Chem. Soc.* ***1993***, *115*, 10871.

[185] Fraenkel, G.; Chow, A.; Fleischer, R.; Liu, H. *J. Am. Chem. Soc.* ***2004***, *126*, 3983.

[186] Graña, P.; Paleo, M.R.; Sardina, F.J. *J. Am. Chem. Soc.* ***2002***, *124*, 12511.

[187] Basu, A.; Thayumanavan, S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 717. See also, Fraenkel, G.; Duncan, J.H.; Martin, K.; Wang, J. *J. Am. Chem. Soc.* ***1999***, *121*, 10538.

[188] Stork, G.; Hudrlik, P.F. *J. Am. Chem. Soc.* ***1968***, *90*, 4464; Bernstein, M.P.; Collum, D.B. *J. Am. Chem. Soc.* ***1993***, *115*, 789; Bernstein, M.P.; Romesberg, F.E.; Fuller, D.J.; Harrison, A.T.; Collum, D.B.; Liu, Q.Y.; Williard, P.G. *J. Am. Chem. Soc.* ***1992***, *114*, 5100; Collum, D.B. *Acc. Chem. Res.* ***1992***, *25*, 448.

isobutyrophenone is a tetramer in THF,[189] but a dimer in DME.[190] X-ray crystallography of ketone enolate anions have shown that they can exist as tetramers and hexamers.[191] There is also evidence that the aggregate structure is preserved in solution and is probably the actual reactive species. Lithium enolates derived from esters are as dimers in the solid state[192] that contain four tetrahydrofuran molecules. It has also been established that the reactivity of enolate anions in alkylation and condensation reactions is influenced by the aggregate state of the enolate. It is also true that the relative proportions of (*E*) and (*Z*) enolate anions are influenced by the extent of solvation and the aggregation state. Addition of LiBr to a lithium enolate anion in THF suppresses the concentration of monomeric enolate.[193] *Ab initio* studies confirm the aggregate state of acetaldehyde.[194] It is also known that α-Li benzonitrile [PhCH(Li)CN] exists as a dimer in ether and with TMEDA.[195] Mixed aggregates of *tert*-butyllithium and lithium *tert*-butoxide are known to be hexameric.[196]

It might be mentioned that matters are much simpler for organometallic compounds with less-polar bonds. Thus Et_2Hg and EtHgCl are both definite compounds, the former a liquid and the latter a solid. Organocalcium reagents are also know, and they are formed from alkyl halides via a single electron-transfer (SET) mechanism with free-radical intermediates.[197]

The Generation and Fate of Carbanions

The two principal ways in which carbanions are generated are parallel with the ways of generating carbocations.

1. A group attached to a carbon leaves without its electron pair:

$$\mathrm{R{-}H} \longrightarrow \mathrm{R}^{\ominus} + \mathrm{H}^{\oplus}$$

The leaving group is most often a proton. This is a simple acid–base reaction, and a base is required to remove the proton.[198] However, other

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[189] Jackman, L.M.; Szeverenyi, N.M. *J. Am. Chem. Soc.* ***1977***, *99*, 4954; Jackman, L.M.; Lange, B.C. *J. Am. Chem. Soc.* ***1981***, *103*, 4494.

[190] Jackman, L.M.; Lange, B.C. *Tetrahedron* ***1977***, *33*, 2737.

[191] Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* ***1986***, *108*, 462; Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* ***1985***, *107*, 3345; Amstutz, R.; Schweizer, W.B.; Seebach, D.; Dunitz, J.D. *Helv. Chim. Acta* ***1981***, *64*, 2617; Seebach, D.; Amstutz, D.; Dunitz, J.D. *Helv. Chim. Acta* ***1981***, *64*, 2622.

[192] Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W.B.; Dunitz, J.D. *J. Am. Chem. Soc.* ***1985***, *107*, 5403.

[193] Abu-Hasanayn, F.; Streitwieser, A. *J. Am. Chem. Soc.* ***1996***, *118*, 8136.

[194] Abbotto, A.; Streitwieser, A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1997***, *119*, 11255.

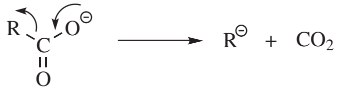
[195] Carlier, P.R.; Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1994***, *116*, 11602.

[196] DeLong, G.T.; Pannell, D.K.; Clarke, M.T.; Thomas, R.D. *J. Am. Chem. Soc.* ***1993***, *115*, 7013.

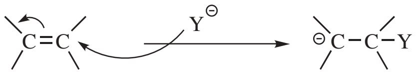
[197] Walborsky, H.M.; Hamdouchi, C. *J. Org. Chem.* ***1993***, *58*, 1187.

[198] For a review of such reactions, see Durst, T., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. B, Elsevier, NY, ***1984***, pp. 239–291.

leaving groups are known (see Chapter 12):



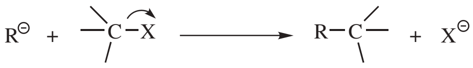
2. A negative ion adds to a carbon–carbon double or triple bond (see Chapter 15):



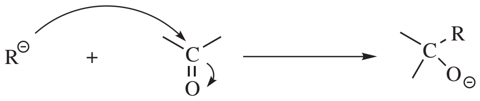
The addition of a negative ion to a carbon–oxygen double bond does not give a carbanion, since the negative charge resides on the oxygen.

The most common reaction of carbanions is combination with a positive species, usually a proton, or with another species that has an empty orbital in its outer shell (a Lewis acid–base reaction):

Carbanions may also form a bond with a carbon that already has four bonds, by displacing one of the four groups (S_N2 reaction, see Chapter 10):



Like carbocations, carbanions can also react in ways in which they are converted to species that are still not neutral molecules. They can add to double bonds (usually C=O double bonds; see Chapters 10 and 16),



or rearrange, although this is rare (see Chapter 18),

$$Ph_3\overset{\ominus}{C}H_2 \longrightarrow Ph_2\overset{\ominus}{C}CH_2Ph$$

or be oxidized to free radicals.[199] A system in which a carbocation $[Ph(p\text{-}Me_2NC_6H_4)_2C^+]$ oxidizes a carbanion $[(p\text{-}NO_2C_6H_4)_3C^-]$ to give two free radicals, reversibly, so that all four species are present in equilibrium, has been demonstrated.[200,201]

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[199] For a review, see Guthrie, R.D., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. A, Elsevier, NY, ***1980***, pp. 197–269.

[200] Arnett, E.M.; Molter, K.E.; Marchot, E.C.; Donovan, W.H.; Smith, P. *J. Am. Chem. Soc.* ***1987***, *109*, 3788.

[201] Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Kinoshita, T.; Aonuma, S.; Nagai, M.; Miyabo, A. *J. Org. Chem.* ***1990***, *55*, 996. See also, Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Miyabo, A. *J. Chem. Soc. Chem. Commun.* ***1988***, 923.

Organometallic compounds that are not ionic, but polar-covalent behave very much as if they were ionic and give similar reactions.

FREE RADICALS

Stability and Structure[202]

A *free radical* (often simply called a *radical*) may be defined as a species that contains one or more unpaired electrons. Note that this definition includes certain stable inorganic molecules (e.g., NO and NO_2), as well as many individual atoms (e.g., Na and Cl). As with carbocations and carbanions, simple alkyl radicals are very reactive. Their lifetimes are extremely short in solution, but they can be kept for relatively long periods frozen within the crystal lattices of other molecules.[203] Many spectral[204] measurements have been made on radicals trapped in this manner. Even under these conditions the methyl radical decomposes with a half-life of 10–15 min in a methanol lattice at 77 K.[205] Since the lifetime of a radical depends not only on its inherent stability, but also on the conditions under which it is generated, the terms *persistent* and *stable* are usually used for the different senses. A stable radical is inherently stable; a persistent radical has a relatively long lifetime under the conditions at which it is generated, although it may not be very stable.

Radicals can be characterized by several techniques, such as mass spectrometry[206] or the characterization of alkoxycarbonyl radicals by Step-Scan Time-Resolved Infrared Spectroscopy.[207] Another technique makes use of the magnetic moment that is associated with the spin of an electron, which can be expressed by a quantum number of $\frac{1}{+2}$ or $\frac{1}{-2}$. According to the Pauli principle, any two electrons occupying the same orbital must have opposite spins, so the total magnetic

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[202] For monographs, see Alfassi, Z.B. *N-Centered Radicals*, Wiley, Chichester, ***1998***; Alfassi, Z.B. *Peroxyl Radicals*, Wiley, Chichester, ***1997***; Alfassi, Z.B. *Chemical Kinetics of Small Organic Radicals*, 4 vols., CRC Press: Boca Raton, FL, ***1988***; Nonhebel, D.C.; Tedder, J.M.; Walton, J.C. *Radicals*, Cambridge University Press, Cambridge, ***1979***; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, Cambridge, ***1974***; Kochi, J.K. *Free Radicals*, 2 vols., Wiley, NY, ***1973***; Hay, J.M. *Reactive Free Radicals*, Academic Press, NY, ***1974***; Pryor, W.A. *Free Radicals*, McGraw-Hill, NY, ***1966***. For reviews, see Kaplan, L. *React. Intermed. (Wiley)* **1985**, *3*, 227; ***1981***, *2*, 251–314; ***1978***, *1*, 163; Griller, D.; Ingold, K.U. *Acc. Chem. Res.* ***1976***, *9*, 13; Huyser, E.S., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 1–59; Isaacs, N.S. *Reactive Intermediates in Organic Chemistry*, Wiley, NY, ***1974***, pp. 294–374.

[203] For a review of the use of matrices to study radicals and other unstable species, see Dunkin, I.R. *Chem. Soc. Rev.* ***1980***, *9*, 1; Jacox, M.E. *Rev. Chem. Intermed.* ***1978***, *2*, 1. For a review of the study of radicals at low temperatures, see Mile, B. *Angew. Chem. Int. Ed.* ***1968***, *7*, 507.

[204] For a review of infrared spectra of radicals trapped in matrices, see Andrews, L. *Annu. Rev. Phys. Chem.* ***1971***, *22*, 109.

[205] Sullivan, P.J.; Koski, W.S. *J. Am. Chem. Soc.* ***1963***, *85*, 384.

[206] Sablier, M.; Fujii, T. *Chem. Rev.* **2002**, *102*, 2855.

[207] Bucher, G.; Halupka, M.; Kolano, C.; Schade, O.; Sander, W. *Eur. J. Org. Chem.* **2001**, 545.

moment is zero for any species in which all the electrons are paired. In radicals, however, one or more electrons are unpaired, so there is a net magnetic moment and the species is paramagnetic. Radicals can therefore be detected by magnetic-susceptibility measurements, but for this technique a relatively high concentration of radicals is required.

A much more important technique is *electron spin resonance* (esr), also called *electron paramagnetic resonance* (epr).[208] The principle of esr is similar to that of nmr, except that electron spin is involved rather than nuclear spin. The two electron spin states ($m_s = \frac{1}{2}$ and $m_s = \frac{1}{-2}$) are ordinarily of equal energy, but in a magnetic field the energies are different. As in NMR, a strong external field is applied and electrons are caused to flip from the lower state to the higher by the application of an appropriate radio-frequency (rf) signal. Inasmuch as two electrons paired in one orbital must have opposite spins which cancel, an esr spectrum arises only from species that have one or more unpaired electrons (i.e., free radicals).

Since only free radicals give an esr spectrum, the method can be used to detect the presence of radicals and to determine their concentration.[209] Furthermore, information concerning the electron distribution (and hence the structure) of free radicals can be obtained from the splitting pattern of the esr spectrum (esr peaks are split by nearby protons).[210] Fortunately (for the existence of most free radicals is very short), it is not necessary for a radical to be persistent for an esr spectrum to be obtained. Electron spin resonance spectra have been observed for radicals with lifetimes considerably <1 s. Failure to observe an esr spectrum does not prove that radicals are not involved, since the concentration may be too low for direct observation. In such cases, the *spin trapping* technique can

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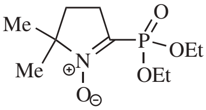
[208] For monographs, see Wertz, J.E.; Bolton, J.R. *Electron Spin Resonance*; McGraw-Hill, NY, ***1972*** [reprinted by Chapman and Hall, NY, and Methuen, London, ***1986***]; Assenheim, H.M. *Introduction to Electron Spin Resonance*, Plenum, NY, ***1967***; Bersohn, R.; Baird, J.C. *An Introduction to Electron Paramagnetic Resonance*, W.A. Benjamin, NY, ***1966***. For reviews, see Bunce, N.J. *J. Chem. Educ.* ***1987***, *64*, 907; Hirota, N.; Ohya-Nishiguchi, H., in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed., pt. 2, Wiley, NY, ***1986***, pp. 605–655; Griller, D.; Ingold, K.U. *Acc. Chem. Res.* ***1980***, *13*, 193; Norman, R.O.C. *Chem. Soc. Rev.* ***1980***, *8*, 1; Fischer, H., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 435–491; Russell, G.A., in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3; Academic Press, NY, ***1971***, pp. 293–341; Rassat, A. *Pure Appl. Chem.* ***1971***, *25*, 623; Kevan, L. *Methods Free-Radical Chem.* ***1969***, *1*, 1; Geske, D.H. *Prog. Phys. Org. Chem.* ***1967***, *4*, 125; Norman, R.O.C.; Gilbert, B.C. *Adv. Phys. Org. Chem.* ***1967***, *5*, 53; Schneider, F.; Möbius, K.; Plato, M. *Angew. Chem. Int. Ed.* ***1965***, *4*, 856. For a review on the application of epr to photochemistry, see Turro, N.J.; Kleinman, M.H.; Karatekin, E. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4437. For a review of the related ENDOR method, see Kurreck, H.; Kirste, B.; Lubitz, W. *Angew. Chem. Int. Ed.* ***1984***, *23*, 173. See also, Poole, Jr., C.P. *Electron Spin Resonance. A Comprehensive Treatise on Experimental Techniques*, 2nd ed., Wiley, NY, ***1983***.

[209] Davies, A.G. *Chem. Soc. Rev.* ***1993***, *22*, 299.

[210] For reviews of the use of esr spectra to determine structures, see Walton, J.C. *Rev. Chem. Intermed.* ***1984***, *5*, 249; Kochi, J.K. *Adv. Free-Radical Chem.* ***1975***, *5*, 189. For esr spectra of a large number of free radicals, see Bielski, B.H.J.; Gebicki, J.M. *Atlas of Electron Spin Resonance Spectra*; Academic Press, NY, ***1967***.

be used.[211] In this technique, a compound is added that is able to combine with very reactive radicals to produce more persistent radicals; the new radicals can be observed by esr. Azulenyl nitrones have been developed as chromotropic spin trapping agents.[212] The most important spin-trapping compounds are nitroso compounds, which react with radicals to give fairly stable nitroxide radicals:[213] $RN{=}O + R'^{\bullet} \rightarrow RR'N{-}O^{\bullet}$. An *N*-oxide spin trap has been developed [**33**; 2(diethylphosphino)-5,5-dimethyl-1-pyrroline-*N*-oxide], and upon trapping a reactive free radical, ^{31}P NMR can be used to identify it.[214] This is an effective technique, and short-lived species such as the oxiranylmethyl radical has been detected by spin trapping.[215] Other molecules have been used to probe the intermediacy of radicals via SET processes. They are called SET probes.[216]



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Because there is an equal probability that a given unpaired electron will have a quantum number of $\frac{1}{+2}$ or $\frac{1}{-2}$, radicals are observed as a single line in an esr spectrum unless they interact with other electronic or nuclear spins or possess magnetic anisotropy, in which case two or more lines may appear in the spectrum.[217]

Another magnetic technique for the detection of free radicals uses an ordinary NMR instrument. It was discovered[218] that if an nmr spectrum is taken during the course of a reaction, certain signals may be enhanced, either in a positive or negative direction; others may be reduced. When this type of behavior, called *chemically*

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[211] For reviews, see Janzen, E.G.; Haire, D.L. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990***, *1*, 253; Gasanov, R.G.; Freidlina, R.Kh. *Russ. Chem. Rev.* ***1987***, *56*, 264; Perkins, M.J. *Adv. Phys. Org. Chem.* ***1980***, *17*, 1; Zubarev, V.E.; Belevskii, V.N.; Bugaenko, L.T. *Russ. Chem. Rev.* ***1979***, *48*, 729; Evans, C.A. *Aldrichimica Acta* ***1979***, *12*, 23; Janzen, E.G. *Acc. Chem. Res.* ***1971***, *4*, 31. See also, the collection of papers on this subject in *Can. J. Chem.* ***1982***, *60*, 1379.

[212] Becker, D.A. *J. Am. Chem. Soc.* ***1996***, *118*, 905; Becker, D.A.; Natero, R.; Echegoyen, L.; Lawson, R.C. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 1289. Also see, Klivenyi, P.; Matthews, R.T.; Wermer, M.; Yang, L.; MacGarvey, U.; Becker, D.A.; Natero, R.; Beal, M.F. *Experimental Neurobiology* ***1998***, *152*, 163.

[213] For a series of papers on nitroxide radicals, see *Pure Appl. Chem.* ***1990***, *62*, 177.

[214] Janzen, E.G.; Zhang, Y.-K. *J. Org. Chem.* ***1995***, *60*, 5441. For the preparation of a new but structurally related spin trap see Karoui, H.; Nsanzumuhire, C.; Le Moigne, F.; Tordo, P. *J. Org. Chem.* ***1999***, *64*, 1471.

[215] Grossi, L.; Strazzari, S. *Chem. Commun.* ***1997***, 917.

[216] Timberlake, J.W.; Chen, T. *Tetrahedron Lett.* ***1994***, *35*, 6043; Tanko, J.M.; Brammer Jr., L.E.; Hervas', M.; Campos, K. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 1407.

[217] Harry Frank, University of Connecticut, Storrs, CT., Personal Communication.

[218] Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 746; Bargon, J.; Fischer, H.; Johnsen, U. *Z. Naturforsch., Teil A* ***1967***, *22*, 1551; Bargon, J.; Fischer, H. *Z. Naturforsch., Teil A* ***1967***, *22*, 1556; Lepley, A.R. *J. Am. Chem. Soc.* ***1969***, *91*, 749; Lepley, A.R.; Landau, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 748.

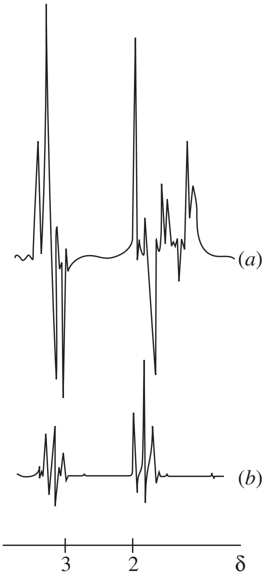

Fig. 5.1 (*a*) The NMR spectrum taken during reaction between EtI and EtLi in benzene (the region between 0.5 and 3.5 δ was scanned with an amplitude twice that of the remainder of the spectrum). The signals at 1.0–1.6 δ are due to butane, some of which is also formed in the reaction. (*b*) Reference spectrum of EtI.[221]

induced dynamic nuclear polarization[219] (CIDNP), is found in the nmr spectrum of the product of a reaction, it means that *at least a portion of that product was formed via the intermediacy of a free radical.*[220] For example, the question was raised whether radicals were intermediates in the exchange reaction between ethyl iodide and ethyllithium (reaction **12-39**):

$$\text{EtI} + \text{EtLi} \rightleftharpoons \text{EtLi} + \text{EtI}$$

Curve *a* in Fig. 5.1[221] shows an NMR spectrum taken during the course of the reaction. Curve *b* is a reference spectrum of ethyl iodide (CH_3 protons at $\delta = 1.85$; CH_2 protons at $\delta = 3.2$). Note that in curve *a* some of the ethyl iodide signals are

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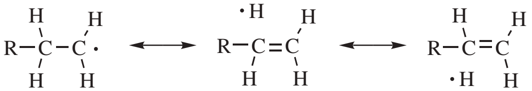
[219] For a monograph on CIDNP, see Lepley, R.L.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, ***1973***. For reviews, see Adrian, F.J. *Rev. Chem. Intermed.* ***1986***, *7*, 173; Closs, G.L.; Miller, R.J.; Redwine, O.D. *Acc. Chem. Res.* ***1985***, *18*, 196; Lawler, R.G.; Ward, H.R., in Nachod, F.C.; Zuckerman, J.J. *Determination of Rates and Mechanisms of Reactions*, Vol. 5, Academic Press, NY, ***1973***, pp. 99–150; Ward, H.R., in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 239–273; *Acc. Chem. Res.* ***1972***, *5*, 18; Closs, G.L. *Adv. Magn. Reson.* ***1974***, *7*, 157; Lawler, R.G. *Acc. Chem. Res.* ***1972***, *5*, 25; Kaptein, R. *Adv. Free-Radical Chem.* ***1975***, *5*, 319; Bethell, D.; Brinkman, M.R. *Adv. Phys. Org. Chem.* ***1973***, *10*, 53.

[220] A related technique is called chemically induced dynamic electron polarization (CIDEP). For a review, see Hore, P.J.; Joslin, C.G.; McLauchlan, K.A. *Chem. Soc. Rev.* ***1979***, *8*, 29.

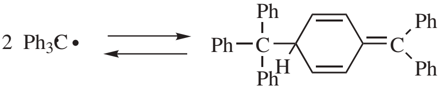
[221] Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 746.

enhanced; others go below the base line (*negative enhancement*; also called *emission*). Thus the ethyl iodide formed in the exchange shows CIDNP, and hence was formed via a free-radical intermediate. Chemically induced dynamic nuclear polarization results when protons in a reacting molecule become dynamically coupled to an unpaired electron while traversing the path from reactants to products. Although the presence of CIDNP almost always means that a free radical is involved,[222] its absence does not prove that a free-radical intermediate is necessarily absent, since reactions involving free-radical intermediates can also take place without observable CIDNP. Also, the presence of CIDNP does not prove that *all* of a product was formed via a free-radical intermediate, only that some of it was. It is noted that dynamic nuclear polarization (DNP) enhance signal intensities in NMR spectra of solids and liquids. In a contemporary DNP experiment, a diamagnetic sample is doped with a paramagnet and the large polarization of the electron spins is transferred to the nuclei via microwave irradiation of the epr spectrum.[223] Dynamic nuclear polarization has been used to examine biradicals.[224]

As with carbocations, the stability order of free radicals is tertiary > secondary > primary, explainable by field effects and hyperconjugation, analogous to that in carbocations (p. 235):



With resonance possibilities, the stability of free radicals increases;[225] some can be kept indefinitely.[226] Benzylic and allylic[227] radicals for which canonical forms can be drawn similar to those shown for the corresponding cations



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(pp. 239, 240) and anions (pp. 252) are more stable than simple alkyl radicals, but still have only a transient existence under ordinary conditions. However, the triphenylmethyl and similar radicals[228] are stable enough to exist in solution

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[222] It has been shown that CIDNP can also arise in cases where para hydrogen (H_2 in which the nuclear spins are opposite) is present: Eisenschmid, T.C.; Kirss, R.U.; Deutsch, P.P.; Hommeltoft, S.I.; Eisenberg, R.; Bargon, J.; Lawler, R.G.; Balch, A.L. *J. Am. Chem. Soc.* ***1987***, *109*, 8089.

[223] Wind, R.A.; Duijvestijn, M.J.; van der Lugt, C.; Manenschijn, A; Vriend, J. *Prog. Nucl. Magn. Reson. Spectrosc.* ***1985***, *17*, 33.

[224] Hu, K.-N.; Yu, H.-h.; Swager, T.M.; Griffin, R.G. *J. Am. Chem. Soc.* ***2004***, *126*, 10844.

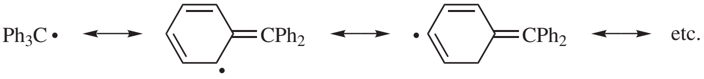
[225] For a discussion, see Robaugh, D.A.; Stein, S.E. *J. Am. Chem. Soc.* ***1986***, *108*, 3224.

[226] For a monograph on stable radicals, including those in which the unpaired electron is not on a carbon atom, see Forrester, A.R.; Hay, J.M.; Thomson, R.H. *Organic Chemistry of Stable Free Radicals*, Academic Press, NY, ***1968***.

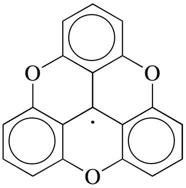
[227] For an electron diffraction study of the allyl radical, see Vajda, E.; Tremmel, J.; Rozsondai, B.; Hargittai, I.; Maltsev, A.K.; Kagramanov, N.D.; Nefedov, O.M. *J. Am. Chem. Soc.* ***1986***, *108*, 4352.

[228] For a review, see Sholle, V.D.; Rozantsev, E.G. *Russ. Chem. Rev.* ***1973***, *42*, 1011.

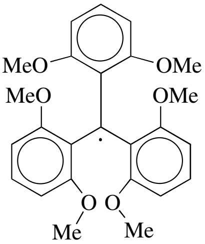
at room temperature, although in equilibrium with a dimeric form. The concentration of triphenylmethyl radical in benzene solution is ~2% at room temperature. For many years it was assumed that Ph_3C•, the first stable free radical known,[229] dimerized to hexaphenylethane (Ph_3C—CPh_3),[230] but UV and NMR investigations have shown that the true structure is **34**.[231] Although triphenylmethyl-type radicals are stabilized by resonance:



it is steric hindrance to dimerization and not resonance that is the major cause of their stability.[232] This was demonstrated by the preparation of the radicals **35** and **36**.[233] These radicals are electronically very similar, but **35**, being planar, has much less steric hindrance to dimerization than Ph_3C•, while **36**, with six groups in ortho positions, has much more. On the other hand, the planarity of **35** means that



35



36

it has a maximum amount of resonance stabilization, while **36** must have much less, since its degree of planarity should be even less than Ph_3C•, which itself is propeller shaped and not planar. Thus if resonance is the chief cause of the stability of Ph_3C•, **36** should dimerize and **35** should not, but if steric hindrance is

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[229] Gomberg, M. *J. Am. Chem. Soc.* ***1900***, *22*, 757, *Ber.* ***1900***, *33*, 3150.

[230] Hexaphenylethane has still not been prepared, but substituted compounds [hexakis(3,5-di-*tert*-butyl-4-biphenylyl)ethane and hexakis(3,5-di-*tert*-butylphenyl)ethane] have been shown by X-ray crystallography to be nonbridged hexaarylethanes in the solid state: Stein, M.; Winter, W.; Rieker, A. *Angew. Chem. Int. Ed.* ***1978***, *17*, 692; Yannoni, N.; Kahr, B.; Mislow, K. *J. Am. Chem. Soc.* ***1988***, *110*, 6670. In solution, both dissociate into free radicals.

[231] Lankamp, H.; Nauta, W.T.; MacLean, C. *Tetrahedron Lett.* ***1968***, 249; Staab, H.A.; Brettschneider, H.; Brunner, H. *Chem. Ber.* ***1970***, *103*, 1101; Volz, H.; Lotsch, W.; Schnell, H. *Tetrahedron* ***1970***, *26*, 5343; McBride, J. *Tetrahedron* ***1974***, *30*, 2009. See also, Guthrie, R.D.; Weisman, G.R. *Chem. Commun.* ***1969***, 1316; Takeuchi, H.; Nagai, T.; Tokura, N. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 753. For an example where a secondary benzilic radical undergoes this type of dimerization, see Peyman, A.; Peters, K.; von Schnering, H.G.; Rüchardt, C. *Chem. Ber.* ***1990***, *123*, 1899.

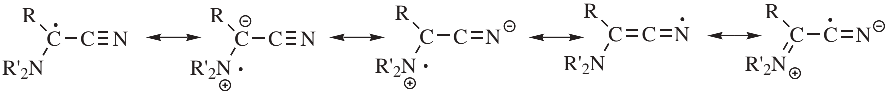
[232] For a review of steric effects in free-radical chemistry, see Rüchardt, C. *Top. Curr. Chem.* ***1980***, *88*, 1.

[233] Sabacky, M.J.; Johnson Jr., C.S.; Smith, R.G.; Gutowsky, H.S.; Martin, J.C. *J. Am. Chem. Soc.* ***1967***, *89*, 2054.

the major cause, the reverse should happen. It was found[233] that **36** gave no evidence of dimerization, even in the solid state, while **35** existed primarily in the dimeric form, which is dissociated to only a small extent in solution,[234] indicating that steric hindrance to dimerization is the major cause for the stability of triarylmethyl radicals. A similar conclusion was reached in the case of $(NC)_3C\bullet$, which dimerizes readily although considerably stabilized by resonance.[235] Nevertheless, that resonance is still an important contributing factor to the stability of radicals is shown by the facts that (*1*) the radical *t*-Bu$(Ph)_2C\bullet$ dimerizes more than $Ph_3C\bullet$, while *p*-$PhCOC_6H_4(Ph_2)C\bullet$ dimerizes less.[236] The latter has more canonical forms than $Ph_3C\bullet$, but steric hindrance should be about the same (for attack at one of the two rings). (*2*) A number of radicals (*p*-$XC_6H_4)_3C\bullet$, with X = F, Cl, O_2N, CN, and so on do not dimerize, but are kinetically stable.[237] Completely chlorinated triarylmethyl radicals are more stable than the unsubstituted kind, probably for steric reasons, and many are quite inert in solution and in the solid state.[238]

Allylic radical are relatively stable, and the pentadienyl radical is particularly stable. In such molecules, (*E,E*)-(*E,Z*)-, and (*Z,Z*)-stereoisomers can form. It has been calculated that (*Z,Z*)-pentadienyl radical is 5.6 kcal mol^{-1}(23.4 kJ mol^{-1}) less stable than (*E,E*)-pentadienyl radical.[239] 2-Phenylethyl radicals have been shown to exhibit bridging of the phenyl group.[240] It is noted that vinyl radical have (*E*)- and (*Z*)-forms and the inversion barrier from one to the other increases as the electronegativity of substituents increase.[241] Enolate radicals are also known.[242]

It has been postulated that the stability of free radicals is enhanced by the presence at the radical center of *both* an electron-donating and an electron-withdrawing group.[243] This is called the *push–pull* or *captodative effect* (see also, pp. 185). The effect arises from increased resonance, for example:



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[234] Müller, E.; Moosmayer, A.; Rieker, A.; Scheffler, K. *Tetrahedron Lett.* ***1967***, 3877. See also, Neugebauer, F.A.; Hellwinkel, D.; Aulmich, G. *Tetrahedron Lett.* ***1978***, 4871.

[235] Kaba, R.A.; Ingold, K.U. *J. Am. Chem. Soc.* ***1976***, *98*, 523.

[236] Zarkadis, A.K.; Neumann, W.P.; Marx, R.; Uzick, W. *Chem. Ber.* ***1985***, *118*, 450; Zarkadis, A.K.; Neumann, W.P.; Uzick, W. *Chem. Ber.* ***1985***, *118*, 1183.

[237] Dünnebacke, D.; Neumann, W.P.; Penenory, A.; Stewen, U. *Chem. Ber.* ***1989***, *122*, 533.

[238] For reviews, see Ballester, M. *Adv. Phys. Org. Chem.* ***1989***, *25*, 267, pp. 354–405, *Acc. Chem. Res.* ***1985***, *18*, 380. See also, Hegarty, A.F.; O'Neill, P. *Tetrahedron Lett.* ***1987***, *28*, 901.

[239] Fort Jr., R.C.; Hrovat, D.A.; Borden, W.T. *J. Org. Chem.* ***1993***, *58*, 211.

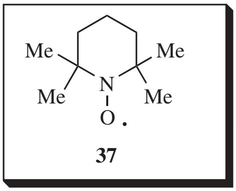
[240] Asensio, A.; Dannenberg, J.J. *J. Org. Chem.* ***2001***, *66*, 5996.

[241] Galli, C.; Guarnieri, A.; Koch, H.; Mencarelli, P.; Rappoport, Z. *J. Org. Chem.* ***1997***, *62*, 4072.

[242] Giese, B.; Damm, W.; Wetterich, F.; Zeltz, H.-G.; Rancourt, J.; Guindon, Y. *Tetrahedron Lett.* ***1993***, *34*, 5885.

[243] For reviews, see Sustmann, R.; Korth, H. *Adv. Phys. Org. Chem.* ***1990***, *26*, 131; Viehe, H.G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* ***1985***, *18*, 148.

There is some evidence in favor[244] of the captodative effect, some of it from esr studies.[245] However, there is also experimental[246] and theoretical[247] evidence against it. There is evidence that while $FCH_2^{\bullet}$ and $F_2CH^{\bullet}$ are more stable than $CH_3^{\bullet}$, the radical $CF_3^{\bullet}$ is less stable; that is, the presence of the third F destabilizes the radical.[248]



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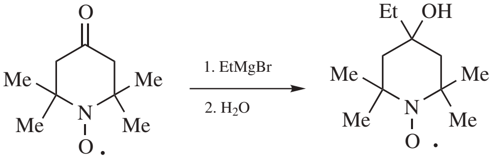

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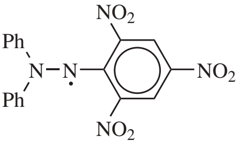
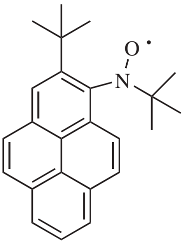


Diphenylpicrylhydrazyl



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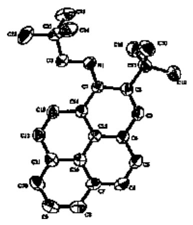

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Certain radicals with the unpaired electron not on a carbon are also very stable.[249] Radicals can be stabilized by intramolecular hydrogen bonding.[250]

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[244] For a summary of the evidence, see Pasto, D.J. *J. Am. Chem. Soc.* ***1988***, *110*, 8164. See also, Ashby, E.C. *Bull. Soc. Chim. Fr.* ***1972***, 2133; *Q. Rev. Chem. Soc.* ***1967***, *21*, 259; Wakefield, B.J. *Organomet. Chem. Rev.* ***1966***, *1*, 131; Bell, N.A. *Educ. Chem.* ***1973***, 143.

[245] See, for example, Korth, H.; Lommes, P.; Sustmann, R.; Sylvander, L.; Stella, L. *New J. Chem.* ***1987***, *11*, 365; Sakurai, H.; Kyushin, S.; Nakadaira, Y.; Kira, M. *J. Phys. Org. Chem.* ***1988***, *1*, 197; Rhodes, C.J.; Roduner, E. *Tetrahedron Lett.* ***1988***, *29*, 1437; Viehe, H.G.; Merényi, R.; Janousek, Z. *Pure Appl. Chem.* ***1988***, *60*, 1635; Creary, X.; Sky, A.F.; Mehrsheikh-Mohammadi, M.E. *Tetrahedron Lett.* ***1988***, *29*, 6839; Bordwell, F.G.; Lynch, T. *J. Am. Chem. Soc.* ***1989***, *111*, 7558.

[246] See, for example, Beckhaus, H.; Rüchardt, C. *Angew. Chem. Int. Ed.* ***1987***, *26*, 770; Neumann, W.P.; Penenory, A.; Stewen, U.; Lehnig, M. *J. Am. Chem. Soc.* ***1989***, *111*, 5845; Bordwell, F.G.; Bausch, M.J.; Cheng, J.P.; Cripe, T.H.; Lynch, T.-Y.; Mueller, M.E. *J. Org. Chem.* ***1990***, *55*, 58; Bordwell, F.G.; Harrelson Jr., J.A. *Can. J. Chem.* ***1990***, *68*, 1714.

[247] See Pasto, D.J. *J. Am. Chem. Soc.* ***1988***, *110*, 8164.

[248] Jiang, X.; Li, X.; Wang, K. *J. Org. Chem.* ***1989***, *54*, 5648.

[249] For reviews of radicals with the unpaired electron on atoms other than carbon, see, in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, the reviews by Nelson, S.F. pp. 527–593 (*N*-centered); Bentrude, W.G. pp. 595–663 (*P*-centered); Kochi, J.K. pp. 665–710 (*O*-centered); Kice, J.L. pp. 711–740 (*S*-centered); Sakurai, H. pp. 741–807 (Si, Ge, Sn, and Pb centered).

[250] Maki, T.; Araki, Y.; Ishida, Y.; Onomura, O.; Matsumura, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 3371.

Diphenylpicrylhydrazyl is a solid that can be kept for years, and stable neutral azine radicals have been prepared.[251] Nitroxide radicals were mentioned previously (p. 273),[252] and the commercially available TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl free radical, **37**) is a stable nitroxyl radical used in chemical reactions such as oxidations.[253] or as a spin trap.[254] Nitroxyl radical **38** is a nitroxide radical so stable that reactions can be performed on it without affecting the unpaired electron[255] (the same is true for some of the chlorinated triarylmethyl radicals mentioned above[256]). Several nitrogen-containing groups are known to stabilize radicals, and the most effective radical stabilization is via spin delocalization.[257] A number of persistent *N*-*tert*-butoxy-1-aminopyrenyl radicals, such as **39**, have been isolated as monomeric radical crystals (see **40**, the X-ray crystal structure of **39**),[258] and monomeric *N*-alkoxyarylaminyls have been isolated.[259] α-Trichloromethylbenzyl(*tert*-butyl)aminoxyl (**41**) is extremely stable.[260] In aqueous media it is stable for >30 days, and in solution in an aromatic hydrocarbon solvent it has survived for more than 90 days.[260] Although the stable nitroxide radicals have the α-carbon blocked to prevent radical formation there, stable nitroxide radicals are also known with hydrogen at the α-carbon,[261] and long-lived vinyl nitroxide radicals are known.[262] A stable organic radical lacking resonance stabilization has been prepared (**42**) and its X-ray crystal structure was

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[251] Jeromin, G.E. *Tetrahedron Lett.* ***2001***, *42*, 1863.

[252] For a study of the electronic structure of persistent nitroxide radicals see Novak, I.; Harrison, L.J.; Kovač, B.; Pratt, L.M. *J. Org. Chem.* ***2004***, *69*, 7628.

[253] See Anelli, P.L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* ***1987***, *52*, 2559; Anelli, P.L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* ***1989***, *54*, 2970; Anelli, P.L.; Montanari, F.; Quici, S. *Org. Synth.* ***1990***, *69*, 212; Fritz-Langhals, E. *Org. Process Res. Dev.* ***2005***, *9*, 577. See also, Rychnovsky, S.D.; Vaidyanathan, R.; Beauchamp, T.; Lin, R.; Farmer, P.J. *J. Org. Chem.* ***1999***, *64*, 6745.

[254] Volodarsky, L.B.; Reznikov, V.A.; Ovcharenko, V.I. *Synthetic Chemistry of Stable Nitroxides*, CRC Press: Boca Raton, FL, ***1994***; Keana, J.F.W. *Chem. Rev.* ***1978***, *78*, 37; Aurich, H.G. *Nitroxides. In Nitrones, Nitronates, Nitroxides*, Patai, S., Rappoport, Z., (Eds.), Wiley, NY, ***1989***; Chapt. 4.

[255] Neiman, M.B.; Rozantsev, E.G.; Mamedova, Yu.G. *Nature* ***1963***, *200*, 256. For reviews of such radicals, see Aurich, H.G., in Patai, S. *The Chemistry of Functional Groups*, *Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 565–622 [This review has been reprinted, and new material added, in Breuer, E.; Aurich, H.G.; Nielsen, A. *Nitrones*, *Nitronates*, *and Nitroxides*, Wiley, NY, ***1989***, pp. 313–399]; Rozantsev, E.G.; Sholle, V.D. *Synthesis* ***1971***, 190, 401.

[256] See Ballester, M.; Veciana, J.; Riera, J.; Castañer, J.; Armet, O.; Rovira, C. *J. Chem. Soc. Chem. Commun.* ***1983***, 982.

[257] Adam, W.; Ortega Schulte, C.M. *J. Org. Chem.* ***2002***, *67*, 4569.

[258] Miura, Y.; Matsuba, N.; Tanaka, R.; Teki, Y.; Takui, T. *J. Org. Chem.* ***2002***, *67*, 8764. For another stable nitroxide radical, see Huang, W.-l.; Chiarelli, R.; Rassat, A. *Tetrahedron Lett.* ***2000***, *41*, 8787.

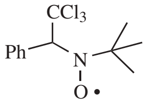
[259] Miura, Y.; Tomimura, T.; Matsuba, N.; Tanaka, R.; Nakatsuji, M.; Teki, Y. *J. Org. Chem.* ***2001***, *66*, 7456.

[260] Janzen, E.G.; Chen, G.; Bray, T.M.; Reinke, L.A.; Poyer, J.L.; McCay, P.B. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1983.

[261] Reznikov, V.A.; Volodarsky, L.B. *Tetrahedron Lett.* ***1994***, *35*, 2239.

[262] Reznikov, V.A.; Pervukhina, N.V.; Ikorskii, V.N.; Ovcharenko, V.I; Grand, A. *Chem. Commun.* ***1999***, 539.

obtained.[263]



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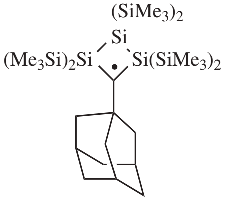

42

Dissociation energies (*D* values) of R—H bonds provide a measure of the relative inherent stability of free radicals R.[264] Table 5.4 lists such values.[265] The higher the *D* value, the less stable the radical. Bond dissociation energies have also been reported for the C—H bond of alkenes and dienes[266] and for the C—H bond in radical precursors XYC—H, where X,Y can be H, alkyl, COOR, COR, SR, CN, NO_2, and so on.[267] Bond dissociation energies for the C—O bond in hydroperoxide radicals (ROO•) have also been reported.[268]

TABLE 5.4. The D_{298} Values for Some R—H Bonds.[265] Free-radical Stability is in the Reverse Order

	D	
R	kcal mol^{-1}	kJ mol^{-1}
Ph•[269]	111	464
CF_3•	107	446
CH_2=CH•	106	444
Cyclopropyl[270]	106	444
Me•	105	438
Et•	100	419

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[263] Apeloig, Y.; Bravo-Zhivotovskii, D.; Bendikov, M.; Danovich, D.; Botoshansky, M.; Vakulrskaya, T.; Voronkov, M.; Samoilova, R.; Zdravkova, M.; Igonin, V.; Shklover, V.; Struchkov, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 8118.

[264] It has been claimed that relative *D* values do not provide such a measure: Nicholas, A.M. de P.; Arnold, D.R. *Can. J. Chem.* ***1984***, *62*, 1850, 1860.

[265] Except where noted, these values are from Kerr, J.A., in Weast, R.C. *Handbook of Chemistry and Physics*, 69th ed.; CRC Press: Boca Raton, FL, ***1988***, p. F-183. For another list of *D* values, see McMillen, D.F.; Golden, D.M. *Annu. Rev. Phys. Chem.* ***1982***, *33*, 493. See also, Tsang, W. *J. Am. Chem. Soc.* ***1985***, *107*, 2872; Holmes, J.L.; Lossing, F.P.; Maccoll, A. *J. Am. Chem. Soc.* ***1988***, *110*, 7339; Holmes, J.L.; Lossing, F.P. *J. Am. Chem. Soc.* ***1988***, *110*, 7343; Roginskii, V.A. *J. Org. Chem. USSR* ***1989***, *25*, 403.

[266] Zhang, X.-M. *J. Org. Chem.* ***1998***, *63*, 1872.

[267] Brocks, J.J.; Beckhaus, H.-D.; Beckwith, A.L.J.; Rüchardt, C. *J. Org. Chem.* ***1998***, *63*, 1935.

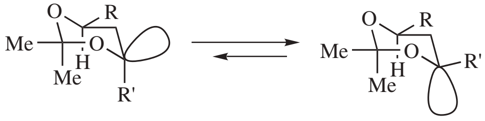
[268] Pratt, D.A.; Porter, N.A. *Org. Lett.* ***2003***, *5*, 387.

[269] For the infra-red of a matrix-isolated phenyl radical see Friderichsen, A.V.; Radziszewski, J.G.; Nimlos, M.R.; Winter, P.R.; Dayton, D.C.; David, D.E.; Ellison, G.B. *J. Am. Chem. Soc.* ***2001***, *123*, 1977.

[270] For a review of cyclopropyl radicals, see Walborsky, H.M. *Tetrahedron* ***1981***, *37*, 1625. See also, Boche, G.; Walborsky, H.M. *Cyclopropane Derived Reactive Intermediates*, Wiley, NY, ***1990***.

$Me_3CCH_2\bullet$	100	418
$Pr\bullet$	100	417
$Cl_3C\bullet$	96	401
$Me_2CH\bullet$	96	401
$Me_3C\bullet$[271]	95.8	401
Cyclohexyl	95.5	400
$PhCH_2\bullet$	88	368
$HCO\bullet$	87	364
$CH_2{=}CH{-}CH_2\bullet$	86	361

There are two possible structures for simple alkyl radicals.[272] They might have sp^2 bonding, in which case the structure would be planar, with the odd electron in a p orbital, or the bonding might be sp^3, which would make the structure pyramidal and place the odd electron in an sp^3 orbital. The esr spectra of $\bullet CH_3$ and other simple alkyl radicals, as well as other evidence indicate that these radicals have planar structures.[273] This is in accord with the known loss of optical activity when a free radical is generated at a chiral carbon.[274] In addition, electronic spectra of the CH_3 and CD_3 radicals (generated by flash photolysis) in the gas phase have definitely established that under these conditions the radicals are planar or near planar.[275] IR spectra of $\bullet CH_3$ trapped in solid argon led to a similar conclusion.[276]



43a **43b**

Despite the usual loss of optical activity noted above, asymmetric radicals can be prepared in some cases. For example, asymmetric nitroxide radicals are known.[277] An anomeric effect was observed in alkoxy radical **43**, where the ratio of **43a/43b** was 1:1.78.[278]

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[271] This value is from Gutman, D. *Acc. Chem. Res.* ***1990***, *23*, 375.

[272] For a review, see Kaplan, L., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 361–434.

[273] See, for example, Cole, T.; Pritchard, D.E.; Davidson, N.; McConnell, H.M. *Mol. Phys.* ***1958***, *1*, 406; Fessenden, R.W.; Schuler, R.H. *J. Chem. Phys.* ***1963***, *39*, 2147; Symons, M.C.R. *Nature* ***1969***, *222*, 1123, *Tetrahedron Lett.* ***1973***, 207; Bonazzola, L.; Leray, E.; Roncin, J. *J. Am. Chem. Soc.* ***1977***, *99*, 8348; Giese, B.; Beckhaus, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 594; Ellison, G.B.; Engelking, P.C.; Lineberger, W.C. *J. Am. Chem. Soc.* ***1978***, *100*, 2556. See, however, Paddon-Row, M.N.; Houk, K.N. *J. Am. Chem. Soc.* ***1981***, *103*, 5047.

[274] There are a few exceptions. See p. $$$.

[275] Herzberg, G.; Shoosmith, J. *Can. J. Phys.* ***1956***, *34*, 523; Herzberg, G. *Proc. R. Soc. London*, *Ser. A* ***1961***, *262*, 291. See also, Tan, L.Y.; Winer, A.M.; Pimentel, G.C. *J. Chem. Phys.* ***1972***, *57*, 4028; Yamada, C.; Hirota, E.; Kawaguchi, K. *J. Chem. Phys.* ***1981***, *75*, 5256.

[276] Andrews, L.; Pimentel, G.C. *J. Chem. Phys.* ***1967***, *47*, 3637; Milligan, D.E.; Jacox, M.E. *J. Chem. Phys.* ***1967***, *47*, 5146.

[277] Tamura, R.; Susuki, S.; Azuma, N.; Matsumoto, A.; Todda, F.; Ishii, Y. *J. Org. Chem.* ***1995***, *60*, 6820.

[278] Rychnovsky, S.D.; Powers, J.P.; LePage, T.J. *J. Am. Chem. Soc.* ***1992***, *114*, 8375.

Evidence from studies on bridgehead compounds shows that although a planar configuration is more stable, pyramidal structures are not impossible. In contrast to the situation with carbocations, free radicals have often been generated at bridgeheads, although studies have shown that bridgehead free radicals are less rapidly formed than the corresponding open-chain radicals.[279] In sum, the available evidence indicates that although simple alkyl free radicals prefer a planar, or near-planar shape, the energy difference between a planar and a pyramidal free radical is not great. However, free radicals in which the carbon is connected to atoms of high electronegativity, for example, $\cdot CF_3$, prefer a pyramidal shape;[280] increasing the electronegativity increases the deviation from planarity.[281] Cyclopropyl radicals are also pyramidal.[282] Free radicals with resonance are definitely planar, although triphenylmethyl-type radicals are propeller-shaped,[283] like the analogous carbocations (p. 245). Radicals possessing simple alkyl substituents attached to the radical carbon (C•) that have C^{sp^3}—C^{sp^3} bonds, and rotation about those bonds is possible. The internal rotation barrier for the *t*-butyl radical ($Me_3C\cdot$), for example, was estimated to be $\sim 1.4\,\text{kcal mol}^{-1}$ ($6\,\text{kJ mol}^{-1}$).[284]

A number of diradicals (also called biradicals) are known,[285] and the thermodynamic stability of diradicals has been examined.[286] Orbital phase theory has been applied to the development of a theoretical model of localized 1,3-diradicals, and used to predict the substitution effects on the spin preference and S–T gaps, and to design stable localized carbon-centered 1,3-diradicals.[287] When the unpaired electrons of a diradical are widely separated, for example, as in $\cdot CH_2CH_2CH_2CH_2\cdot$,

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[279] Lorand, J.P.; Chodroff, S.D.; Wallace, R.W. *J. Am. Chem. Soc.* ***1968***, *90*, 5266; Humphrey, L.B.; Hodgson, B.; Pincock, R.E. *Can. J. Chem.* ***1968***, *46*, 3099; Oberlinner, A.; Rüchardt, C. *Tetrahedron Lett.* ***1969***, 4685; Danen, W.C.; Tipton, T.J.; Saunders, D.G. *J. Am. Chem. Soc.* ***1971***, *93*, 5186; Fort, Jr., R.C.; Hiti, J. *J. Org. Chem.* ***1977***, *42*, 3968; Lomas, J.S. *J. Org. Chem.* ***1987***, *52*, 2627.

[280] Fessenden, R.W.; Schuler, R.H. *J. Chem. Phys.* ***1965***, *43*, 2704; Rogers, M.T.; Kispert, L.D. *J. Chem. Phys.* ***1967***, *46*, 3193; Pauling, L. *J. Chem. Phys.* ***1969***, *51*, 2767.

[281] For example, 1,1-dichloroalkyl radicals are closer to planarity than the corresponding 1,1-difluoro radicals, though still not planar: Chen, K.S.; Tang, D.Y.H.; Montgomery, L.K.; Kochi, J.K. *J. Am. Chem. Soc.* ***1974***, *96*, 2201. For a discussion, see Krusic, P.J.; Bingham, R.C. *J. Am. Chem. Soc.* ***1976***, *98*, 230.

[282] See Deycard, S.; Hughes, L.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1987***, *109*, 4954.

[283] Adrian, F.J. *J. Chem. Phys.* ***1958***, *28*, 608; Andersen, P. *Acta Chem. Scand.* ***1965***, *19*, 629.

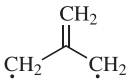
[284] Kubota, S.; Matsushita, M.; Shida, T.; Abu-Raqabah, A.; Symons, M.C.R.; Wyatt, J.L. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 140.

[285] For a monograph, see Borden, W.T. *Diradicals*, Wiley, NY, ***1982***. For reviews, see Johnston, L.J.; Scaiano, J.C. *Chem. Rev.* ***1989***, *89*, 521; Doubleday, Jr., C.; Turro, N.J.; Wang, J. *Acc. Chem. Res.* ***1989***, *22*, 199; Scheffer, J.R.; Trotter, J. *Rev. Chem. Intermed.* ***1988***, *9*, 271; Wilson, R.M. *Org. Photochem.* ***1985***, *7*, 339; Borden, W.T. *React. Intermed. (Wiley)* ***1985***, *3*, 151; ***1981***, *2*, 175; Borden, W.T.; Davidson, E.R. *Acc. Chem. Res.* ***1981***, *14*, 69; Salem, L.; Rowland, C. *Angew. Chem. Int. Ed.* ***1972***, *11*, 92; Salem, L. *Pure Appl. Chem.* ***1973***, *33*, 317; Jones II, G. *J. Chem. Educ.* ***1974***, *51*, 175; Morozova, I.D.; Dyatkina, M.E. *Russ. Chem. Rev.* ***1968***, *37*, 376. See also, Döhnert, D.; Koutecky, J. *J. Am. Chem. Soc.* ***1980***, *102*, 1789. For a series of papers on diradicals, see *Tetrahedron* ***1982***, *38*, 735.

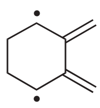
[286] Zhang, D.Y.; Borden, W.T. *J. Org. Chem.* ***2002***, *67*, 3989.

[287] Ma, J.; Ding, Y.; Hattori, K.; Inagaki, S. *J. Org. Chem.* ***2004***, *69*, 4245.

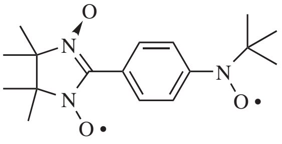
the species behaves spectrally like two doublets. When they are close enough for interaction or can interact through an unsaturated system as in trimethylenemethane,[288] they can have total spin numbers of +1, 0, or −1, since each electron could be either $\frac{1}{+2}$ or $\frac{1}{-2}$. Spectroscopically they are called *triplets*,[289] since each of the three possibilities is represented among the molecules and gives rise to its own spectral peak. In triplet molecules the two unpaired electrons have the same spin. Not all diradicals have a triplet ground state. In 2,3-dimethylelecycohexane-1,4-diyl (**44**), the singlet and triplet states were found to be almost degenerate.[290] Some diradicals, such as **45**, are very stable with a triplet ground state.[291] Diradicals are generally short-lived species. The lifetime of **46** was measured to be <0.1 ns and other diradicals were found to have lifetimes in the 4–316-ns range.[292] Diradical **47** [3,5-di-*tert*-butyl-3′-(*N*-*tert*-butyl-*N*-aminoxy)-4-oxybiphenyl] was found to have a lifetime of weeks even in the presence of oxygen, and survived brief heating in toluene up to ~60°C.[293] Radicals with both unpaired electrons on the same carbon are discussed under carbenes.



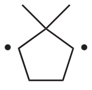
Trimethylenemethane



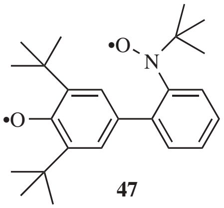
44



45



46



47

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[288] For reviews of trimethylenemethane, see Borden, W.T.; Davidson, E.R. *Ann. Rev. Phys. Chem.* ***1979***, *30*, 125; Bergman, R.G., in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 141–149.

[289] For discussions of the triplet state, see Wagner, P.J.; Hammond, G.S. *Adv. Photochem.* ***1968***, *5*, 21; Turro, N.J. *J. Chem. Educ.* ***1969***, *46*, 2. For a discussion of esr spectra of triplet states, see Wasserman, E.; Hutton, R.S. *Acc. Chem. Res.* ***1977***, *10*, 27. For the generation and observation of triplet 1,3-biradicals see Ichinose, N.; Mizuno, K.; Otsuji, Y.; Caldwell, R.A.; Helms, A.M. *J. Org. Chem.* ***1998***, *63*, 3176.

[290] Matsuda, K.; Iwamura, H. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 1023. Also see, Roth, W.R.; Wollweber, D.; Offerhaus, R.; Rekowski, V.; Lenmartz, H.-W.; Sustmann, R.; Müller, W. *Chem. Ber.* ***1993***, *126*, 2701.

[291] Inoue, K.; Iwamura, H. *Angew. Chem. Int. Ed.* ***1995***, *34*, 927. Also see, Ulrich, G.; Ziessel, R.; Luneau, D.; Rey, P. *Tetrahedron Lett.* ***1994***, *35*, 1211.

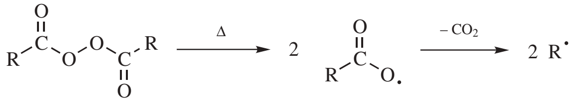
[292] Engel, P.S.; Lowe, K.L. *Tetrahedron Lett.* ***1994***, *35*, 2267.

[293] Liao, Y.; Xie, C.; Lahti, P.M.; Weber, R.T.; Jiang, J.; Barr, D.P. *J. Org. Chem.* ***1999***, *64*, 5176.

The Generation and Fate of Free Radicals[294]

Free radicals are formed from molecules by breaking a bond so that each fragment keeps one electron.[295,296] The energy necessary to break the bond is supplied in one of two ways.

1. *Thermal Cleavage*. Subjection of any organic molecule to a high enough temperature in the gas phase results in the formation of free radicals. When the molecule contains bonds with *D* values or 20–40 kcal mol^{-1} (80–170 kJ mol^{-1}), cleavage can be caused in the liquid phase. Two common examples are cleavage of diacyl peroxides to acyl radicals that decompose to alkyl radicals[297] and cleavage of azo compounds to alkyl radicals[298]

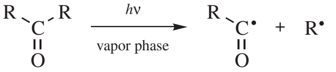


$$RC(=O)OOC(=O)R \xrightarrow{\Delta} 2\ RC(=O)O^{\bullet} \xrightarrow{-CO_2} 2\ R^{\bullet}$$

$$R{-}N{=}N{-}R \xrightarrow{\Delta} 2\ R^{\bullet} + N_2$$

2. *Photochemical Cleavage* (see p. 335). The energy of light of 600–300 nm is 48–96 kcal mol^{-1} (200–400 kJ mol^{-1}), which is of the order of magnitude of covalent-bond energies. Typical examples are photochemical cleavage of alkyl halides in the presence of triethylamine,[299] alcohols in the presence of mercuric oxide and iodine,[300] alkyl 4-nitrobenzenesulfenates,[301] chlorine, and of ketones:

$$Cl_2 \xrightarrow{h\nu} 2\ Cl^{\bullet}$$



$$R_2C{=}O \xrightarrow[\text{vapor phase}]{h\nu} RC^{\bullet}{=}O + R^{\bullet}$$

The photochemistry of radicals and biradicals has been reviewed.[302]

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[294] For a summary of methods of radical formation, see Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Elmsford, NY, ***1986***, pp. 267–281. For a review on formation of free radicals by thermal cleavage, see Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry*; Academic Press, NY, ***1980***, pp. 44–61.

[295] It is also possible for free radicals to be formed by the collision of two nonradical species. For a review, see Harmony, J.A.K. *Methods Free-Radical Chem.* ***1974***, *5*, 101.

[296] For a review of homolytic cleavage of carbon–metal bonds, see Barker, P.J.; Winter, J.N., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 151–218.

[297] Chateauneuf, J.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1988***, *110*, 2877, 2886; Matsuyama, K.; Sugiura, T.; Minoshima, Y. *J. Org. Chem.* ***1995***, *60*, 5520; Ryzhkov, L.R. *J. Org. Chem.* ***1996***, *61*, 2801. For a review of free radical mechanisms involving peroxides in solution, see Howard, J.A., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 235–258. For a review of pyrolysis of peroxides in the gas phase, see Batt, L.; Liu, M.T.H. in the same volume, pp. 685–710.

[298] For a review of the cleavage of azoalkanes, see Engel, P.S. *Chem. Rev.* ***1980***, *80*, 99. For summaries of later work, see Adams, J.S.; Burton, K.A.; Andrews, B.K.; Weisman, R.B.; Engel, P.S. *J. Am. Chem. Soc.* ***1986***, *108*, 7935; Schmittel, M.; Rüchardt, C. *J. Am. Chem. Soc.* ***1987***, *109*, 2750.

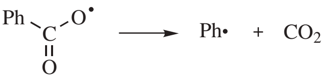
[299] Cossy, J.; Ranaivosata, J.-L.; Bellosta, V. *Tetrahedron Lett.* ***1994***, *35*, 8161.

[300] Courtneidge, J.L. *Tetrahedron Lett.* ***1992***, *33*, 3053.

[301] Pasto, D.J.; Cottard, F. *Tetrahedron Lett.* ***1994***, *35*, 4303.

[302] Johnston, L.J. *Chem. Rev.* ***1993***, *93*, 251.

Radicals are also formed from other radicals, either by the reaction between a radical and a molecule (which *must* give another radical, since the total number of electrons is odd) or by cleavage of a radical[303] to give another radical, for example,



Radicals can also be formed by oxidation or reduction, including electrolytic methods.

Reactions of free radicals either give stable products (termination reactions) or lead to other radicals, which themselves must usually react further (propagation reactions). The most common termination reactions are simple combinations of similar or different radicals:

$$R\bullet \ + \ R'\bullet \longrightarrow R{-}R'$$

Another termination process is disproportionation:[304]

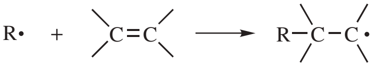
There are four principal propagation reactions, of which the first two are most common:

$$2CH_3{-}CH_2^{\bullet} \longrightarrow CH_3{-}CH_3 + CH_2{=}CH_2$$

1. *Abstraction of Another Atom or Group, Usually a Hydrogen Atom* (see Chapter 14):

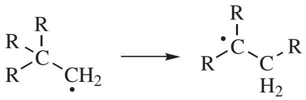
$$R\bullet \ + \ R'{-}H \longrightarrow R{-}H \ + \ R'\bullet$$

2. *Addition to a Multiple Bond* (see Chapter 15):



The radical formed here may add to another double bond and so on. This is one of the chief mechanisms for vinyl polymerization.

3. *Decomposition*. This can be illustrated by the decomposition of the benzoxy radical (above).
4. *Rearrangement*:



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[303] For a deterimination of activation barriers in the homolytic cleavage of radicals and ion radicals see Costentin, C.; Robert, M.; Saveant, J.-M. *J. Am. Chem. Soc.* ***2003***, *125*, 105.

[304] For reviews of termination reactions, see Pilling, M.J. *Int. J. Chem. Kinet.* ***1989***, *21*, 267; Khudyakov, I.V.; Levin, P.P.; Kuz'min, V.A. *Russ. Chem. Rev.* ***1980***, *49*, 982; Gibian, M.J.; Corley, R.C. *Chem. Rev.* ***1973***, *73*, 441.

This is less common than rearrangement of carbocations, but it does occur (though not when R = alkyl or hydrogen; see Chapter 18). Perhaps the best-known rearrangement is that of cyclopropylcarbinyl radicals to a butenyl radical.[305] The rate constant for this rapid ring opening has been measured in certain functionalized cyclopropylcarbinyl radicals by picosecond radical kinetics.[306] Substituent effects on the kinetics of ring opening in substituted cyclopropylcarbinyl radicals has been studied.[307] "The cyclopropylcarbinyl radical has found an important application as a radical clock.[308] Various radical processes can be clocked by the competition of direct reaction with the cyclopropylcarbinyl radical (k_t) and opening of that radical to the 1-buten-4-yl radical (k_r) followed by trapping. Relative rates (k_t/k_r) can be determined from yields of 4-X-1-butene and cyclopropylcarbinyl products as a function of the radical trap[309] (X—Y) concentration. Absolute rate constants have been determined for a number of radicals with various radical traps by laser flash photolysis methods.[310] From these absolute rate constants, reasonably accurate values of k_t can be estimated, and with the relative rate (k_t/k_r), a value for k_r can be calculated. From the calibrated radical-clock reaction rate (k_r), rates (k_t) of other competing reactions can be determined from relative rate data (k_t/k_r)."[306] Other radical clocks are known.[311]

Free radicals can also be oxidized to carbocations or reduced to carbanions.[312]

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[305] For a discussion of radical vs. radical anion character see Stevenson, J. P.; Jackson, W. F.; Tanko, J. M. *J. Am. Chem. Soc.* ***2002***, *124*, 4271.

[306] LeTadic-Biadatti, M.-H.; Newcomb, M. *J. Chem. Soc. Perkin Trans. 2* ***1996***, 1467. See also, Choi, S.-Y.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* ***2000***, *65*, 4447. For determination of k for rearrangement and for and competing reactions, see Cooksy, A. L.; King, H.F.; Richardson, W.H. *J. Org. Chem.* ***2003***, *68*, 9441. For the ring opening of fluorinated cyclopropylcarbinyl systems see Tian, F.; Dolbier Jr., W.R. *Org. Lett.* ***2000***, *2*, 835.

[307] Halgren, T.A.; Roberts, J.D.; Horner, J.H.; Martinez, F.N.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* ***2000***, *122*, 2988.

[308] Griller, D.; Ingold, K.U. *Acc. Chem. Res.* ***1980***, *13*, 317; Newcomb, M.; Choi, S.-Y.; Toy, P.H. *Can. J. Chem.* ***1999***, *77*, 1123; Le Tadic-Biadatti, M.-H.; Newcomb, M. *J. Chem. Soc., Perkin Trans. 2* ***1996***, 1467; Choi, S.Y.; Newcomb, M. *Tetrahedron* ***1995***, *51*, 657; Newcomb, M. *Tetrahedron* ***1993***, *49*, 1151; Newcomb, M.; Johnson, C.; Manek, M.B.; Varick, T.R. *J. Am. Chem. Soc.* ***1992***, *114*, 10915; Nevill, S.M.; Pincock, J.A. *Can. J. Chem.* ***1997***, *75*, 232.

[309] For an alkyl radical trap in aqueous medium see Barton, D.H.R.; Jacob, M.; Peralez, E. *Tetrahedron Lett.* ***1999***, *40*, 9201.

[310] Choi, S.-Y.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* ***2000***, *65*, 4447; Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Lusztyk, J. *J. Org. Chem.* ***1997***, *62*, 1210; Johnston, L.J.; Lusztyk, J.; Wayner, D.D.M.; Abeywickreyma, A.N.; Beckwith, A.L.J.; Scaiano, J.J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1985***, *107*, 4594; Chatgilialoglu, C.; Ingold, K.U.; Scaiano, J.J. *J. Am. Chem. Soc.* ***1981***, *103*, 7739.

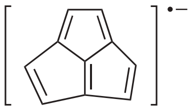
[311] For example, see Leardini, R.; Lucarini, M.; Pedulli, G.F.; Valgimigli, L. *J. Org. Chem.* ***1999***, *64*, 3726.

[312] For a review of the oxidation and reduction of free radicals, see Khudyakov, I.V.; Kuz'min, V.A. *Russ. Chem. Rev.* ***1978***, *47*, 22.

Radical Ions[313]

Several types of radical anions are known with the unpaired electron or the charge or both on atoms other than carbon. Examples include semiquinones[314] (**48**),

48



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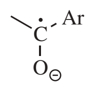

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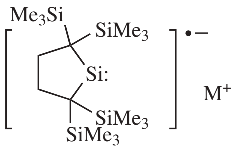
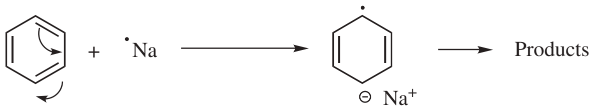


51

M = Cs, Rb, Na, Li

acepentalenes (**49**),[315] ketyls[316] (**50**) and the radical anion of the isolable dialkylsilylene **51**.[317] Reactions in which alkali metals are reducing agents often involve radical anion intermediates, for example, reaction **15-13**:



Several types of radical cation are also known.[318] Typical examples include alkyl azulene cation radicals (**52**),[319] trialkyl amine radical cations,[320]

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[313] For a monograph, see Kaiser, E.T.; Kevan, L. *Radical Ions*, Wiley, NY, ***1968***. For reviews, see Gerson, F.; Huber, W. *Acc. Chem. Res.* ***1987***, *20*, 85; Todres, Z.V. *Tetrahedron* ***1985***, *41*, 2771; Russell, G.A.; Norris, R.K., in McManus, S.P. *Organic Reactive Intermediates*; Academic Press, NY, ***1973***, pp. 423–448; Holy, N.L.; Marcum, J.D. *Angew. Chem. Int. Ed.* ***1971***, *10*, 115; Bilevitch, K.A.; Okhlobystin, O.Yu. *Russ. Chem. Rev.* ***1968***, *37*, 954; Szwarc, M. *Prog. Phys. Org. Chem.* ***1968***, *6*, 322. For a related review, see Chanon, M.; Rajzmann, M.; Chanon, F. *Tetrahedron* ***1990***, *46*, 6193. For a series of papers on this subject, see *Tetrahedron* ***1986***, *42*, 6097.

[314] For a review of semiquinones, see Depew, M.C.; Wan, J.K.S., in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 2, Wiley, NY, ***1988***, pp. 963–1018. For a discussion of the thermodynamic stability of aromatic radical anions see Huh, C.; Kang, C.H.; Lee, H.W.; Nakamura, H.; Mishima, M.; Tsuno, Y.; Yamataka, H. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1083.

[315] de Meijere, A.; Gerson, F.; Schreiner, P.R.; Merstetter, P.; Schüngel, F.-M. *Chem. Commun.* ***1999***, 2189.

[316] For a review of ketyls, see Russell, G.A., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, pp. 471–512. See Davies, A.G.; Neville, A.G. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 163, 171 for ketyl and thioketyl cation radicals.

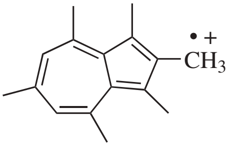
[317] Ishida, S.; Iwamoto, T.; Kira, M. *J. Am. Chem. Soc.* ***2003***, *125*, 3212. For bis(tri-*tert*-butylsilyl)silylene: triplet ground state silylene see Sekiguchi, A.; Tanaka, T.; Ichinohe, M.; Akiyama, K.; Tero-Kubota, S. *J. Am. Chem. Soc.* ***2003***, *125*, 4962.

[318] For reviews, see Roth, H.D. *Acc. Chem. Res.* ***1987***, *20*, 343; Courtneidge, J.L.; Davies, A.G. *Acc. Chem. Res.* ***1987***, *20*, 90; Hammerich, O.; Parker, V.D. *Adv. Phys. Org. Chem.* ***1984***, *20*, 55; Symons, M.C.R. *Chem. Soc. Rev.* ***1984***, *13*, 393; Bard, A.J.; Ledwith, A.; Shine, H.J. *Adv. Phys. Org. Chem.* ***1976***, *13*, 155.

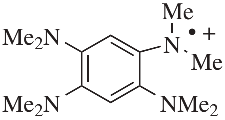
[319] Gerson, F.; Scholz, M.; Hansen, H.-J.; Uebelhart, P. *J. Chem. Soc. Perkin Trans. 2* ***1995***, 215.

[320] de Meijere, A.; Chaplinski, V.; Gerson, F.; Merstetter, P.; Haselbach, E. *J. Org. Chem.* ***1999***, *64*, 6951.

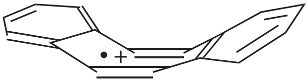
1,2-bis(dialkylamino)benzenes radical cations, such as **53**,[321] dimethylsulfonium cation radicals ($Me_2S^{+\bullet}$),[322] *N*-alkyl substituted imine cation radicals ($Ph_2C{=}NEt^{\bullet+}$),[323] dibenzo[*a,e*]cyclooctene (**54**, a nonplanar cation radical),[324] and [*n.n*]paracyclophane cation radicals.[325] A twisted radical cation derived from bicyclo[2.2.2]oct-2-ene has been reported.[326]



52



53



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CARBENES

Stability and Structure[327]

Carbenes are highly reactive species, practically all having lifetimes considerably under 1 s. With exceptions noted below (p. 289), carbenes have been isolated only by entrapment in matrices at low temperatures (77 K or less).[328] The parent species CH_2 is usually called *methylene*, although derivatives are more often named by the carbene nomenclature. Thus CCl_2 is generally known as dichlorocarbene, although it can also be called dichloromethylene.

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[321] Neugebauer, F.A.; Funk, B.; Staab, H.A. *Tetrahedron Lett.* ***1994***, *35*, 4755. See Stickley, K.R.; Blackstock, S.C. *Tetrahedron Lett.* ***1995***, *36*, 1585 for a *tris*-diarylaminobenzene cation radical.

[322] Dauben, W.G.; Cogen, J.M.; Behar, V.; Schultz, A.G.; Geiss, W.; Taveras, A.G. *Tetrahedron Lett.* ***1992***, *33*, 1713.

[323] Rhodes, C.J.; AgirBas H. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 397.

[324] Gerson, F.; Felder, P.; Schmidlin, R.; Wong, H.N.C. *J. Chem. Soc. Chem. Commun.* ***1994***, 1659.

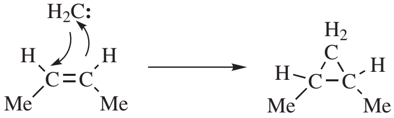
[325] Wartini, A.R.; Valenzuela, J.; Staab, H.A.; Neugebauer, F.A. *Eur. J. Org. Chem.* ***1998***, 139.

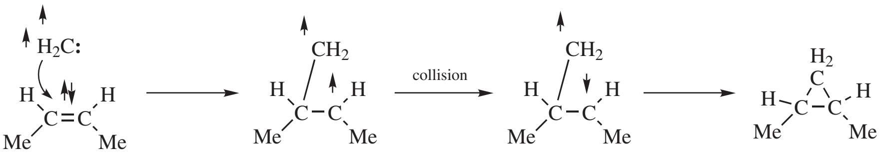
[326] Nelson, S.F.; Reinhardt, L.A.; Tran, H.Q.; Clark, T.; Chen, G.-F.; Pappas, R.S.; Williams, F. *Chem. Eur. J.* ***2002***, *8*, 1074.

[327] For monographs, see Jones, Jr., M.; Moss, R.A. *Carbenes*, 2 vols., Wiley, NY, ***1973–1975***; Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic Press, NY, ***1971***; Rees, C.W.; Gilchrist, T.L. *Carbenes, Nitrenes, and Arynes*, Nelson, London, ***1969***. For reviews, see Minkin, V.I.; Simkin, B.Ya.; Glukhovtsev, M.N. *Russ. Chem. Rev.* ***1989***, *58*, 622; Moss, R.A.; Jones, Jr., M. *React. Intermed. (Wiley)* ***1985***, *3*, 45; ***1981***, *2*, 59; ***1978***, *1*, 69; Isaacs, N.S. *Reactive Intermediates in Organic Chemistry*, Wiley, NY, ***1974***, pp. 375–407; Bethell, D. *Adv. Phys. Org. Chem.* ***1969***, *7*, 153; Bethell, D., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 61–126; Closs, G.L. *Top. Stereochem.* ***1968***, *3*, 193; Herold, B.J.; Gaspar, P.P. *Fortschr. Chem. Forsch.*, ***1966***, *5*, 89; Rozantsev, G.G.; Fainzil'berg, A.A.; Novikov, S.S. *Russ. Chem. Rev.* ***1965***, *34*, 69. For a theoretical study, see Liebman, J.F.; Simons, J. *Mol. Struct. Energ.* ***1986***, *1*, 51.

[328] For example, see Murray, R.W.; Trozzolo, A.M.; Wasserman, E.; Yager, W.A. *J. Am. Chem. Soc.* ***1962***, *84*, 3213; Brandon, R.W.; Closs, G.L.; Hutchison, C.A. *J. Chem. Phys.* ***1962***, *37*, 1878; Milligan, D.E.; Mann, D.E.; Jacox, M.E.; Mitsch, R.A. *J. Chem. Phys.* ***1964***, *41*, 1199; Nefedov, O.M.; Maltsev, A.K.; Mikaelyan, R.G. *Tetrahedron Lett.* ***1971***, 4125; Wright, B.B. *Tetrahedron* ***1985***, *41*, 1517. For reviews, see Zuev, P.S.; Nefedov, O.M. *Russ. Chem. Rev.* ***1989***, *58*, 636; Sheridan, R.S. *Org. Photochem.* ***1987***, *8*, 159, pp. 196–216; Trozzolo, A.M. *Acc. Chem. Res.* ***1968***, *1*, 329.

The two nonbonded electrons of a carbene can be either paired or unpaired. If they are paired, the species is spectrally a *singlet*, while, as we have seen (p. 278), two unpaired electrons appear as a *triplet*. An ingenious method of distinguishing between the two possibilities was developed by Skell,[329] based on the common reaction of addition of carbenes to double bonds to form cyclopropane derivatives (**15-51**). If the singlet species adds to *cis*-2-butene, the resulting cyclopropane should be the cis isomer since the movements of the two pairs of electrons should occur either simultaneously or with one rapidly succeeding another. However, if the attack is by a triplet species, the two unpaired electrons cannot both go into a new covalent bond, since by Hund's rule they have parallel spins. So one of the unpaired electrons will form a bond with the electron from the double bond that has the opposite spin, leaving two unpaired electrons that have the same spin and therefore cannot form a bond at once but must wait until, by some collision process, one of the electrons can reverse its spin. During this time, there is free rotation about the C—C bond and a mixture of *cis*- and *trans*-1,2-dimethylcyclopropanes should result.[330]





The results of this type of experiment show that CH_2 itself is usually formed as a singlet species, which can decay to the triplet state, which consequently has a lower energy (molecular-orbital calculations[331] and experimental determinations show that the difference in energy between singlet and triplet CH_2 is ~8–10 kcal mol^{-1} or 33–42 kJ mol^{-1} [332]). However, it is possible to prepare triplet CH_2 directly by a

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[329] Skell, P.S.; Woodworth, R.C. *J. Am. Chem. Soc.* ***1956***, *78*, 4496; Skell, P.S. *Tetrahedron* ***1985***, *41*, 1427.

[330] These conclusions are generally accepted though the reasoning given here may be oversimplified. For discussions, see Closs, G.L. *Top. Stereochem.* ***1968***, *3*, 193, pp. 203–210; Bethell, D. *Adv. Phys. Org. Chem.* ***1969***, *7*, 153, pp. 194; Hoffmann, R. *J. Am. Chem. Soc.* ***1968***, *90*, 1475.

[331] Richards, Jr., C.A.; Kim, S.-J.; Yamaguchi, Y.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1995***, *117*, 10104.

[332] See, for example, Hay, P.J.; Hunt, W.J.; Goddard III, W.A. *Chem. Phys. Lett.* ***1972***, *13*, 30; Dewar, M.J.S.; Haddon, R.C.; Weiner, P.K. *J. Am. Chem. Soc.* ***1974***, *96*, 253; Frey, H.M.; Kennedy, G.J. *J. Chem. Soc. Chem. Commun.* ***1975***, 233; Lucchese, R.R.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1977***, *99*, 6765; Roos, B.O.; Siegbahn, P.M. *J. Am. Chem. Soc.* ***1977***, *99*, 7716; Lengel, R.K.; Zare, R.N. *J. Am. Chem. Soc.* ***1978***, *100*, 7495; Borden, W.T.; Davidson, E.R. *Ann. Rev. Phys. Chem.* ***1979***, *30*, 125, see pp. 128–134; Leopold, D.G.; Murray, K.K.; Lineberger, W.C. *J. Chem. Phys.* ***1984***, *81*, 1048.

photosensitized decomposition of diazomethane.[333] The CH_2 group is so reactive[334] that it generally reacts as the singlet before it has a chance to decay to the triplet state.[335] As to other carbenes, some react as triplets, some as singlets, and others as singlets or triplets, depending on how they are generated. There are, however, molecules that generate persistent triplet carbenes.[336] Indeed, remarkably stable diaryl triplet carbenes have been prepared.[337]

There is a limitation to the use of stereospecificity of addition as a diagnostic test for singlet or triplet carbenes.[338] When carbenes are generated by photolytic methods, they are often in a highly excited singlet state. When they add to the double bond, the addition is stereospecific; but the cyclopropane formed carries excess energy; that is, it is in an excited state. It has been shown that under certain conditions (low pressures in the gas phase) the excited cyclopropane may undergo cis-trans isomerization *after* it is formed, so that triplet carbene may seem to be involved although in reality the singlet was present.[339]

Studies of the IR spectrum of CCl_2 trapped at low temperatures in solid argon indicate that the ground state for this species is the singlet.[340] The geometrical structure of triplet methylene can be investigated by esr measurements,[341] since triplet species are diradicals. Such measurements made on triplet CH_2 trapped in matrices at very low temperatures (4 K) show that triplet CH_2 is a bent molecule, with an angle of $\sim$136°.[342] Epr measurements cannot be made on singlet species, but from electronic spectra of CH_2 formed in flash photolysis of diazomethane it was concluded that singlet CH_2 is also bent, with an angle of $\sim$103°.[343] Singlet CCl_2[286] and CBr_2[344] are also bent, with angles of 100 and 114°, respectively. It

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[333] Kopecky, K.R.; Hammond, G.S.; Leermakers, P.A. *J. Am. Chem. Soc.* ***1961***, *83*, 2397; ***1962***, *84*, 1015; Duncan, F.J.; Cvetanović, R.J. *J. Am. Chem. Soc.* ***1962***, *84*, 3593.

[334] For a review of the kinetics of CH_2 reactions, see Laufer, A.H. *Rev. Chem. Intermed.* ***1981***, *4*, 225.

[335] Decay of singlet and triplet CH_2 has been detected in solution, as well as in the gas phase: Turro, N.J.; Cha, Y.; Gould, I.R. *J. Am. Chem. Soc.* ***1987***, *109*, 2101.

[336] Tomioka, H. *Acc. Chem. Res.* ***1997***, *30*, 315; Kirmse, W. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2117.

[337] Hirai, K.; Tomioka, H. *J. Am. Chem. Soc.* ***1999***, *121*, 10213; Woodcock, H.L.; Moran, D.; Schleyer, P.v.R.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***2001***, *123*, 4331.

[338] For other methods of distinguishing singlet from triplet carbenes, see Hendrick, M.E.; Jones Jr., M. *Tetrahedron Lett.* ***1978***, 4249; Creary, X. *J. Am. Chem. Soc.* ***1980***, *102*, 1611.

[339] Rabinovitch, B.S.; Tschuikow-Roux, E.; Schlag, E.W. *J. Am. Chem. Soc.* ***1959***, *81*, 1081; Frey, H.M. *Proc. R. Soc. London, Ser. A* ***1959***, *251*, 575. It has been reported that a singlet carbene (CBr_2) can add nonstereospecifically: Lambert, J.B.; Larson, E.G.; Bosch, R.J. *Tetrahedron Lett.* ***1983***, *24*, 3799.

[340] Andrews, L. *J. Chem. Phys.* ***1968***, *48*, 979.

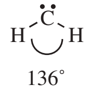
[341] The technique of spin trapping (p. 268) has been applied to the detection of transient triplet carbenes: Forrester, A.R.; Sadd, J.S. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1273.

[342] Wasserman, E.; Kuck, V.J.; Hutton, R.S.; Anderson, E.D.; Yager, W.A. *J. Chem. Phys.* ***1971***, *54*, 4120; Bernheim, R.A.; Bernard, H.W.; Wang, P.S.; Wood, L.S.; Skell, P.S. *J. Chem. Phys.* ***1970***, *53*, 1280; ***1971***, *54*, 3223.

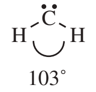
[343] Herzberg, G.; Johns, J.W.C. *Proc. R. Soc. London, Ser. A* ***1967***, *295*, 107, *J. Chem. Phys.* ***1971***, *54*, 2276 and cited references.

[344] Ivey, R.C.; Schulze, P.D.; Leggett, T.L.; Kohl, D.A. *J. Chem. Phys.* ***1974***, *60*, 3174.

has long been known that triplet aryl carbenes are bent.[345]

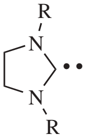


Triplet
methylene



Singlet
methylene

The most common carbenes are :CH_2 and: CCl_2,[346] but many others have been reported, [347] including heterocyclic carbenes, such as **55** (stabilized by the steric constraints of the ring geometry),[348] **56** (an aminocarbene without π conjugation),[349] bicyclo[2.2.2]octylidene, **57**,[350] alkylidene carbenes, such as **58**,[351] conformationally restricted cyclopropylcarbenes, such as **59**,[352] β-Silylcarbenes, such as **60**,[353] α-keto carbenes,[354] vinyl carbenes,[355] and chiral carbenoids.[356] In the case of **55** (R = Ph),[357] the precursor is a tetraaminoethylene, and when potassium hydride is present to preclude electrophilic catalysis, starting tetraaminoethylenes are recovered unchanged.



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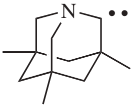

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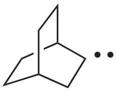

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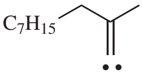

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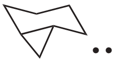

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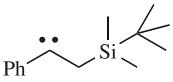

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[345] Trozzolo, A.M.; Wasserman, E.; Yager, W.A. *J. Am. Chem. Soc.* ***1965***, *87*, 129; Senthilnathan, V.P.; Platz, M.S. *J. Am. Chem. Soc.* ***1981***, *103*, 5503; Gilbert, B.C.; Griller, D.; Nazran, A.S. *J. Org. Chem.* ***1985***, *50*, 4738.

[346] For reviews of halocarbenes, see Burton, D.J.; Hahnfeld, J.L. *Fluorine Chem. Rev.* ***1977***, *8*, 119; Margrave, J.L.; Sharp, K.G.; Wilson, P.W. *Fort. Chem. Forsch.* ***1972***, *26*, 1, pp. 3–13.

[347] For reviews of unsaturated carbenes, see Stang, P.J. *Acc. Chem. Res.* ***1982***, *15*, 348; *Chem. Rev.* ***1978***, *78*, 383. For a review of carbalkoxycarbenes, see Marchand, A.P.; Brockway, N.M. *Chem. Rev.* ***1974***, *74*, 431. For a review of arylcarbenes, see Schuster, G.B. *Adv. Phys. Org. Chem.* ***1986***, *22*, 311. For a review of carbenes with neighboring hetero atoms, see Taylor, K.G. *Tetrahedron* ***1982***, *38*, 2751.

[348] Denk, M.K.; Thadani, A.; Hatano, K.; Lough, A.J. *Angew. Chem. Int. Ed.* ***1997***, *36*, 2607; Herrmann, W.A. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1290.

[349] Ye, Q.; Komarov, I.V.; Kirby, A.J.; Jones, Jr., M. *J. Org. Chem.* ***2002***, *67*, 9288.

[350] Ye, Q.; Jones, Jr., M.; Chen, T.; Shevlin, P.B. *Tetrahedron Lett.* ***2001***, *42*, 6979.

[351] Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc. Chem. Commun.* ***1992***, 721; Walsh, R.; Wolf, C.; Untiedt, S.; de Meijere, A. *J. Chem. Soc. Chem. Commun.* ***1992***, 421, 422; Ohira, S.; Yamasaki, K.; Nozaki, H.; Yamato, M.; Nakayama, M. *Tetrahedron Lett.* ***1995***, *36*, 8843. For dimethylvinylidene carbene, see Reed, S.C.; Capitosti, G.J.; Zhu, Z.; Modarelli, D.A. *J. Org. Chem.* ***2001***, *66*, 287. For a review of akylidenecarbenes, see Knorr, R. *Chem. Rev.* ***2004***, *104*, 3795.

[352] Fernamberg, K.; Snoonian, J.R.; Platz, M.S. *Tetrahedron Lett.* ***2001***, *42*, 8761.

[353] Creary, X.; Butchko, M.A. *J. Org. Chem.* ***2002***, *67*, 112.

[354] Bonnichon, F.; Richard, C.; Grabner, G. *Chem. Commun.* ***2001***, 73.

[355] Zuev, P.S.; Sheridan, R.S. *J. Am. Chem. Soc.* ***2004***, *126*, 12220.

[356] Topolski, M.; Duraisamy, M.; Rachoń, J.; Gawronski, J.; Gawronska, K.; Goedken, V.; Walborsky, H.M. *J. Org. Chem.* ***1993***, *58*, 546.

[357] See Wanzlick, H.-W.; Schikora, E. *Angew. Chem.* ***1960***, *72*, 494.

Flash photolysis of $CHBr_3$ produced the intermediate CBr.[358]

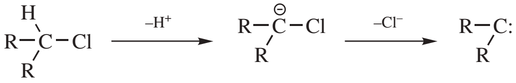
$$CHBr_3 \xrightarrow[\text{photolysis}]{\text{flash}} \cdot\bar{C}{-}Br$$

This is a *carbyne*. The intermediates CF and CCl were generated similarly from $CHFBr_2$ and $CHClBr_2$, respectively.

The Generation and Fate of Carbenes[359]

Carbenes are chiefly formed in two ways, although other pathways are also known.

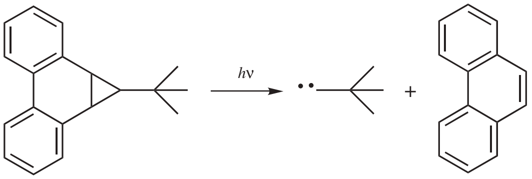
1. In α elimination, a carbon loses a group without its electron pair, usually a proton, and then a group with its pair, usually a halide ion:[360]



$$R_2CH{-}Cl \xrightarrow{-H^+} R_2\overset{\ominus}{C}{-}Cl \xrightarrow{-Cl^-} R_2C:$$

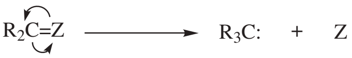
The most common example is formation of dichlorocarbene by treatment of chloroform with a base (see reaction **10-3**) and geminal alkyl dihalides with Me_3Sn^-,[361] but many other examples are known, such as

$$CCl_3{-}COO^{\ominus} \xrightarrow{\Delta} CCl_2 + CO_2 + Cl^{\ominus}$$ Ref. 362



Ref. 363

2. Disintegration of compounds containing certain types of double bonds:



$$R_2C{=}Z \longrightarrow R_3C: + Z$$

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[358] Ruzsicska, B.P.; Jodhan, A.; Choi, H.K.J.; Strausz, O.P. *J. Am. Chem. Soc.* ***1983***, *105*, 2489.

[359] For reviews, see Jones Jr., M. *Acc. Chem. Res.* ***1974***, *7*, 415; Kirmse, W., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9; Elsevier, NY, ***1973***, pp. 373–415; Ref. 327. For a review of electrochemical methods of carbene generation, see Petrosyan, V.E.; Niyazymbetov, M.E. *Russ. Chem. Rev.* ***1989***, *58*, 644.

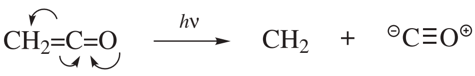
[360] For a review of formation of carbenes in this manner, see Kirmse, W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 1.

[361] Ashby, E.C.; Deshpande, A.K.; Doctorovich, F. *J. Org. Chem.* ***1993***, *58*, 4205.

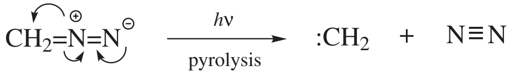
[362] Wagner, W.M. *Proc. Chem. Soc.* ***1959***, 229.

[363] Glick, H.C.; Likhotvovik, I.R.; Jones Jr., M. *Tetrahedron Lett.* ***1995***, *36*, 5715; Stang, P.J. *Acc. Chem. Res.* ***1982***, *15*, 348; *Chem. Rev.* ***1978***, *78*, 383.

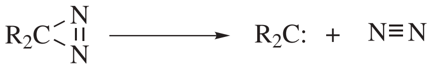
The two most important ways of forming $:CH_2$ are examples: the photolysis of ketene



and the isoelectronic decomposition of diazomethane.[364]



Diazirines[365] (isomeric with diazoalkanes) give carbenes,[366] but arylmethyl radicals have also been generated from diazirines.[367] In a different study, thermolysis of diaryloxydiazirines gave the anticipated carbene products, but photolysis gave both carbenes and aryloxy radicals by α-scission.[368]



Because most carbenes are so reactive, it is often difficult to prove that they are actually present in a given reaction. The lifetime of formylcarbene was measured by transient absorption and transient grating spectroscopy to be 0.15–0.73 ns in dichloromethane.[369] In many instances where a carbene is *apparently* produced by an α elimination or by disintegration of a double-bond compound there is evidence that no free carbene is actually involved. The neutral term *carbenoid* is used where it is known that a free carbene is not present or in cases where there is doubt. α-Halo organometallic compounds, R_2CXM, are often called carbenoids because they readily give a elimination reactions[370] (e.g., see **12-39**).

The reactions of carbenes are more varied than those of the species previously discussed in this chapter. Solvent effects have been observed in carbene reactions. The selectivity of certain carbenes is influenced by the nature of the solvent.[371] the distribution of rearrangement products (see below) from *tert*-butylcarbene[372] are

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[364] For a review, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 170–184.

[365] For syntheses, see Martinu, T.; Dailey, W.P. *J. Org. Chem.* ***2004***, *69*, 7359; Likhotvorik, I.R.; Tae, E.L.; Ventre, C.; Platz, M.S. *Tetahedron Lett.* ***2000***, *41*, 795.

[366] For a treatise, see Liu, M.T.H. *Chemistry of Diazirines*, 2 vols., CRC Press, Boca Raton, FL, ***1987***. For reviews, see Liu, M.T.H. *Chem. Soc. Rev.* ***1982***, *11*, 127; Frey, H.M. *Adv. Photochem.* ***1966***, *4*, 225.

[367] Moss, R.A.; Fu, X. *Org. Lett.* ***2004***, *6*, 3353.

[368] Fede, J.-M.; Jockusch, S.; Lin, N.; Moss, R.A.; Turro, N.J. *Org. Lett.* ***2003***, *5*, 5027.

[369] Toscano, J.P.; Platz, M.S.; Nikolaev, V.; Cao, Y.; Zimmt, M.B. *J. Am. Chem. Soc.* ***1996***, *118*, 3527.

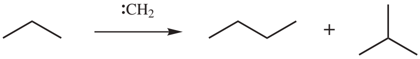
[370] For a review, see Nefedov, O.M.; D'yachenko, A.I.; Prokof'ev, A.K. *Russ. Chem. Rev.* ***1977***, *46*, 941.

[371] Tomioka, H.; Ozaki, Y.; Izawa, Y. *Tetrahedron* ***1985***, *41*, 4987.

[372] Moss, R.A.; Yan, S.; Krogh-Jesperson, K. *J. Am. Chem. Soc.* ***1998***, *120*, 1088.; Krogh-Jesperson, K.; Yan, S.; Moss, R.A. *J. Am. Chem. Soc.* ***1999***, *121*, 6269.

influenced by changes in solvent.[373] It is known that singlet methylene forms a charge-transfer complex with benzene.[374] Solvent interactions for chlorophenylcarbene and fluorophenylcarbene, however, are weak.[375]

1. Additions to carbon–carbon double bonds have already been mentioned. Carbenes also add to aromatic systems, but the immediate products rearrange, usually with ring enlargement (see **15-65**). Additions of carbenes to other double bonds, such as C=N (**16-46** and **16-48**), and to triple bonds have also been reported.
2. An unusual reaction of carbenes is that of insertion into C—H bonds (**12-21**). Thus, $:CH_2$ reacts with methane to give ethane and with propane to give



n-butane and isobutane, as shown. Elimination to give an alkene is a competing side reaction in polar solvents, but this is suppressed in nonpolar solvents.[376] Simple alkyl carbenes, such as this, are not very useful for synthetic purposes, but do illustrate the extreme reactivity of carbene. However, carbenoids generated by rhodium catalyzed decomposition of diazoalkanes are very useful (p. 803) and have been used in a variety of syntheses. Treatment in the liquid phase of an alkane, such as pentane with carbene formed from the photolysis of diazomethane, gives the three possible products in statistical ratios[377] demonstrating that carbene is displaying no selectivity. For many years, it was a generally accepted principle that the lower the selectivity the greater the reactivity; however, this principle is no longer regarded as general because many exceptions have been found.[378] Singlet CH_2 generated by photolysis of diazomethane is probably the most reactive organic species known, but triplet CH_2 is somewhat less reactive, and other carbenes are still less reactive. The following series of carbenes of decreasing reactivity has

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[373] Ruck, R.T.; Jones Jr., M. *Tetrahedron Lett.* ***1998***, *39*, 2277.

[374] Khan, M.I.; Goodman, J.L. *J. Am. Chem. Soc.* ***1995***, *117*, 6635.

[375] Sun, Y.; Tippmann, E.M.; Platz, M.S. *Org. Lett.* ***2003***, *5*, 1305.

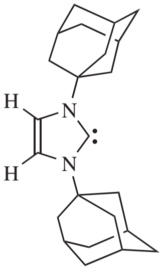
[376] Ruck, R.T.; Jones Jr., M. *Tetrahedron Lett.* ***1998***, *39*, 2277.

[377] Doering, W. von E.; Buttery, R.G.; Laughlin, R.G.; Chaudhuri, N. *J. Am. Chem. Soc.* ***1956***, *78*, 3224; Richardson, D.B.; Simmons, M.C.; Dvoretzky, I. *J. Am. Chem. Soc.* ***1961***, *83*, 1934; Halberstadt, M.L.; McNesby, J.R. *J. Am. Chem. Soc.* ***1967***, *89*, 3417.

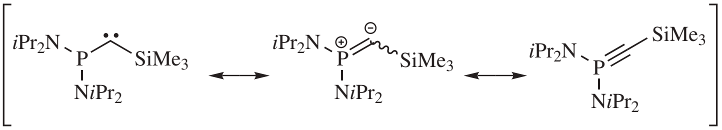
[378] For reviews of this question, see Buncel, E.; Wilson, H. *J. Chem. Educ.* ***1987***, *64*, 475; Johnson, C.D. *Tetrahedron* ***1980***, *36*, 3461; *Chem. Rev.* ***1975***, *75*, 755; Giese, B. *Angew. Chem. Int. Ed.* ***1977***, *16*, 125; Pross, A. *Adv. Phys. Org. Chem.* ***1977***, *14*, 69. See also, Ritchie, C.D.; Sawada, M. *J. Am. Chem. Soc.* ***1977***, *99*, 3754; Argile, A.; Ruasse, M. *Tetrahedron Lett.* ***1980***, *21*, 1327; Godfrey, M. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 645; Kurz, J.L.; El-Nasr, M.M.S. *J. Am. Chem. Soc.* ***1982***, *104*, 5823; Srinivasan, C.; Shunmugasundaram, A.; Arumugam, N. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 17; Bordwell, F.G.; Branca, J.C.; Cripe, T.A. *Isr. J. Chem.* ***1985***, *26*, 357; Formosinho, S.J. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 839; Johnson, C.D.; Stratton, B. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1903. For a group of papers on this subject, see *Isr. J. Chem.* ***1985***, *26*, 303.

been proposed on the basis of discrimination between insertion and addition reactions: $CH_2 > HCCOOR > PhCH > BrCH \sim ClCH$.[379] Dihalocarbenes generally do not give insertion reactions at all. Insertion of carbenes into other bonds has also been demonstrated, although not insertion into C—C bonds.[380]

Two carbenes that are stable at room temperature have been reported.[381] These are **61** and **62**. In the absence of oxygen and moisture, **61** exists as stable crystals with a melting point of 240–241°C.[382] Its structure was proved by X-ray crystallography.



61



62

3. It would seem that dimerization should be an important reaction of carbenes

$$R_2C\colon \; + \; R_2C\colon \; \longrightarrow \; R_2C{=}CR_2$$

but it is not, because the reactivity is so great that the carbene species do not have time to find each other and because the dimer generally has so much energy that it dissociates again. Apparent dimerizations have been observed, but it is likely that the products in many reported instances of "dimerization" do not arise from an actual dimerization of two carbenes but from attack by a carbene on a molecule of carbene precursor, for example,

$$R_2C\colon \; + \; R_2CN_2 \; \longrightarrow \; R_2C{=}CR_2 \; + \; N_2$$

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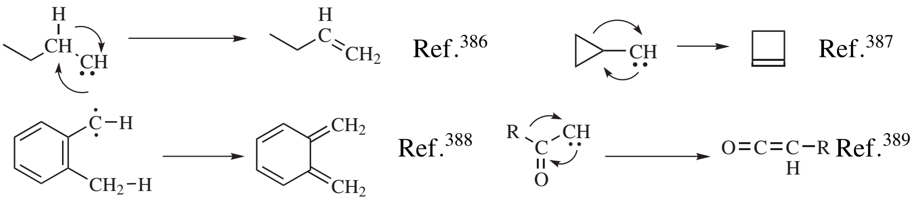
[379] Closs, G.L.; Coyle, J.J. *J. Am. Chem. Soc.* ***1965***, *87*, 4270.

[380] See, for example, Doering, W. von E.; Knox, L.H.; Jones, Jr., M. *J. Org. Chem.* ***1959***, *24*, 136; Franzen, V. *Liebigs Ann. Chem.* ***1959***, *627*, 22; Bradley, J.; Ledwith, A. *J. Chem. Soc.* ***1961***, 1495; Frey, H.M.; Voisey, M.A. *Chem. Commun.* ***1966***, 454; Seyferth, D.; Damrauer, R.; Mui, J.Y.; Jula, T.F. *J. Am. Chem. Soc.* ***1968***, *90*, 2944; Tomioka, H.; Ozaki, Y.; Izawa, Y. *Tetrahedron* ***1985***, *41*, 4987; Frey, H.M.; Walsh, R.; Watts, I.M. *J. Chem. Soc. Chem. Commun.* ***1989***, 284.

[381] For a discussion, see Regitz, M. *Angew. Chem. Int. Ed.* ***1991***, *30*, 674.

[382] Arduengo III, A.J.; Harlow, R.L.; Kline, M. *J. Am. Chem. Soc.* ***1991***, *113*, 361.

4. Alkylcarbenes can undergo rearrangement, with migration of alkyl or hydrogen.[383] Indeed these rearrangements are generally so rapid[384] that additions to multiple bonds and insertion reactions, which are so common for CH_2, are seldom encountered with alkyl or dialkyl carbenes. Unlike rearrangement of the species previously encountered in this chapter, most rearrangements of carbenes directly give stable molecules. A carbene intermediate has been suggested for the isomerization of cyclopropane.[385] Some examples of carbene rearrangement are



The rearrangement of acylcarbenes to ketenes is called the Wolff rearrangement (reaction **18-8**). A few rearrangements in which carbenes rearrange to other carbenes are also known.[390] Of course, the new carbene must stabilize itself in one of the ways we have mentioned.

[383] For a probe of migratory aptitudes of hydrogen to carbenes see Locatelli, F.; Candy, J.-P.; Didillon, B.; Niccolai, G.P.; Uzio, D.; Basset, J.-M. *J. Am. Chem. Soc.* ***2001***, *123*, 1658. For reviews of carbene and nitrene rearrangements, see Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry*, Academic Press, NY, ***1980***, pp. 115–163; Wentrup, C. *Adv. Heterocycl. Chem.* ***1981***, *28*, 231; *React. Intermed. (Plenum)* ***1980***, *1*, 263; *Top. Curr. Chem.* ***1976***, *62*, 173; Jones, W.M., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 95–160; Schaefer III, H.F. *Acc. Chem. Res.* ***1979***, *12*, 288; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 457–496.

[384] The activation energy for the 1,2-hydrogen shift has been estimated at 1.1 kcal mol^{-1} (4.5 kJ mol^{-1}), an exceedingly low value: Stevens, I.D.R.; Liu, M.T.H.; Soundararajan, N.; Paike, N. *Tetrahedron Lett.* ***1989***, *30*, 481. Also see, Pezacki, J.P.; Couture, P.; Dunn, J.A.; Warkentin, J.; Wood, P.D.; Lusztyk, J.; Ford, F.; Platz, M.S. *J. Org. Chem.* ***1999***, *64*, 4456.

[385] Bettinger, H.F.; Rienstra-Kiracofe, J.C.; Hoffman, B.C.; Schaefer III, H.F.; Baldwin, J.E.; Schleyer, P.v.R. *Chem. Commun.* ***1999***, 1515.

[386] Kirmse, W.; Doering, W. von E. *Tetrahedron* ***1960***, *11*, 266. For kinetic studies of the rearrangement: $\text{Cl—}\bar{\text{C}}\text{—CHR}_2 \rightarrow \text{ClCH=CR}_2$, see Liu, M.T.H.; Bonneau, R. *J. Am. Chem. Soc.* ***1989***, *111*, 6873; Jackson, J.E.; Soundararajan, N.; White, W.; Liu, M.T.H.; Bonneau, R.; Platz, M.S. *J. Am. Chem. Soc.* ***1989***, *111*, 6874; Ho, G.; Krogh-Jespersen, K.; Moss, R.A.; Shen, S.; Sheridan, R.S.; Subramanian, R. *J. Am. Chem. Soc.* ***1989***, *111*, 6875; LaVilla, J.A.; Goodman, J.L. *J. Am. Chem. Soc.* ***1989***, *111*, 6877.

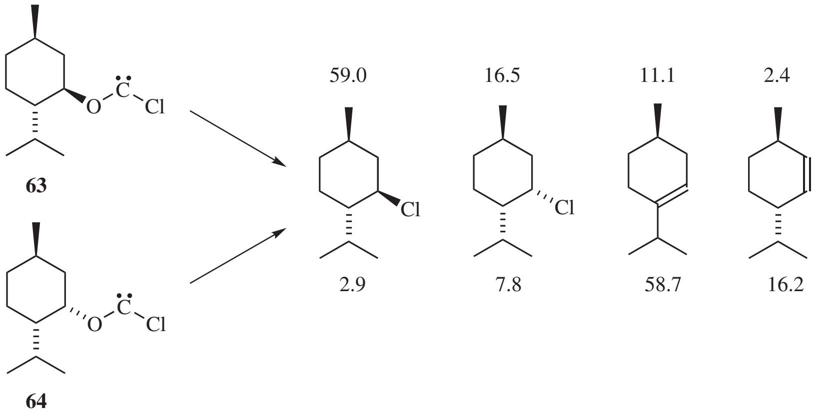
[387] Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* ***1960***, *82*, 1002.

[388] McMahon, R.J.; Chapman, O.L. *J. Am. Chem. Soc.* ***1987***, *109*, 683.

[389] Friedman, L.; Berger, J.G. *J. Am. Chem. Soc.* ***1961***, *83*, 492, 500.

[390] For a review, see Jones, W.M. *Acc. Chem. Res.* ***1977***, *10*, 353.

5. The fragmentation reactions of alicyclic oxychlorocarbenes such as **63** and **64**[391] give substitution and elimination products. Menthyloxychlorocarbene, **63**, gave primarily the substitution product, whereas neomenthyloxychlorocarbene, **64**, gave primarily the elimination product, as shown. In this case, the substitution product is likely due to rearrangement of the chlorocarbene.[392] It is known that fragmentation of nortricyclyloxychlorocarbene in pentane occurs by an S_Ni-like process to give nortricyclyl chloride.[393] In more polar solvents, fragmentation leads to nortricyclyl cation–chloride anion pair that gives nortricyclyl chloride and a small amount of *exo*-2-norbornenyl chloride. Fragmentation can also lead to radicals.[394]



6. Triplet carbenes can abstract hydrogen or other atoms to give free radicals, for example,

$$\cdot\dot{C}H_2 \quad + \quad CH_3CH_3 \quad \longrightarrow \quad \cdot CH_3 \quad + \quad \cdot CH_2CH_3$$

This is not surprising, since triplet carbenes are free radicals. But singlet carbenes can also give this reaction, although in this case only halogen atoms are abstracted, not hydrogen.[395]

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[391] Moss, R.A.; Johnson, L.A.; Kacprzynski, M.; Sauers, R.R. *J. Org. Chem.* ***2003***, *68*, 5114.

[392] A rearrangement product was noted for adamantylchlorocarbenes, possibly due to rearrangement of the chlorine atom from a chlorocarbene. See Yao, G.; Rempala, P.; Bashore, C.; Sheridan, R.S. *Tetrahedron Lett.* ***1999***, *40*, 17.

[393] Moss, R.A.; Ma, Y.; Sauers, R.R.; Madni, M. *J. Org. Chem.* ***2004***, *69*, 3628.

[394] Mekley, N.; El-Saidi, M.; Warkentin, J. *Can. J. Chem.* ***2000***, *78*, 356.

[395] Roth, H.D. *J. Am. Chem. Soc.* ***1971***, *93*, 1527, 4935, *Acc. Chem. Res.* ***1977***, *10*, 85.

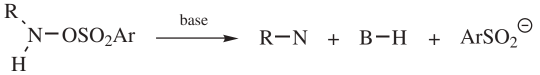
NITRENES

Nitrenes,[396] R—N, are the nitrogen analogs of carbenes, and most of what we have said about carbenes also applies to them. Nitrenes are too reactive for isolation under ordinary conditions,[397] although *ab initio* calculations show that nitrenes are more stable than carbenes with an enthalpy difference of 25–26 kcal mol^{-1} (104.7–108.8 kJ mol^{-1}).[398]

Alkyl nitrenes have been isolated by trapping in matrices at 4 K,[399] while aryl nitrenes, which are less reactive, can be trapped at 77 K.[400] The ground state of NH, and probably of most nitrenes,[401] is a triplet, although nitrenes can be generated in both triplet[402] and singlet states. In additions of EtOOC—N to C=C double bonds two species are involved, one of which adds in a stereospecific manner and the other not. By analogy with Skell's proposal involving carbenes (p. 284) these are taken to be the singlet and triplet species, respectively.[403]

The two principal means of generating nitrenes are analogous to those used to form carbenes.

1. *Elimination*. An example is



$$\mathrm{RNH{-}OSO_2Ar} \xrightarrow{\text{base}} \mathrm{R{-}N} + \mathrm{B{-}H} + \mathrm{ArSO_2}^{\ominus}$$

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[396] For monographs, see Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, **1984**; Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***. For reviews, see Scriven, E.F.V. *React. Intermed. (Plenum)* ***1982***, *2*, 1; Lwowski, W. *React. Intermed. (Wiley)* ***1985***, *3*, 305; ***1981***, *2*, 315; ***1978***, *1*, 197; *Angew. Chem. Int. Ed.* ***1967***, *6*, 897; Abramovitch, R.A., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 127–192; Hünig, S. *Helv. Chim. Acta* ***1971***, *54*, 1721; Belloli, R. *J. Chem. Educ.* ***1971***, *48*, 422; Kuznetsov, M.A.; Ioffe, B.V. *Russ. Chem. Rev.* ***1989***, *58*, 732 (*N*- and *O*-nitrenes); Meth-Cohn, O. *Acc. Chem. Res.* ***1987***, *20*, 18 (oxycarbonylnitrenes); Abramovitch, R.A.; Sutherland, R.G. *Fortsch. Chem. Forsch.*, ***1970***, *16*, 1 (sulfonyl nitrenes); Ioffe, B.V.; Kuznetsov, M.A. *Russ. Chem. Rev.* ***1972***, *41*, 131 (*N*-nitrenes).

[397] McClelland, R.A. *Tetrahedron* ***1996***, *52*, 6823.

[398] Kemnitz, C.R.; Karney, W.L.; Borden, W.T. *J. Am. Chem. Soc.* ***1998***, *120*, 3499.

[399] Wasserman, E.; Smolinsky, G.; Yager, W.A. *J. Am. Chem. Soc.* ***1964***, *86*, 3166. For the structure of CH_3–N:, as determined in the gas phase, see Carrick, P.G.; Brazier, C.R.; Bernath, P.F.; Engelking, P.C. *J. Am. Chem. Soc.* ***1987***, *109*, 5100.

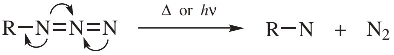
[400] Smolinsky, G.; Wasserman, E.; Yager, W.A. *J. Am. Chem. Soc.* ***1962***, *84*, 3220. For a review, see Sheridan, R.S. *Org. Photochem.* ***1987***, *8*, 159, pp. 159–248.

[401] A few nitrenes have been shown to have singlet ground states. See Sigman, M.E.; Autrey, T.; Schuster, G.B. *J. Am. Chem. Soc.* ***1988***, *110*, 4297.

[402] For the direct detection of triplet alkyl nitrenes in solution via photolysis of α-azidoacetophenones see Singh, P.N.D.; Mandel, S.M.; Robinson, R.M.; Zhu, Z.; Franz, R.; Ault, B.S.; Gudmundsdottir, A.D. *J. Org. Chem.* ***2003***, *68*, 7951.

[403] McConaghy, Jr., J.S.; Lwowski, W. *J. Am. Chem. Soc.* ***1967***, *89*, 2357, 4450; Mishra, A.; Rice, S.N.; Lwowski, W. *J. Org. Chem.* ***1968***, *33*, 481.

2. *Breakdown of Certain Double-Bond Compounds*. The most common method of forming nitrenes is photolytic or thermal decomposition of azides,[404]



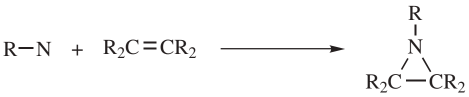
$$R-N=N=N \xrightarrow{\Delta \text{ or } h\nu} R-N + N_2$$

The unsubstituted nitrene NH has been generated by photolysis of or electric discharge through NH_3, N_2H_4, or HN_3.

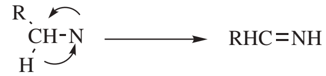
The reactions of nitrenes are also similar to those of carbenes.[405] As in that case, many reactions in which nitrene intermediates are suspected probably do not involve free nitrenes. It is often very difficult to obtain proof in any given case that a free nitrene is or is not an intermediate.

1. *Insertion* (see reaction **12-13**). Nitrenes, especially acyl nitrenes and sulfonyl nitrenes, can insert into C—H and certain other bonds, for example,

2. *Addition to C=C Bonds* (see reaction **15-54**):



3. *Rearrangements*.[383] Alkyl nitrenes do not generally give either of the two preceding reactions because rearrangement is more rapid, for example,



Such rearrangements are so rapid that it is usually difficult to exclude the possibility that a free nitrene was never present at all, that is, that migration takes place at the same time that the nitrene is formed[406] (see p. 1606). However, the rearrangement of naphthylnitrenes to novel bond-shift isomers has been reported.[407]

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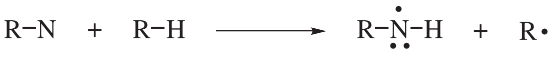
[404] For reviews, see Dyall, L.K., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 287–320; Dürr, H.; Kober, H. *Top. Curr. Chem.* ***1976***, *66*, 89; L'Abbé, G. *Chem. Rev.* ***1969***, *69*, 345.

[405] For a discussion of nitrene reactivity, see Subbaraj, A.; Subba Rao, O.; Lwowski, W. *J. Org. Chem.* ***1989***, *54*, 3945.

[406] For example, see Moriarty, R.M.; Reardon, R.C. *Tetrahedron* ***1970***, *26*, 1379; Abramovitch, R.A.; Kyba, E.P. *J. Am. Chem. Soc.* ***1971***, *93*, 1537.

[407] Maltsev, A.; Bally, T.; Tsao, M.-L.; Platz, M.S.; Kuhn, A.; Vosswinkel, M.; Wentrup, C. *J. Am. Chem. Soc.* ***2004***, *126*, 237.

4. *Abstraction*, for example,



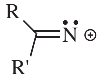
$$R{-}N \;+\; R{-}H \longrightarrow R{-}\overset{\bullet}{\underset{\bullet\bullet}{N}}{-}H \;+\; R\bullet$$

5. *Dimerization*. One of the principal reactions of NH is dimerization to diimide N_2H_2. Azobenzenes are often obtained in reactions where aryl nitrenes are implicated:[408]

$$2\ Ar{-}N \longrightarrow Ar{-}N{=}N{-}Ar$$

It would thus seem that dimerization is more important for nitrenes than it is for carbenes, but again it has not been proved that free nitrenes are actually involved.

65



66

At least two types of *nitrenium ions*,[409] the nitrogen analogs of carbocations, can exist as intermediates, although much less work has been done in this area than on carbocations. In one type (**65**), the nitrogen is bonded to two atoms (R or R′ can be H)[410] and in the other (**66**) to only one atom.[411] When R = H in **65** the species is a protonated nitrene. Like carbenes and nitrenes, nitrenium ions can exist in singlet or triplet states.[412]

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[408] See, for example, Leyva, E.; Platz, M.S.; Persy, G.; Wirz, J. *J. Am. Chem. Soc.* ***1986***, *108*, 3783.

[409] Falvey, D.E. *J. Phys. Org. Chem.* ***1999***, *12*, 589; Falvey, D.E., in Ramamurthy, V., Schanze, K. *Organic, Physical, and Materials Photochemistry*, Marcel Dekker, NY, ***2000***; pp. 249–284; Novak, M.; Rajagopal, S. *Adv. Phys. Org. Chem.* ***2001***, *36*, 167; Falvey, D.E., in Moss, R.A., Platz, M.S., Jones, Jr., M. *Reactve Intermediate Chemistry*, Wiley-Interscience: Hoboken, NJ, ***2004***; Vol. 1, pp. 593–650.

[410] Winter, A.H.; Falvey, D.E.; Cramer, C.J. *J. Am. Chem. Soc.*, ***2004***, *126*, 9661.

[411] For reviews of **65**, see Abramovitch, R.A.; Jeyaraman, R., in Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, ***1984***, pp. 297–357; Gassman, P.G. *Acc. Chem. Res.* ***1970***, *3*, 26. For a review of **66**, see Lansbury, P.T., in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, pp. 405–419.

[412] Gassman, P.G.; Cryberg, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 5176.

CHAPTER 6

Mechanisms and Methods of Determining Them

A mechanism is the actual process by which a reaction takes place: which bonds are broken, in what order, how many steps are involved, the relative rate of each step, and so on. In order to state a mechanism completely, we should have to specify the positions of all atoms, including those in solvent molecules, and the energy of the system, at every point in the process. A proposed mechanism must fit all the facts available. It is always subject to change as new facts are discovered. The usual course is that the gross features of a mechanism are the first to be known and then increasing attention is paid to finer details. The tendency is always to probe more deeply, to get more detailed descriptions.

Although for most reactions gross mechanisms can be written today with a good degree of assurance, no mechanism is known completely. There is much about the fine details that is still puzzling, and for some reactions even the gross mechanism is not yet clear. The problems involved are difficult because there are so many variables. Many examples are known where reactions proceed by different mechanisms under different conditions. In some cases, there are several proposed mechanisms, each of which completely explains all the data.

TYPES OF MECHANISM

In most reactions of organic compounds, one or more covalent bonds are broken. We can divide organic mechanisms into three basic types, depending on how the bonds break.

1. If a bond breaks in such a way that both electrons remain with one fragment, the mechanism is called *heterolytic*. Such reactions do not necessarily involve ionic intermediates, although they usually do. The important thing is that the electrons are never unpaired. For most reactions, it is convenient to call one reactant the *attacking reagent* and the other the *substrate*. In this book,

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Michael B. Smith and Jerry March

we will always designate as the substrate that molecule that supplies carbon to the new bond. When carbon–carbon bonds are formed, it is necessary to be arbitrary about which is the substrate and which is the attacking reagent. In heterolytic reactions, the reagent generally brings a pair of electrons to the substrate or takes a pair of electrons from it. A reagent that brings an electron pair is called a *nucleophile* and the reaction is *nucleophilic*. A reagent that takes an electron pair is called an *electrophile* and the reaction is *electrophilic*. In a reaction in which the substrate molecule becomes cleaved, part of it (the part not containing the carbon) is usually called the *leaving group*. A leaving group that carries away an electron pair is called a *nucleofuge*. If it comes away without the electron pair, it is called an *electrofuge*.

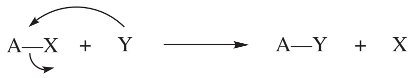
2. If a bond breaks in such a way that each fragment gets one electron, free radicals are formed and such reactions are said to take place by *homolytic* or *free-radical mechanisms*.
3. It would seem that all bonds must break in one of the two ways previously noted. But there is a third type of mechanism in which electrons (usually six, but sometimes some other number) move in a closed ring. There are no intermediates, ions or free radicals, and it is impossible to say whether the electrons are paired or unpaired. Reactions with this type of mechanism are called *pericyclic*.[1]

Examples of all three types of mechanisms are given in the next section.

TYPES OF REACTION

The number and range of organic reactions is so great as to seem bewildering, but actually almost all of them can be fitted into just six categories. In the description of the six types that follows, the immediate products are shown, although in many cases they then react with something else. All the species are shown without charges, since differently charged reactants can undergo analogous changes. The descriptions given here are purely formal and are for the purpose of classification and comparison. All are discussed in detail in Part 2 of this book.

1. *Substitutions*. If heterolytic, these can be classified as nucleophilic or electrophilic depending on which reactant is designated as the substrate and which as the attacking reagent (very often Y must first be formed by a previous bond cleavage).
   a. Nucleophilic substitution (Chapters 10, 13).



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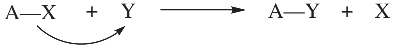
[1] For a classification of pericyclic reactions, see Hendrickson, J.B. *Angew. Chem. Int. Ed.* ***1974***, *13*, 47. Also see, Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***.

b. Electrophilic substitution (Chapters 11, 12).



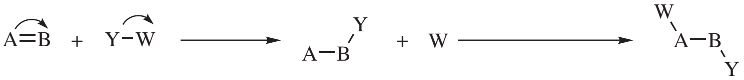
c. Free-radical substitution (Chapter 14).

$$A{-}X + Y\bullet \longrightarrow A{-}Y + X\bullet$$

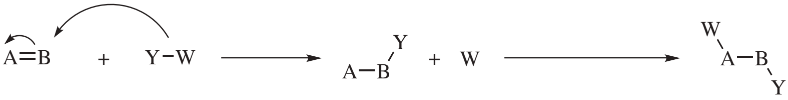
In free-radical substitution, Y• is usually produced by a previous free-radical cleavage, and X• goes on to react further.

2. *Additions to Double or Triple Bonds* (Chapters 15, 16). These reactions can take place by all three of the mechanistic possibilities.

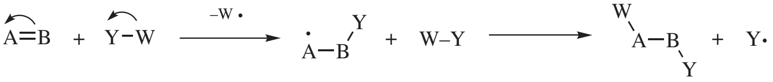
a. Electrophilic addition (heterolytic).



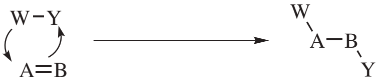
b. Nucleophilic addition (heterolytic).



c. Free-radical addition (homolytic).

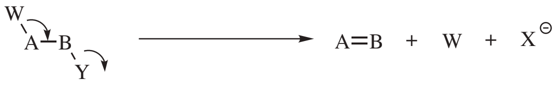


d. Simultaneous addition (pericyclic).



The examples show Y and W coming from the same molecule, but very often (except in simultaneous addition) they come from different molecules. Also, the examples show the Y—W bond cleaving at the same time that Y is bonding to B, but often (again except for simultaneous addition) this cleavage takes place earlier.

3. β *Elimination* (Chapter 17).



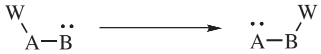
These reactions can take place by either heterolytic or pericyclic mechanisms. Examples of the latter are shown on p. $$$. Free-radical β eliminations are extremely rare. In heterolytic eliminations W and X may or may not leave simultaneously and may or may not combine.

4. *Rearrangement* (Chapter 18). Many rearrangements involve migration of an atom or group from one atom to another. There are three types, depending on how many electrons the migrating atom or group carries with it.

a. Migration with electron pair (nucleophilic).

b. Migration with one electron (free-radical).

c. Migration without electrons (electrophilic; rare).



The illustrations show 1,2 rearrangements, in which the migrating group moves to the adjacent atom. These are the most common, although longer rearrangements are also possible. There are also some rearrangements that do not involve simple migration at all (see Chapter 18). Some of the latter involve pericyclic mechanisms.

5. *Oxidation and Reduction* (Chapter 19). Many oxidation and reduction reactions fall naturally into one of the four types mentioned above, but many others do not. For a description of oxidation–reduction mechanistic types, see p. 1704.

6. *Combinations of the above.* Note that arrows are used to show movement of *electrons.* An arrow always follows the motion of electrons and never of a nucleus or anything else (it is understood that the rest of the molecule follows the electrons). Ordinary arrows (double-headed) follow electron pairs, while single-headed arrows follow unpaired electrons. Double-headed arrows are also used in pericyclic reactions for convenience, although in these reactions we do not really know how or in which direction the electrons are moving.

THERMODYNAMIC REQUIREMENTS FOR REACTION

In order for a reaction to take place spontaneously, the free energy of the products must be lower than the free energy of the reactants; that is, ΔG must be negative. Reactions can go the other way, of course, but only if free energy is added. Like water on the surface of the earth, which only flows downhill and never uphill (though it can be carried or pumped uphill), molecules seek the lowest possible potential energy. Free energy is made up of two components, enthalpy H and entropy S. These quantities are related by the equation

$$\Delta G = \Delta H - T\Delta S$$

The enthalpy change in a reaction is essentially the difference in bond energies (including resonance, strain, and solvation energies) between the reactants and the products. The enthalpy change can be calculated by totaling the bond energies of all the bonds broken, subtracting from this the total of the bond energies of all the bonds formed, and adding any changes in resonance, strain, or solvation energies. Entropy changes are quite different, and refer to the disorder or randomness of the system. The less order in a system, the greater the entropy. The preferred conditions in Nature are *low* enthalpy and *high* entropy, and in reacting systems, enthalpy spontaneously decreases while entropy spontaneously increases.

For many reactions entropy effects are small and it is the enthalpy that mainly determines whether the reaction can take place spontaneously. However, in certain types of reaction entropy is important and can dominate enthalpy. We will discuss several examples.

1. In general, liquids have lower entropies than gases, since the molecules of gas have much more freedom and randomness. Solids, of course, have still lower entropies. Any reaction in which the reactants are all liquids and one or more of the products is a gas is therefore thermodynamically favored by the increased entropy; the equilibrium constant for that reaction will be higher than it would otherwise be. Similarly, the entropy of a gaseous substance is higher than that of the same substance dissolved in a solvent.
2. In a reaction in which the number of product molecules is equal to the number of reactant molecules, for example, $A + B \rightarrow C + D$, entropy effects are usually small, but if the number of molecules is increased, for example, $A \rightarrow B + C$, there is a large gain in entropy because more arrangements in space are possible when more molecules are present. Reactions in which a molecule is cleaved into two or more parts are therefore thermodynamically favored by the entropy factor. Conversely, reactions in which the number of product molecules is less than the number of reactant molecules show entropy decreases, and in such cases there must be a sizable decrease in enthalpy to overcome the unfavorable entropy change.
3. Although reactions in which molecules are cleaved into two or more pieces have favorable entropy effects, many potential cleavages do not take place because of large increases in enthalpy. An example is cleavage of ethane into two methyl radicals. In this case, a bond of $\sim$79 kcal mol^{-1} (330 kJ mol^{-1}) is broken, and no new bond is formed to compensate for this enthalpy increase. However, ethane can be cleaved at very high temperatures, which illustrates the principle that *entropy becomes more important as the temperature increases*, as is obvious from the equation $\Delta G = \Delta H - T\Delta S$. The

enthalpy term is independent of temperature, while the entropy term is directly proportional to the absolute temperature.

4. An acyclic molecule has more entropy than a similar cyclic molecule because there are more conformations (cf. hexane and cyclohexane). Ring opening therefore means a gain in entropy and ring closing a loss.

KINETIC REQUIREMENTS FOR REACTION

Just because a reaction has a negative ΔG does not necessarily mean that it will take place in a reasonable period of time. A negative ΔG is a *necessary*, but not a *sufficient*, condition for a reaction to occur spontaneously. For example, the reaction between H_2 and O_2 to give H_2O has a large negative ΔG, but mixtures of H_2 and O_2 can be kept at room temperature for many centuries without reacting to any significant extent. In order for a reaction to take place, *free energy of activation* $\Delta G^{\ddagger}$ must be added.[2] This situation is illustrated in Fig. 6.1,[3] which is an energy

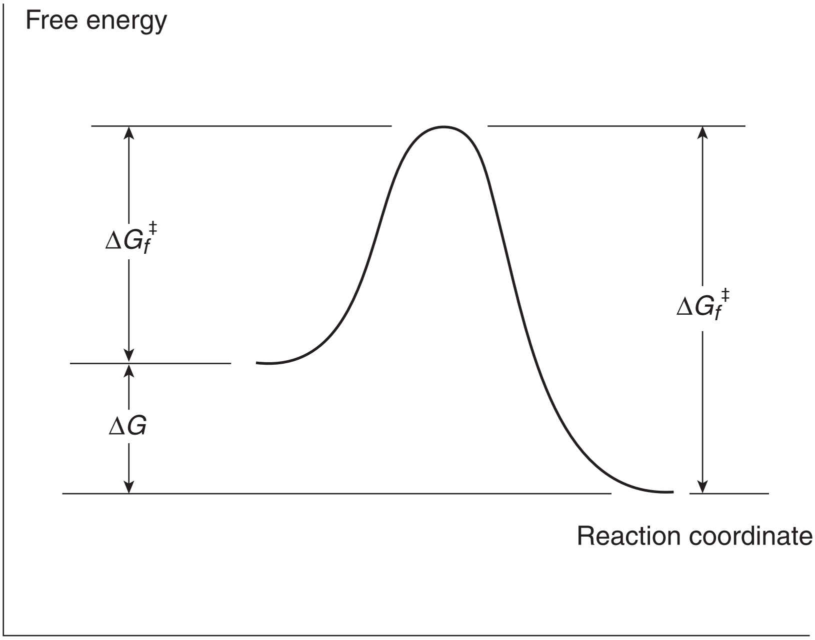


Fig. 6.1. Free-energy profile of a reaction without an intermediate where the products have a lower free energy than the reactants.

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[2] For mixtures of H_2 and O_2 this can be done by striking a match.

[3] Strictly speaking, this is an energy profile for a reaction of the type $XY + Z \rightarrow X + YZ$. However, it may be applied, in an approximate way, to other reactions.

profile for a one-step reaction without an intermediate. In this type of diagram, the horizontal axis (called the *reaction coordinate*)[4] signifies the progression of the reaction. The parameter $\Delta G_f^{\ddagger}$ is the free energy of activation for the forward reaction. If the reaction shown in Fig. 6.1 is reversible, must be $>\Delta G_f^{\ddagger}$, since it is the sum of ΔG and $\Delta G_f^{\ddagger}$.

When a reaction between two or more molecules has progressed to the point corresponding to the top of the curve, the term *transition state* is applied to the positions of the nuclei and electrons. The transition state possesses a definite geometry and charge distribution but has no finite existence; the system passes through it. The system at this point is called an *activated complex*.[5]

In the *transition-state theory*[6] the starting materials and the activated complex are taken to be in equilibrium, the equilibrium constant being designated $K^{\ddagger}$. According to the theory, all activated complexes go on to product at the same rate (which, although at first sight surprising, is not unreasonable, when we consider that they are all "falling downhill") so that the rate constant (see p. 315) of the reaction depends only on the position of the equilibrium between the starting materials and the activated complex, that is, on the value of $K^{\ddagger}$. The parameter $\Delta G^{\ddagger}$ is related to $K^{\ddagger}$ by

$$\Delta G^{\ddagger} = -2.3\ RT\ \log\ K^{\ddagger}$$

so that a higher value of $\Delta G^{\ddagger}$ is associated with a smaller rate constant. The rates of nearly all reactions increase with increasing temperature because the additional energy thus supplied helps the molecules to overcome the activation energy barrier.[7] Some reactions have no free energy of activation at all, meaning that $K^{\ddagger}$ is essentially infinite and that virtually all collisions lead to reaction. Such processes are said to be *diffusion-controlled*.[8]

Like ΔG, $\Delta G^{\ddagger}$ is made up of enthalpy and entropy components

$$\boldsymbol{\Delta G^{\ddagger} = \Delta H^{\ddagger} - \mathrm{T}\Delta S^{\ddagger}}$$

$\Delta H^{\ddagger}$, the *enthalpy of activation*, is the difference in bond energies, including strain, resonance, and solvation energies, between the starting compounds and the *transition state*. In many reactions, bonds have been broken or partially broken by the time the transition state is reached; the energy necessary for this is $\Delta H^{\ddagger}$. It is

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[4] For a review of reaction coordinates and structure–energy relationships, see Grunwald, E. *Prog. Phys. Org. Chem.* ***1990***, *17*, 55.

[5] For a discussion of transition states, see Laidler, K.J. *J. Chem. Educ.* ***1988***, *65*, 540.

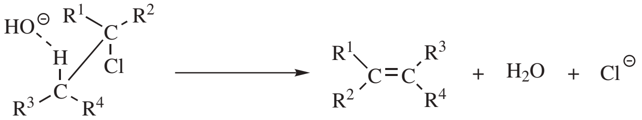
[6] For fuller discussions, see Kreevoy, M.M.; Truhlar, D.G. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 13–95; Moore, J.W.; Pearson, R.G. *Kinetics and Mechanism*, 3rd ed, Wiley, NY, ***1981***, pp. 137–181; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***; pp. 227–378.

[7] For a review concerning the origin and evolution of reaction barriers see Donahue, N.M. *Chem. Rev.* ***2003***, *103*, 4593.

[8] For a monograph on diffusion-controlled reactions, see Rice, S.A. *Comprehensive Chemical Kinetics*, Vol. 25 (edited by Bamford, C.H.; Tipper, C.F.H.; Compton, R.G.); Elsevier: NY, ***1985***.

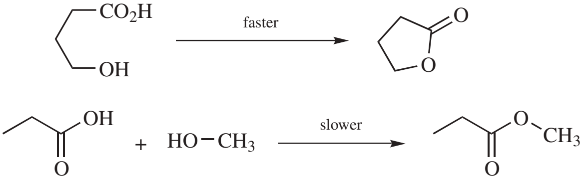
true that additional energy will be supplied by the formation of new bonds, but if this occurs after the transition state, it can affect only ΔH and not $\Delta H^{\ddagger}$.

Entropy of activation, $\Delta S^{\ddagger}$, which is the difference in entropy between the starting compounds and the transition state, becomes important when two reacting molecules must approach each other in a specific orientation in order for the reaction to take place. For example, the reaction between a simple noncyclic alkyl chloride and hydroxide ion to give an alkene (reaction **17-13**) takes place only if, in the transition state, the reactants are oriented as shown.



Not only must the $^{-}$OH be near the hydrogen, but the hydrogen must be oriented anti to the chlorine atom.[9] When the two reacting molecules collide, if the $^{-}$OH should be near the chlorine atom or near R^1 or R^2, no reaction can take place. In order for a reaction to occur, the molecules must surrender the freedom they normally have to assume many possible arrangements in space and adopt only that one that leads to reaction. Thus, a considerable loss in entropy is involved, that is, $\Delta S^{\ddagger}$ is negative.

Entropy of activation is also responsible for the difficulty in closing rings[10] larger then six membered. Consider a ring-closing reaction in which the two groups that must interact are situated on the ends of a 10-carbon chain. In order for reaction to take place, the groups must encounter each other. But a 10-carbon chain has many conformations, and in only a few of these are the ends of the chain near each other. Thus, forming the transition state requires a great loss of entropy.[11] This factor is also present, although less so, in closing rings of six members or less (except three-membered rings), but with rings of this size the



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[9] As we will see in Chapter 17, with some molecules elimination is also possible if the hydrogen is oriented syn, instead of anti, to the chlorine atom. Of course, this orientation also requires a considerable loss of entropy.

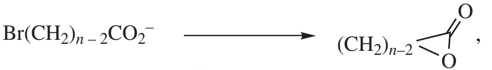
[10] For discussions of the entropy and enthalpy of ring-closing reactions, see De Tar, D.F.; Luthra, N.P. *J. Am. Chem. Soc.* ***1980***, *102*, 4505; Mandolini, L. *Bull. Soc. Chim. Fr.* ***1988***, 173. For a related discussion, see Menger, F.M. *Acc. Chem. Res.* ***1985***, *18*, 128.

[11] For reviews of the cyclization of acyclic molecules, see Nakagaki. R.; Sakuragi, H.; Mutai, K. *J. Phys. Org. Chem.* ***1989***, *2*, 187; Mandolini, L. *Adv. Phys. Org. Chem.* ***1986***, *22*, 1. For a review of the cyclization and conformation of hydrocarbon chains, see Winnik, M.A. *Chem. Rev.* ***1981***, *81*, 491. For a review of steric and electronic effects in heterolytic ring closures, see Valters, R. *Russ. Chem. Rev.* ***1982***, *51*, 788.

TABLE 6.1. Relative Rate Constants at 50°C.[a] The rate for an eight-membered ring = 1 for the reaction.

Ring Size	Relative Rate
3	21.7
4	5.4×10^3
5	1.5×10^6
6	1.7×10^4
7	97.3
8	1.00
9	1.12
10	3.35
11	8.51
12	10.6
13	32.2
14	41.9
15	45.1
16	52.0
18	51.2
23	60.4

[a] (Eight-membered ring = 1) for the reaction



where n = the ring size[12].

entropy loss is less than that of bringing two individual molecules together. For example, a reaction between an OH group and a COOH group in the same molecule to form a lactone with a five- or six-membered ring takes place much faster than the same reaction between a molecule containing an OH group and another containing a COOH group. although $\Delta H^\ddagger$ is about the same, $\Delta S^\ddagger$ is much less for the cyclic case. However, if the ring to be closed has three or four members, small-angle strain is introduced and the favorable $\Delta S^\ddagger$ may not be sufficient to overcome the unfavorable $\Delta H^\ddagger$ change. Table 6.1 shows the relative rate constants for the closing of rings of 3–23 members all by the same reaction.[12] Reactions in which the transition state has more disorder than the starring compounds, for example, the pyrolytic conversion of cyclopropane to propene, have positive $\Delta S^\ddagger$ values and are thus favored by the entropy effect.

Reactions with intermediates are two-step (or more) processes. In these reactions there is an energy "well." There are two transition states, each with an energy higher than the intermediate (Fig. 6.2). The deeper the well, the more stable the intermediate. In Fig. 6.2*a*, the second peak is higher than the first. The opposite situation

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[12] The values for ring sizes 4, 5, and 6 are from Mandolini, L. *J. Am. Chem. Soc.* ***1978***, *100*, 550; the others are from Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* ***1977***, *99*, 2591. See also, Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* ***1981***, *14*, 95. See, however, van der Kerk, S.M.; Verhoeven, J.W.; Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1355; Benedetti, F.; Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 605.

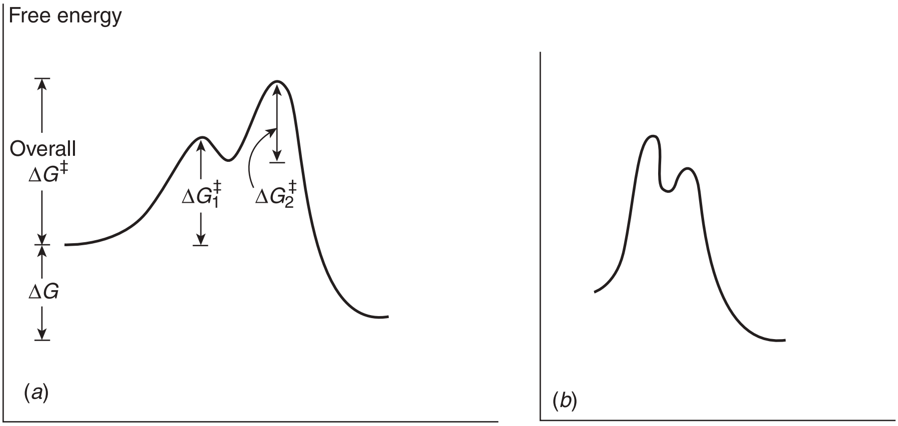

Fig. 6.2. (*a*) Free-energy profile for a reaction with an intermediate $\Delta G_1^\ddagger$ and $\Delta G_2^\ddagger$ are the free energy of activation for the first and second stages, respectively. (*b*) Free-energy profile for a reaction with an intermediate in which the first peak is higher than the second.

is shown in Fig. 6.2*b*. Note that in reactions in which the second peak is higher than the first, the overall $\Delta G^\ddagger$ is less than the sum of the $\Delta G^\ddagger$ values for the two steps. Minima in free-energy-profile diagrams (*intermediates*) correspond to real species, which have a finite although usually short existence. These may be the carbocations, carbanions, free radicals, etc., discussed in Chapter 5 or molecules in which all the atoms have their normal valences. In either case, under the reaction conditions they do not live long (because $\Delta G_2^\ddagger$ is small), but rapidly go on to products. Maxima in these curves, however, do not correspond to actual species but only to transition states in which bond breaking and/or bond making have partially taken place. Transition states have only a transient existence with an essentially zero lifetime.[13]

THE BALDWIN RULES FOR RING CLOSURE[14]

In previous sections, we discussed, in a general way, the kinetic and thermodynamic aspects of ring-closure reactions. J. E. Baldwin has supplied a more specific set of rules for certain closings of three- to seven-membered rings.[15] These rules

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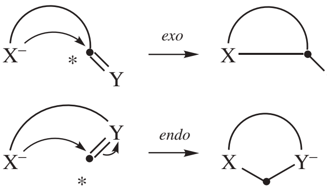
[13] Despite their transient existences, it is possible to study transition states of certain reactions in the gas phase with a technique called laser femtochemistry: Zewall, A.H.; Bernstein, R.B. *Chem. Eng. News* ***1988***, *66*, No. 45 (Nov. 7), 24–43. For another method, see Collings, B.A.; Polanyi, J.C.; Smith, M.A.; Stolow, A.; Tarr, A.W. *Phys. Rev. Lett.* ***1987***, *59*, 2551.

[14] See Smith, M.B. *Organic Synthesis,* 2nd ed., McGraw-Hill, NY, ***2001***, pp. 517–523.

[15] Baldwin, J.E. *J. Chem. Soc. Chem. Commun.* ***1976***, 734; Baldwin, J.E., in *Further Perspectives in Organic Chemistry* (*Ciba Foundation Symposium 53*), Elsevier North Holland, Amsterdam, The Netherlands, ***1979***, pp. 85–99. See also, Baldwin, J.E.; Thomas, R.C.; Kruse, L.I.; Silberman, L. *J. Org. Chem.* ***1977***, *42*, 3846; Baldwin, J.E.; Lusch, M.J. *Tetrahedron* ***1982***, *38*, 2939; Anselme, J. *Tetrahedron Lett.* ***1977***, 3615; Fountain, K.R.; Gerhardt, G. *Tetrahedron Lett.* ***1978***, 3985.

distinguish two types of ring closure, called Exo and Endo, and three kinds of atoms at the starred positions: *Tet* for sp^3, *Trig* for sp^2, and *Dig* for *sp*. The following are Baldwin's rules for closing rings of three to seven members.



Rule 1. Tetrahedral systems
  (a) 3–7-*Exo–Tet* are all favored processes
  (b) 5–6-*Endo–Tet* are disfavored

Rule 2. Trigonal systems
  (a) 3–7-*Exo–Trig* are favored
  (b) 3–5-*Endo–Trig* are disfavored[16]
  (c) 6–7-*Endo–Trig* are favored

Rule 3. Digonal systems
  (a) 3–4-*Exo–Dig* are disfavored
  (b) 5–7-*Exo–Dig* are favored
  (c) 3–7-*Endo–Dig* are favored

"Disfavored" does not mean it cannot be done: only that it is more difficult than the favored cases. These rules are empirical and have a stereochemical basis. The favored pathways are those in which the length and nature of the linking chain enables the terminal atoms to achieve the proper geometries for reaction. The disfavored cases require severe distortion of bond angles and distances. Many cases in the literature are in substantial accord with these rules, and they important in the formation of five- and six-membered rings.[17]

Although Baldwin's rules can be applied to ketone enolates,[18] additional rules were added to make the terminology more specific.[19] The orientation of the orbital as it approaches the reactive center must be considered for determining

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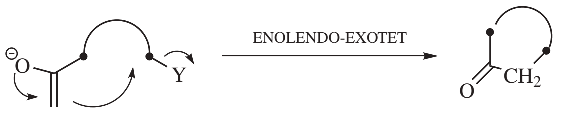
[16] For some exceptions to the rule in this case, see Trost, B.M.; Bonk, P.J. *J. Am. Chem. Soc.* ***1985***, *107*, 1778; Auvray, P.; Knochel, P.; Normant, J.F. *Tetrahedron Lett.* ***1985***, *26*, 4455; Torres, L.E.; Larson, G.L. *Tetrahedron Lett.* ***1986***, *27*, 2223.

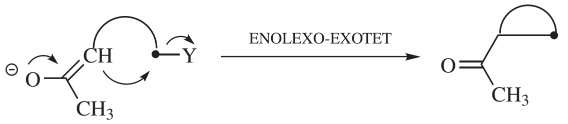
[17] Johnson, C.D. *Acc. Chem. Res.* ***1997***, *26*, 476.

[18] Baldwin, J.E.; Kruse, L.I. *J. Chem. Soc. Chem. Commun.* ***1977***, 233.

[19] Baldwin, J.E.; Lusch, M.J. *Tetrahedron* ***1982***, *38*, 2939.

the correct angle of approach. Diagrams that illustrate the enolate rules are

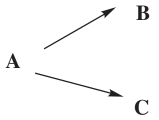




The rules are

(a) 6–7 enolendo–exo–tet reactions are favored.
(b) 3–5 enolendo–exo–tet reactions are disfavored.
(c) 3–7 enolexo–exo–tet reactions are favored.
(d) 3–7 enolexo–exo–trig reactions are favored.
(e) 6–7 enolendo–exo–trig reactions are favored.
(f) 3–5 enolendo–exo–trig reactions are disfavored.

KINETIC AND THERMODYNAMIC CONTROL



There are many cases in which a compound under a given set of reaction conditions can undergo competing reactions to give different products:

Figure 6.3 shows a free-energy profile for a reaction in which **B** is thermodynamically more stable than **C** (ΔG_B is $> \Delta G_C$), but **C** is formed faster (lower $\Delta G^\ddagger$). If neither reaction is reversible, **C** will be formed in larger amount because it is formed faster. The product is said to be *kinetically controlled*. However, if the reactions are reversible, this will not necessarily be the case. If such a process is stopped well before the equilibrium has been established, the reaction will be kinetically controlled since more of the faster-formed product will be present.

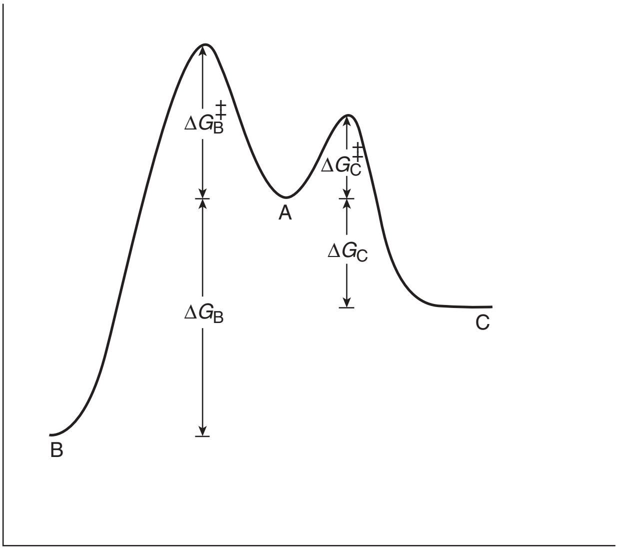


Fig. 6.3. Free-energy profile illustrating kinetic versus thermodynamic control of products. The starting compounds (**A**) can react to give either **B** or **C**.

However, if the reaction is permitted to approach equilibrium, the predominant or even exclusive product will be **B.** Under these conditions the **C** that is first formed reverts to **A**, while the more stable **B** does so much less. We say the product is *thermodynamically controlled.*[20] Of course, Fig. 6.3 does not describe all reactions in which a compound **A** can give two different products. In many cases the more stable product is also the one that is formed faster. In such cases, the product of kinetic control is also the product of thermodynamic control.

THE HAMMOND POSTULATE

Since transition states have zero lifetimes, it is impossible to observe them directly and information about their geometries must be obtained from inference. In some cases our inferences can be very strong. For example, in the S_N2 reaction (p. 426) between CH_3I and I^- (a reaction in which the product is identical to the starting compound), the transition state should be perfectly symmetrical. In most cases, however, we cannot reach such easy conclusions, and we are greatly aided by the *Hammond postulate*,[21] which states that for any single reaction step, *the geometry of the transition state for that step resembles the side to which it is closer*

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[20] For a discussion of thermodynamic versus kinetic control, see Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 36–89.

[21] Hammond, G.S. *J. Am. Chem. Soc.* ***1955***, *77*, 334. For a discussion, see Fărcaşiu, D. *J. Chem. Educ.* ***1975***, *52*, 76.

in free energy. Thus, for an exothermic reaction like that shown in Fig. 6.1, the transition state resembles the reactants more than the products, although not much more because there is a substantial $\Delta G^{\ddagger}$ on both sides. The postulate is most useful in dealing with reactions with intermediates. In the reaction illustrated in Fig. 6.2*a*, the first transition state lies much closer in energy to the intermediate than to the reactants, and we can predict that the geometry of the transition state resembles that of the intermediate more than it does that of the reactants. Likewise, the second transition state also has a free energy much closer to that of the intermediate than to the products, so that both transition states resemble the intermediate more than they do the products or reactants. This is generally the case in reactions that involve very reactive intermediates. Since we usually know more about the structure of intermediates than of transition states, we often use our knowledge of intermediates to draw conclusions about the transition states (e.g., see pp. 479, 1019).

MICROSCOPIC REVERSIBILITY

In the course of a reaction, the nuclei and electrons assume positions that at each point correspond to the lowest free energies possible. If the reaction is reversible, these positions must be the same in the reverse process, too. This means that the forward and reverse reactions (run under the same conditions) must proceed by the same mechanism. This is called the *principle of microscopic reversibility*. For example, if in a reaction **A** → **B** there is an intermediate **C**, then **C** must also be an intermediate in the reaction **B** → **A**. This is a useful principle since it enables us to know the mechanism of reactions in which the equilibrium lies far over to one side. Reversible photochemical reactions are an exception, since a molecule that has been excited photochemically does not have to lose its energy in the same way (Chapter 7).

MARCUS THEORY

It is often useful to compare the reactivity of one compound with that of similar compounds. What we would like to do is to find out how a reaction coordinate (and in particular the transition state) changes when one reactant molecule is replaced by a similar molecule. Marcus theory is a method for doing this.[22]

In this theory, the activation energy $\Delta G^{\ddagger}$ is thought of as consisting of two parts.

1. An *intrinsic* free energy of activation, which would exist if the reactants and products had the same ΔG°.[23] This is a kinetic part, called the *intrinsic barrier* $\Delta G^{\ddagger}_{\text{int}}$
2. A thermodynamic part, which arises from the ΔG° for the reaction.

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[22] For reviews, see Albery, W.J. *Annu. Rev. Phys. Chem.* ***1980***, *31*, 227; Kreevoy, M.M.; Truhlar, D.G., in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 13–95.

[23] The parameter ΔG° is the standard free energy; that is, ΔG at atmospheric pressure.

The Marcus equation says that the overall $\Delta G^\ddagger$ for a one-step reaction is[24]

$$\Delta G^\ddagger = \Delta G^\ddagger_{\text{int}} + \frac{1}{2}\Delta G^\Delta + \frac{(\Delta G^\Delta)^2}{16(\Delta G^\ddagger_{\text{int}} - w^{\text{R}})}$$

where the term ΔG^Δ stands for

$$\Delta G^\Delta = \Delta G^\circ - w^{\text{R}} + w^{\text{P}}$$

w^{R}, a work term, is the free energy required to bring the reactants together and w^{P} is the work required to form the successor configuration from the products.

For a reaction of the type $\text{AX} + \text{B} \rightarrow \text{BX}$, the intrinsic barrier[25] $\Delta G^\ddagger_{\text{int}}$ is taken to be the average $\Delta G^\ddagger$ for the two symmetrical reactions

$$\text{AX} + \text{A} \longrightarrow \text{AX} + \text{A} \qquad \Delta G^\ddagger_{\text{A,A}}$$

$$\text{BX} + \text{B} \longrightarrow \text{BX} + \text{B} \qquad \Delta G^\ddagger_{\text{B,B}}$$

so that

$$\Delta G^\ddagger_{\text{int}} + \frac{1}{2}(\Delta G^\ddagger_{\text{A,A}} + \Delta G^\ddagger_{\text{B,B}})$$

One type of process that can successfully be treated by the Marcus equation is the $\text{S}_\text{N}2$ mechanism (p. 426)

$$\text{R—X} + \text{Y} \longrightarrow \text{R—Y} + \text{X}$$

When R is CH_3 the process is called *methyl transfer.*[26] For such reactions, the work terms w^{R} and w^{P} are assumed to be very small compared to ΔG°, and can be neglected, so that the Marcus equation simplifies to

$$\Delta G^\ddagger = \Delta G^\ddagger_{\text{int}} + \frac{1}{2}\Delta G^\circ + \frac{(\Delta G)^2}{16\Delta G^\ddagger_{\text{int}}}$$

The Marcus equation allows $\Delta G^\ddagger$ for $\text{RX} + \text{Y} \rightarrow \text{RY} + \text{X}$ to be calculated from the barriers of the two symmetrical reactions $\text{RX} + \text{X} \rightarrow \text{RX} + \text{X}$ and

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[24] Albery, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1978****, 16*, 87, pp. 98–99.

[25] For discussions of intrinsic barriers, see Lee, I. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 943, *Chem. Soc. Rev.* ***1990***, *19*, 133.

[26] For a review of Marcus theory applied to methyl transfer, see Albery, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1978***, *16*, 87. See also, Lee, I. *J. Chem. Soc., Perkin Trans. 2* ***1989***, 943; Lewis, E.S.; Kukes, S.; Slater, C.D. *J. Am. Chem. Soc.* ***1980***, *102*, 1619; Lewis, E.S.; Hu, D.D. *J. Am. Chem. Soc.* ***1984***, *106*, 3292; Lewis, E.S.; McLaughlin, M.L.; Douglas, T.A. *J. Am. Chem. Soc.* ***1985***, *107*, 6668; Lewis, E.S. *Bull. Soc. Chim. Fr.* ***1988***, 259.

RY + Y → RY + Y. The results of such calculations are generally in agreement with the Hammond postulate.

Marcus theory can be applied to any single-step process where something is transferred from one particle to another. It was originally derived for electron transfers,[27] and then extended to transfers of H^+ (see p. 372),

H^-,[28] and H•,[29] as well as methyl transfers.

METHODS OF DETERMINING MECHANISMS

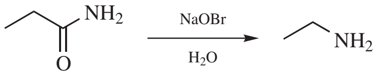
There are a number of commonly used methods for determining mechanisms.[30] In most cases, one method is not sufficient, and the problem is generally approached from several directions.

Identification of Products

Obviously, any mechanism proposed for a reaction must account for all the products obtained and for their relative proportions, including products formed by side reactions. Incorrect mechanisms for the von Richter reaction (reaction **13-30**) were accepted for many years because it was not realized that nitrogen was a major product. A proposed mechanism cannot be correct if it fails to predict the products in approximately the observed proportions. For example, any mechanism for the reaction

$$CH_4 + Cl_2 \xrightarrow{h\nu} CH_3Cl$$

that fails to account for the formation of a small amount of ethane cannot be correct (see **14-1**), and any mechanism proposed for the Hofmann rearrangement (**18-13**):



must account for the fact that the missing carbon appears as CO_2.

Determination of the Presence of an Intermediate

Intermediates are postulated in many mechanisms. There are several ways, none of them foolproof,[31] for attempting to learn whether or not an intermediate is present and, if so, its structure.

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[27] Marcus, R.A. *J. Phys. Chem.* ***1963***, *67*, 853, *Annu. Rev. Phys. Chem.* ***1964***, *15*, 155; Eberson, L. *Electron Transfer Reactions in Organic Chemistry*; Springer: NY, ***1987***.

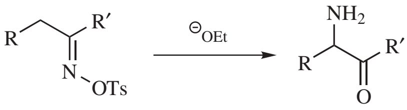
[28] Kim, D.; Lee, I.H.; Kreevoy, M.M. *J. Am. Chem. Soc.* ***1990***, *112*, 1889, and references cited therein.

[29] See, for example, Dneprovskii, A.S.; Eliseenkov, E.V. *J. Org. Chem. USSR* ***1988***, *24*, 243.

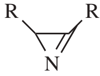
[30] For a treatise on this subject, see Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), 2 pts., Wiley, NY, ***1986***. For a monograph, see Carpenter, B.K. *Determination of Organic Reaction Mechanisms*, Wiley, NY, ***1984***.

[31] For a discussion, see Martin, R.B. *J. Chem. Educ.* ***1985***, *62*, 789.

1. *Isolation of an Intermediate*. It is sometimes possible to isolate an intermediate from a reaction mixture by stopping the reaction after a short time or by the use of very mild conditions. For example, in the Neber rearrangement (reaction **18-12**)

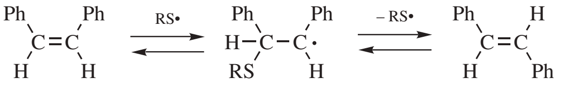


the intermediate **1** (an azirene)[32] has been isolated. If it can be shown that the isolated compound gives the same product when subjected to the reaction conditions and at a rate no slower than the starting compound, this constitutes strong evidence that the reaction involves that intermediate, although it is not conclusive, since the compound may arise by an alternate path and by coincidence give the same product.



1

2. *Detection of an intermediate*. In many cases, an intermediate cannot be isolated, but can be detected by IR, NMR, or other spectra.[33] The detection by Raman spectra of NO_2^+ was regarded as strong evidence that this is an intermediate in the nitration of benzene (see **11-2**). Free radical and triplet intermediates can often be detected by esr and by CIDNP (see Chapter 5). Free radicals (as well as radical ions and EDA complexes) can also be detected by a method that does not rely on spectra. In this method, a double-bond compound is added to the reaction mixture, and its fate traced.[34] One possible result is cis–trans conversion. For example, *cis*-stilbene is isomerized to the trans isomer in the presence of RS• radicals, by this mechanism:



cis-Stilbene

trans-Stilbene

Since the trans isomer is more stable than the cis, the reaction does not go the other way, and the detection of the isomerized product is evidence for the presence of the RS• radicals.

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[32] See Gentilucci, L.; Grijzen, Y.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* ***1995***, *36*, 4665 for the synthesis of an azirene derivative.

[33] For a review on the use of electrochemical methods to detect intermediates, see Parker, V.D. *Adv. Phys. Org. Chem.* ***1983***, *19*, 131. For a review of the study of intermediates trapped in matrixes, see Sheridan, R.S. *Org. Photochem.* ***1987***, *8*, 159.

[34] For a review, see Todres, Z.V. *Tetrahedron* ***1987***, *43*, 3839.

3. *Trapping of an Intermediate.* In some cases, the suspected intermediate is known to be one that reacts in a given way with a certain compound. The intermediate can then be trapped by running the reaction in the presence of that compound. For example, benzynes (p. 859) react with dienes in the Diels–Alder reaction (reaction **15-60**). In any reaction where a benzyne is a suspected intermediate, the addition of a diene and the detection of the Diels–Alder adduct indicate that the benzyne was probably present.
4. *Addition of a Suspected Intermediate.* If a certain intermediate is suspected, and if it can be obtained by other means, then under the same reaction conditions it should give the same products. This kind of experiment can provide conclusive negative evidence: if the correct products are not obtained, the suspected compound is not an intermediate. However, if the correct products are obtained, this is not conclusive since they may arise by coincidence. The von Richter reaction (reaction **13-30**) provides us with a good example here too. For many years, it had been assumed that an aryl cyanide was an intermediate, since cyanides are easily hydrolyzed to carboxylic acids (**16-4**). In fact, in 1954, *p*-chlorobenzonitrile was shown to give *p*-chlorobenzoic acid under normal von Richter conditions.[35] However, when the experiment was repeated with 1-cyanonaphthalene, no 1-naphthoic acid was obtained, although 2-nitronaphthalene gave 13% 1-naphthoic acid under the same conditions.[36] This proved that 2-nitronaphthalene must have been converted to 1-naphthoic acid by a route that does not involve 1-cyanonaphthalene. It also showed that even the conclusion that *p*-chlorobenzonitrile was an intermediate in the conversion of *m*-nitrochlorobenzene to *p*-chlorobenzoic acid must now be suspect, since it is not likely that the mechanism would substantially change in going from the naphthalene to the benzene system.

The Study of Catalysis[37]

Much information about the mechanism of a reaction can be obtained from a knowledge of which substances catalyze the reaction, which inhibit it, and which do neither. Of course, just as a mechanism must be compatible with the products, so must it be compatible with its catalysts. In general, catalysts perform their actions by providing an alternate pathway for the reaction in which $\Delta G^{\ddagger}$ is less than it would be without the catalyst. Catalysts do not change ΔG.

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[35] Bunnett, J.F.; Rauhut, M.M.; Knutson, D.; Bussell, G.E. *J. Am. Chem. Soc.* ***1954***, *76*, 5755.

[36] Bunnett, J.F.; Rauhut, M.M. *J. Org. Chem.* ***1956***, *21*, 944.

[37] For treatises, see Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***; Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley, NY, ***1971***. For reviews, see Coenen, J.W.E. *Recl. Trav. Chim. Pays-Bas* ***1983***, *102*, 57; and in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, the articles by Keeffe, J.R.; Kresge, A.J. pp. 747–790; Haller, G.L.; Delgass, W.N. pp. 951–979.

Isotopic Labeling[38]

Much useful information has been obtained by using molecules that have been isotopically labeled and tracing the path of the reaction in that way. For example, in the reaction

$$R\overset{*}{C}OO \;+\; BrCN \longrightarrow R\overset{*}{C}N$$

does the CN group in the product come from the CN in the BrCN? The use of ^{14}C supplied the answer, since $R^{14}CO_2^-$ gave *radioactive* RCN.[39] This surprising result saved a lot of labor, since it ruled out a mechanism involving the replacement of CO_2 by CN (see reaction **16-94**). Other radioactive isotopes are also frequently used as tracers, but even stable isotopes can be used. An example is the hydrolysis of esters

Which bond of the ester is broken, the acyl–O or the alkyl–O bond? The answer is found by the use of $H_2^{18}O$. If the acyl–O bond breaks, the labeled oxygen will appear in the acid; otherwise it will be in the alcohol (see **16-59**). Although neither compound is radioactive, the one that contains ^{18}O can be determined by submitting both to mass spectrometry. In a similar way, deuterium can be used as a label for hydrogen. In this case, it is not necessary to use mass spectrometry, since ir and nmr spectra can be used to determine when deuterium has been substituted for hydrogen. Carbon-13 NMR is also nonradioactive: It can be detected by ^{13}C NMR.[40]

In the labeling technique, it is not generally necessary to use completely labeled compounds. Partially labeled material is usually sufficient.

Stereochemical Evidence[41]

If the products of a reaction are capable of existing in more than one stereoisomeric form, the form that is obtained may give information about the mechanism. For example, (+)-malic acid was discovered by Walden[42] to give (−)-chlorosuccinic acid when treated with PCl_5 and the (+) enantiomer when treated with $SOCl_2$,

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[38] For reviews see Wentrup, C., in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 613–661; Collins, C.J. *Adv. Phys. Org. Chem.* ***1964***, *2*, 3. See also, the series *Isotopes in Organic Chemistry.*

[39] Douglas, D.E.; Burditt, A.M. *Can. J. Chem.* ***1958***, *36*, 1256.

[40] For a review, see Hinton, J.; Oka, M.; Fry, A. *Isot. Org. Chem.* ***1977***, *3*, 41.

[41] For lengthy treatments of the relationship between stereochemistry and mechanism, see Billups, W.E.; Houk, K.N.; Stevens, R.V., in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 663–746; Eliel, E.L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: NY, ***1962***; Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***.

[42] Walden, P. *Ber.* ***1896***, *29*, 136; ***1897***, *30*, 3149; ***1899***, *32*, 1833.

showing that the mechanisms of these apparently similar conversions could not be the same (see pp. 427, 469). Much useful information has been obtained about nucleophilic substitution, elimination, rearrangement, and addition reactions from this type of experiment. The isomers involved need not be enantiomers. Thus, the fact that *cis*-2-butene treated with $KMnO_4$ gives *meso*-2,3-butanediol and not the racemic mixture is evidence that the two OH groups attack the double bond from the same side (see reaction **15-48**).

Kinetic Evidence[43]

The rate of a homogeneous reaction[44] is the rate of disappearance of a reactant or appearance of a product. The rate nearly always changes with time, since it is usually proportional to concentration and the concentration of reactants decreases with time. However, the rate is not always proportional to the concentration of all reactants. In some cases, a change in the concentration of a reactant produces no change at all in the rate, while in other cases the rate may be proportional to the concentration of a substance (a catalyst) that does not even appear in the stoichiometric equation. A study of which reactants affect the rate often tells a good deal about the mechanism.

If the rate is proportional to the change in concentration of only one reactant (**A**), the *rate law* (the rate of change of concentration of **A** with time *t*) is

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}]$$

where k is the *rate constant* for the reaction.[45] There is a minus sign because the concentration of **A** decreases with time. A reaction that follows such a rate law is called a *first-order reaction*. The units of k for a first-order reaction are s^{-1}. The rate of a *second-order reaction* is proportional to the concentration of two reactants, or to the square of the concentration of one:

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}][\mathbf{B}] \qquad \text{or} \qquad \text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}]^2$$

For a second-order reaction the units are $L\ mol^{-1}\ s^{-1}$ or some other units expressing the reciprocal of concentration or pressure per unit time interval.

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[43] For the use of kinetics in determining mechanisms, see Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics*, Wiley, NY, ***1984***; Drenth, W.; Kwart, H. *Kinetics Applied to Organic Reactions*, Marcel Dekker, NY, ***1980***; Hammett, L.P. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: NY, ***1970***, pp. 53–100; Gardiner, Jr., W.C. *Rates and Mechanisms of Chemical Reactions*, W.A. Benjamin, NY, ***1969***; Leffler, J.E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*, Wiley, NY, ***1963***; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***, pp. 555–614; Refs. 6 and 26

[44] A homogeneous reaction occurs in one phase. Heterogeneous kinetics have been studied much less.

[45] Colins, C.C.; Cronin, M.F.; Moynihan, H.A.; McCarthy, D.G. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 1267 for the use of Marcus theory to predict rate constants in organic reactions.

Similar expressions can be written for third-order reactions. A reaction whose rate is proportional to [**A**] and to [**B**] is said to be first order in **A** and in **B**, second order overall. A reaction rate can be measured in terms of any reactant or product, but the rates so determined are not necessarily the same. For example, if the stoichiometry of a reaction is $2\mathbf{A} + \mathbf{B} \rightarrow \mathbf{C} + \mathbf{D}$ then, on a molar basis, **A** must disappear twice as fast as **B**, so that $-d[\mathbf{A}]/dt$ and $-d[\mathbf{B}]/dt$ are not equal, but the former is twice as large as the latter.

The rate law of a reaction is an experimentally determined fact. From this fact, we attempt to learn the *molecularity*, which may be defined as the number of molecules that come together to form the activated complex. It is obvious that if we know how many (and which) molecules take part in the activated complex, we know a good deal about the mechanism. The experimentally determined rate order is not necessarily the same as the molecularity. Any reaction, no matter how many steps are involved, has only one rate law, but each step of the mechanism has its own molecularity. For reactions that take place in one step (reactions without an intermediate) the order is the same as the molecularity. A first-order, one-step reaction is always unimolecular; a one-step reaction that is second order in **A** always involves two molecules of **A**; if it is first order in **A** and in **B**, then a molecule of **A** reacts with one of **B**, and so on. For reactions that take place in more than one step, the order *for each step* is the same as the molecularity *for that step*. This fact enables us to predict the rate law for any proposed mechanism, although the calculations may get lengthy at times.[46] If any one step of a mechanism is considerably slower than all the others (this is usually the case), the rate of the overall reaction is essentially the same as that of the slow step, which is consequently called the *rate-determining* step.[47]

For reactions that take place in two or more steps, two broad cases can be distinguished:

1. The first step is slower than any subsequent step and is consequently rate determining. In such cases, the rate law simply includes the reactants that participate in the slow step. For example, if the reaction $\mathbf{A} + 2\mathbf{B} \rightarrow \mathbf{C}$ has the mechanism

$$\mathbf{A} + \mathbf{B} \xrightarrow{\text{slow}} \mathbf{I}$$

$$\mathbf{I} + \mathbf{B} \xrightarrow{\text{fast}} \mathbf{C}$$

where I is an intermediate, the reaction is second order, with the rate law

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}][\mathbf{B}]$$

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[46] For a discussion of how order is related to molecularity in many complex situations, see Szabó, Z.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 2; Elsevier: NY, ***1969***, pp. 1–80.

[47] Many chemists prefer to use the term *rate-limiting step or rate-controlling step* for the slow step, rather than *rate-determining step*. See the definitions, in Gold, V.; Loening, K.L.; McNaught, A.D.; Sehmi, P. *IUPAC Compedium of Chemical Terminology;* Blackwell Scientific Publications: Oxford, ***1987***, p. 337. For a discussion of rate-determining steps, see Laidler, K.J. *J. Chem. Educ.* ***1988***, *65*, 250.

2. When the first step is not rate determining, determination of the rate law is usually much more complicated. For example, consider the mechanism

$$\mathbf{A} + \mathbf{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{I}$$

$$\mathbf{I} + \mathbf{B} \xrightarrow{k_2} \mathbf{C}$$

where the first step is a rapid attainment of equilibrium, followed by a slow reaction to give **C**. The rate of disappearance of **A** is

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k_1[\mathbf{A}][\mathbf{B}] - k_{-1}[\mathbf{I}]$$

Both terms must be included because **A** is being formed by the reverse reaction as well as being used up by the forward reaction. This equation is of very little help as it stands since we cannot measure the concentration of the intermediate. However, the combined rate law for the formation and disappearance of **I** is

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k_1[\mathbf{A}][\mathbf{B}] - k_{-1}[\mathbf{I}] - k_2[\mathbf{I}][\mathbf{B}]$$

At first glance, we seem no better off with this equation, but we can make the assumption that *the concentration of **I** does not change with time*, since it is an intermediate that is used up (going either to **A** + **B** or to **C**) as fast as it is formed. This assumption, called the assumption of the *steady state*,[48] enables us to set $d[\mathbf{I}]/dt$ equal to zero and hence to solve for [**I**] in terms of the measurable quantities [**A**] and [**B**]:

$$[\mathbf{I}] = \frac{k_1[\mathbf{A}][\mathbf{B}]}{k_2[\mathbf{B}] + k_{-1}}$$

We now insert this value for [**I**] into the original rate expression to obtain

$$\frac{-d[\mathbf{A}]}{dt} = \frac{k_1 k_2[\mathbf{A}][\mathbf{B}]^2}{k_2[\mathbf{B}] + k_{-1}}$$

Note that this rate law is valid whatever the values of k_1, k_{-1}, and k_2. However, our original hypothesis was that the first step was faster than the second, or that

$$k_1[\mathbf{A}][\mathbf{B}] \gg k_2[\mathbf{I}][\mathbf{B}]$$

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[48] For a discussion, see Raines, R.T.; Hansen, D.E. *J. Chem. Educ.* ***1988***, *65*, 757.

Since the first step is an equilibrium

$$k_1[\mathbf{A}][\mathbf{B}] = k_{-1}[\mathbf{I}]$$

we have

$$k_{-1}[\mathbf{I}] \gg k_2[\mathbf{I}][\mathbf{B}]$$

Canceling [**I**], we get

$$k_{-1} \gg k_2[\mathbf{B}]$$

We may thus neglect $k_2[\mathbf{B}]$ in comparison with k_{-1} and obtain

$$\frac{-d[\mathbf{A}]}{dt} = \frac{k_1 k_2}{k_{-1}}[\mathbf{A}][\mathbf{B}]^2$$

The overall rate is thus third order: first order in **A** and second order in **B**. Incidentally, if the first step is rate determining (as was the case in the preceding paragraph), then

$$k_2[\mathbf{B}] \gg k_{-1} \qquad \text{and} \qquad \frac{-d[\mathbf{A}]}{dt} = k_1[\mathbf{A}][\mathbf{B}]$$

which is the same rate law we deduced from the rule that where the first step is rate determining, the rate law includes the reactants that participate in that step.

It is possible for a reaction to involve **A** and **B** in the rate-determining step, although only [**A**] appears in the rate law. This occurs when a large excess of **B** is present, say 100 times the molar quantity of **A**. In this case, the complete reaction of **A** uses up only 1 equivalent of **B**, leaving 99 equivalents. It is not easy to measure the change in concentration of **B** with time in such a case, and it is seldom attempted, especially when **B** is also the solvent. Since [**B**], for practical purposes, does not change with time, the reaction appears to be first order in **A** although actually both **A** and **B** are involved in the rate-determining step. This is often referred to as a *pseudo-first-order* reaction. Pseudo-order reactions can also come about when one reactant is a catalyst whose concentration does not change with time because it is replenished as fast as it is used up and when a reaction is conducted in a medium that keeps the concentration of a reactant constant, for example, in a buffer solution where H^+ or ^-OH is a reactant. Pseudo-first-order conditions are frequently used in kinetic investigations for convenience in experimentation and calculations.

What is actually being measured is the change in concentration of a product or a reactant with time. Many methods have been used to make such measurements.[49]

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[49] For a monograph on methods of interpreting kinetic data, see Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics*, Wiley, NY, ***1984***. For a review of methods of obtaining kinetic data, see Batt, L. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics,* Vol. 1, Elsevier, NY, ***1969***, pp. 1–111.

The choice of a method depends on its convenience and its applicability to the reaction being studied. Among the most common methods are

1. *Periodic or Continuous Spectral Readings.* In many cases, the reaction can be carried out in the cell while it is in the instrument. Then all that is necessary is that the instrument be read, periodically or continuously. Among the methods used are ir and uv spectroscopy, polarimetry, nmr, and esr.[50]
2. *Quenching and Analyzing.* A series of reactions can be set up and each stopped in some way (perhaps by suddenly lowering the temperature or adding an inhibitor) after a different amount of time has elapsed. The materials are then analyzed by spectral readings, titrations, chromatography, polarimetry, or any other method.
3. *Removal of Aliquots at Intervals.* Each aliquot is then analyzed as in method 2.
4. *Measurement of Changes in Total Pressure, for Gas-Phase Reactions.*[51]
5. *Calorimetric Methods.* The output or absorption of heat can be measured at time intervals.

Special methods exist for kinetic measurements of very fast reactions.[52]

In any case, what is usually obtained is a graph showing how a concentration varies with time. This must be interpreted[53] to obtain a rate law and a value of k. If a reaction obeys simple first- or second-order kinetics, the interpretation is generally not difficult. For example, if the concentration at the start is $\mathbf{A}_0$, the first-order rate law

$$\frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}] \qquad \text{or} \qquad \frac{-d[\mathbf{A}]}{[\mathbf{A}]} = kdt$$

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[50] For a review of esr to measure kinetics, see Norman, R.O.C. *Chem. Soc. Rev.* ***1979***, *8*, 1.

[51] For a review of the kinetics of reactions in solution at high pressures, see le Noble, W.J. *Prog. Phys. Org. Chem.* ***1967***, *5*, 207. For reviews of synthetic reactions under high pressure, see Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* ***1985***, 1; Matsumoto, K.; Sera, A. *Synthesis* ***1985***, 999.

[52] For reviews, see Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***, pp. 133–186; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics*, Wiley, NY, ***1984***, pp. 247–327; Krüger, H. *Chem. Soc. Rev.* ***1982***, *11*, 227; Hague, D.N. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 1, Elsevier, NY, ***1969***, pp. 112–179, Elsevier, NY, ***1969***; Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 2, Wiley, NY, ***1986***,. See also, Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 24, Elsevier, NY, ***1983***.

[53] For discussions, much fuller than that given here, of methods for interpreting kinetic data, see Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***, pp. 17–131; Ritchie, C.D. *Physical Organic Chemistry*, 2nd ed., Marcel Dekker, NY, ***1990***, pp. 1–35; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics,* Wiley, NY, ***1984***; Margerison, D., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 1, Elsevier, NY, ***1969***, pp. 343–421; Moore, J.W.; Pearson, R.G. *Kinetics and Mechanism*, 3rd ed., Wiley, NY, ***1981***, pp. 12–82; in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, the articles by Bunnett, J.F. pp. 251–372, Noyes Pub., pp. 373–423, Bernasconi, C.F. pp. 425–485, Wiberg, K.B. pp. 981–1019.

can be integrated between the limits $t = 0$ and $t = t$ to give

$$-\ln\frac{[\mathbf{A}]}{\mathbf{A}_0} = kt \qquad \text{or} \qquad \ln[\mathbf{A}] = -kt + \ln\mathbf{A}_0$$

Therefore, if a plot of ln [**A**] against t is linear, the reaction is first order and k can be obtained from the slope. For first-order reactions, it is customary to express the rate not only by the rate constant k, but also by the *half-life*, which is the time required for one-half of any given quantity of a reactant to be used up. Since the half-life $t_{1/2}$ is the time required for [**A**] to reach $\mathbf{A}_0/2$, we may say that

$$\ln\frac{\mathbf{A}_0}{2} = kt_{1/2} + \ln\mathbf{A}_0$$

so that

$$t_{1/2} = \frac{\ln\left[\frac{\mathbf{A}_0}{\mathbf{A}_0/2}\right]}{k} = \frac{\ln 2}{k} = \frac{0.693}{k}$$

For the general case of a reaction first order in **A** and first order in **B**, second order overall, integration is complicated, but it can be simplified if equimolar amounts of **A** and **B** are used, so that $\mathbf{A}_0 = \mathbf{B}_0$. In this case,

$$\frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}][\mathbf{B}]$$

is equivalent to

$$\frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}]^2 \qquad \text{or} \qquad \frac{-d[\mathbf{A}]}{[\mathbf{A}]^2} = k\,dt$$

Integrating as before gives

$$\frac{1}{[\mathbf{A}]} - \frac{1}{\mathbf{A}_0} = kt$$

Thus, under equimolar conditions, if a plot of 1/[**A**] against t is linear, the reaction is second order with a slope of k. It is obvious that the same will hold true for a reaction second order in **A**.[54]

Although many reaction-rate studies do give linear plots, which can therefore be easily interpreted, the results in many other studies are not so simple. In some cases, a reaction may be first order at low concentrations but second order at higher concentrations. In other cases, fractional orders are obtained, and even negative orders. The interpretation of complex kinetics often requires much skill and effort. Even where the kinetics are relatively simple, there is often a problem in interpreting the data because of the difficulty of obtaining precise enough measurements.[55]

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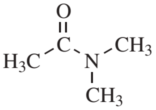
[54] We have given the integrated equations for simple first- and second-order kinetics. For integrated equations for a large number of kinetic types, see Margerison, D., in Bamford, C.H.; Tipper C.F.H. *Comprehensive Chemical Kinetics,* Vol. 1, Elsevier, NY, ***1969***, p. 361.

[55] See, Hammett, L.P. *Physical Organic Chemistry,* 2nd ed., McGraw-Hill, NY, ***1970***, pp. 62–70.

Nuclear magnetic resonance spectra can be used to obtain kinetic information in a completely different manner from that mentioned on p. 319. This method, which involves the study of NMR line shapes,[56] depends on the fact that NMR spectra have an inherent time factor: If a proton changes its environment less rapidly than $\sim 10^3$ times/s, an NMR spectrum shows a separate peak for each position the proton assumes. For example, if the rate of rotation around



the C—N bond of *N,N*-dimethylacetamide is slower than 10^3 rotations per second, the two *N*-methyl groups each have separate chemical shifts since they are not equivalent, one being cis to the oxygen and the other trans. However, if the environmental change takes place more rapidly than $\sim 10^3$ times per second, only one line is found, at a chemical shift that is the weighted average of the two individual positions. In many cases, two or more lines are found at low temperatures, but as the temperature is increased, the lines coalesce because the interconversion rate increases with temperature and passes the 10^3 per second mark. From studies of the way line shapes change with temperature it is often possible to calculate rates of reactions and of conformational changes. This method is not limited to changes in proton line shapes but can also be used for other atoms that give nmr spectra and for esr spectra.

Several types of mechanistic information can be obtained from kinetic studies.

1. From the order of a reaction, information can be obtained about which molecules and how many take part in the rate-determining step. Such knowledge is very useful and often essential in elucidating a mechanism. For any mechanism that can be proposed for a given reaction, a corresponding rate law can be calculated by the methods discussed on pp. 316–320. If the experimentally obtained rate law fails to agree with this, the proposed mechanism is wrong. However, it is often difficult to relate the order of a reaction to the mechanism, especially when the order is fractional or negative. In addition, it is frequently the case that two or more proposed mechanisms for a reaction are kinetically indistinguishable, that is, they predict the same rate law.
2. Probably the most useful data obtained kinetically are the rate constants themselves. They are important since they can tell us the effect on the rate of

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[56] For a monograph, see Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***. For reviews, see Fraenkel, G., in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 2, Wiley, NY, ***1986***, pp. 547–604; Aganov, A.V.; Klochkov, V.V.; Samitov, Yu.Yu. *Russ. Chem. Rev.* ***1985***, *54*, 931; Roberts, J.D. *Pure Appl. Chem.* ***1979***, *51*, 1037; Binsch, G. *Top. Stereochem.* ***1968***, *3*, 97; Johnson Jr., C.S. *Adv. Magn. Reson.* ***1965***, *1*, 33.

a reaction of changes in the structure of the reactants (see Chapter 9), the solvent, the ionic strength, the addition of catalysts, and so on.

3. If the rate is measured at several temperatures, in most cases a plot of ln k against $1/T$ (T stands for absolute temperature) is nearly linear[57] with a negative slope, and fits the equation

$$\ln k = \frac{-E_a}{RT} + \ln A$$

where R is the gas constant and A is a constant called the *frequency factor*. This permits the calculation of E_a, which is the Arrhenius activation energy of the reaction. The parameter $\Delta H^{\ddagger}$ can then be obtained by

$$E_a = \Delta H^{\ddagger} + RT$$

It is also possible to use these data to calculate $\Delta S^{\ddagger}$ by the formula[58]

$$\frac{\Delta S^{\ddagger}}{4.576} = \log k - 10.753 - \log T + \frac{E_a}{4.576T}$$

for energies in calorie units. For joule units the formula is

$$\frac{\Delta S^{\ddagger}}{19.15} = \log k - 10.753 - \log T + \frac{E_a}{19.15T}$$

One then obtains $\Delta G^{\ddagger}$ from $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

Isotope Effects

When a hydrogen in a reactant molecule is replaced by deuterium, there is often a change in the rate. Such changes are known as *deuterium isotope effects*[59] and are

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[57] For a review of cases where such a plot is nonlinear, see Blandamer, M.J.; Burgess, J.; Robertson, R.E.; Scott, J.M.W. *Chem. Rev.* ***1982***, *82*, 259.

[58] For a derivation of this equation, see Bunnett, J.F., in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, p. 287.

[59] For a monograph, see Melander, L.; Saunders, Jr., W.H. *Reaction Rates of Isotopic Molecules*, Wiley, NY, ***1980***. For reviews, see Isaacs, N.S. *Physical Organic Chemistry*, Longman Scientific and Technical, Essex, ***1987***, pp. 255–281; Lewis, E.S. *Top. Curr. Chem.* ***1978***, *74*, 31; Saunders, Jr., W.H. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 565–611; Bell, R.P. *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, ***1973***, pp. 226–296, *Chem. Soc. Rev.* ***1974***, *3*, 513; Bigeleisen, J.; Lee, M.W.; Mandel, F. *Annu. Rev. Phys. Chem.* ***1973***, *24*, 407; Wolfsberg, M. *Annu. Rev. Phys. Chem.* ***1969***, *20*, 449; Saunders, Jr., W.H. *Surv. Prog. Chem.* ***1966***, *3*, 109; Simon, H.; Palm, D. *Angew. Chem. Int. Ed.* ***1966***, *5*, 920; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***, pp. 243–281. For a review of temperature dependence of primary isotope effects as a mechanistic criterion, see Kwart, H. *Acc. Chem. Res.* ***1982***, *15*, 401. For a review of the effect of pressure on isotope effects, see Isaacs, E.S. *Isot. Org. Chem.* ***1984***, *6*, 67. For a review of isotope effects in the study of reactions in which there is branching from a common intermediate, see Thibblin, A.; Ahlberg, P. *Chem. Soc. Rev.* ***1989***, *18*, 209. See also, the series *Isotopes in Organic Chemistry*.

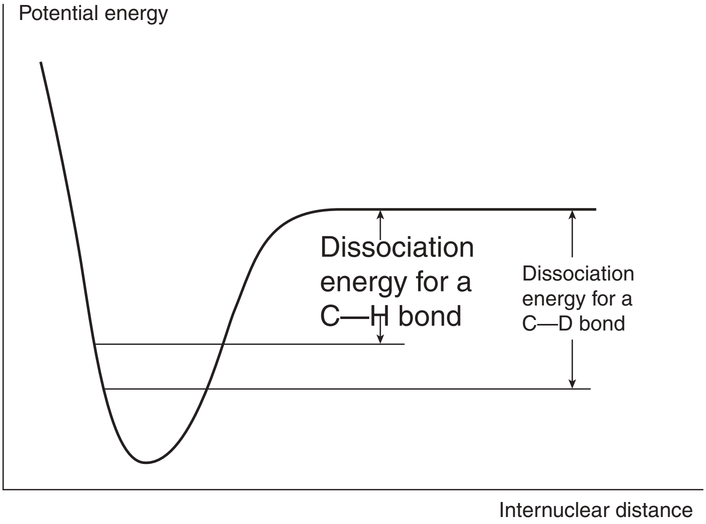


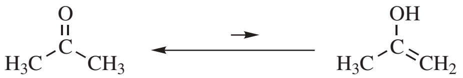
Fig. 6.4. A C—D bond has a lower zero point than does a corresponding C—H bond; thus the dissociation energy is higher.

expressed by the ratio k_H/k_D. The ground-state vibrational energy (called the zero-point vibrational energy) of a bond depends on the mass of the atoms and is lower when the reduced mass is higher.[60] Therefore, D—C, D—O, D—N bonds, and so on, have lower energies in the ground state than the corresponding H—C, H—O, H—N bonds, and so on. Complete dissociation of a deuterium bond consequently requires more energy than that for a corresponding hydrogen bond in the same environment (Fig. 6.4). If an H—C, H—O, or H—N bond is not broken at all in a reaction or is broken in a nonrate-determining step, substitution of deuterium for hydrogen causes no change in the rate (see below for an exception to this statement), but if the bond is broken in the rate-determining step, the rate must be lowered by the substitution.

This provides a valuable diagnostic tool for determination of mechanism. For example, in the bromination of acetone (reaction **12-4**)

$$CH_3COCH_3 + Br_2 \longrightarrow CH_3COCH_2Br$$

the fact that the rate is independent of the bromine concentration led to the postulate that the rate-determining step was prior tautomerization of the acetone:



In turn, the rate-determining step of the tautomerization involves cleavage of a C—H bond (see **12-3**). Thus there should be a substantial isotope effect if deuterated

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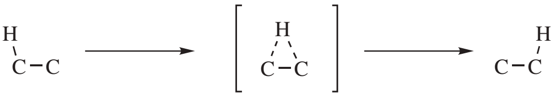
[60] The reduced mass μ of two atoms connected by a covalent bond is $\mu = m_1m_2/(m_1 + m_2)$.

acetone is brominated. In fact, k_H/k_D was found to be ~7.[61] Deuterium isotope effects usually range from 1 (no isotope effect at all) to ~7 or 8, although in a few cases, larger[62] or smaller values have been reported.[63] Values of $k_H/k_D < 1$ are called *inverse isotope effects*. Isotope effects are greatest when, in the transition state, the hydrogen is symmetrically bonded to the atoms between which it is being transferred.[64] Also, calculations show that isotope effects are at a maximum when the hydrogen in the transition state is on the straight line connecting the two atoms between which the hydrogen is being transferred and that for sufficiently nonlinear configurations they decrease to $k_H/k_D = 1–2$.[65] Of course, in open systems there is no reason for the transition state to be nonlinear, but this is not the case in many intramolecular mechanisms, for example, in a 1,2 migration of a hydrogen



Transition state

To measure isotope effects it is not always necessary to prepare deuterium-enriched starting compounds. It can also be done by measuring the change in deuterium concentration at specific sites between a compound containing deuterium in natural abundance and the reaction product, using a high-field NMR instrument.[66]

The substitution of tritium for hydrogen gives isotope effects that are numerically larger. Isotope effects have also been observed with other elements, but they are much smaller, ~1.02–1.10. For example, $k_{^{12}C}/k_{^{13}C}$ for

$$\mathrm{Ph^*CH_2Br} + \mathrm{CH_3O^{\ominus}} \xrightarrow{\mathrm{CH_3OH}} \mathrm{Ph^*CH_2OCH_3}$$

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[61] Reitz, O.; Kopp, J. *Z. Phys. Chem. Abt. A* ***1939***, *184*, 429.

[62] For an example of a reaction with a deuterium isotope effect of 24.2, see Lewis, E.S.; Funderburk, L.H. *J. Am. Chem. Soc.* ***1967***, *89*, 2322. The high isotope effect in this case has been ascribed to *tunneling* of the proton: because it is so small a hydrogen atom can sometimes get through a thin potential barrier without going over the top, that is, without obtaining the usually necessary activation energy. A deuterium, with a larger mass, is less able to do this. The phenomenon of tunneling is a consequence of the uncertainty principle. k_H/k_D for the same reaction is 79: Lewis, E.S.; Robinson, J.K. *J. Am. Chem. Soc.* ***1968***, *90*, 4337. An even larger deuterium isotope effect (~50) has been reported for the oxidation of benzyl alcohol. This has also been ascribed to tunneling: Roecker, L.; Meyer, T.J. *J. Am. Chem. Soc.* ***1987***, *109*, 746. For discussions of high isotope effects, see Kresge, A.J.; Powell, M.F. *J. Am. Chem. Soc.* ***1981***, *103*, 201; Caldin, E.F.; Mateo, S.; Warrick, P. *J. Am. Chem. Soc.* ***1981***, *103*, 202. For arguments that high isotope effects can be caused by factors other than tunneling, see McLennan, D.J. *Aust. J. Chem.* ***1979***, *32*, 1883; Thibblin, A. *J. Phys. Org. Chem.* ***1988***, *1*, 161; Kresge, A.J.; Powell, M.F. *J. Phys. Org. Chem.* ***1990***, *3*, 55.

[63] For a review of a method for calculating the magnitude of isotope effects, see Sims, L.B.; Lewis, D.E. *Isot. Org. Chem.* ***1984***, *6*, 161.

[64] Kwart, H.; Latimore, M.C. *J. Am. Chem. Soc.* ***1971***, *93*, 3770; Pryor, W.A.; Kneipp, K.G. *J. Am. Chem. Soc.* ***1971***, *93*, 5584; Bell, R.P.; Cox, B.G. *J. Chem. Soc. B* ***1971***, 783; Bethell, D.; Hare, G.J.; Kearney, P.A. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 684, and references cited therein. See, however, Motell, E.L.; Boone, A.W.; Fink, W.H. *Tetrahedron* ***1978***, *34*, 1619.

[65] More O'Ferrall, R.A. *J. Chem. Soc. B* ***1970***, 785, and references cited therein.

[66] Pascal, R.A.; Baum, M.W.; Wagner, C.K.; Rodgers, L.R.; Huang, D. *J. Am. Chem. Soc.* ***1986***, *108*, 6477.

is 1.053.[67] Although they are small, heavy-atom isotope effects can be measured quite accurately and are often very useful.[68]

Deuterium isotope effects have been found even where it is certain that the C—H bond does not break at all in the reaction. Such effects are called *secondary isotope effects*,[69] the term *primary isotope effect* being reserved for the type discussed previously. Secondary isotope effects can be divided into α and β effects. In a β secondary isotope effect, substitution of deuterium for hydrogen β to the position of bond breaking slows the reaction. An example is solvolysis of isopropyl bromide:

$$(CH_3)_2CHBr \quad + \quad H_2O \quad \xrightarrow{k_H} \quad (CH_3)_2CHOH$$

$$(CD_3)_2CHBr \quad + \quad H_2O \quad \xrightarrow{k_D} \quad (CD_3)_2CHOH$$

where k_H/k_D was found to be 1.34.[70] The cause of β isotope effects has been a matter of much controversy, but they are most likely due to hyperconjugation effects in the transition state. The effects are greatest when the transition state has considerable carbocation character.[71] Although the C—H bond in question is not broken in the transition state, the carbocation is stabilized by hyperconjugation involving this bond. Because of hyperconjugation, the difference in vibrational energy between the C—H bond and the C—D bond in the transition state is less than it is in the ground state, so the reaction is slowed by substitution of deuterium for hydrogen.

Support for hyperconjugation as the major cause of β isotope effects is the fact that the effect is greatest when D is anti to the leaving group[72] (because of the requirement that all atoms in a resonance system be coplanar, planarity of the D—C—C—X system would most greatly increase the hyperconjugation), and the fact that secondary isotope effects can be transmitted through unsaturated systems.[73] There is evidence that at least some β isotope effects are steric in

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[67] Stothers, J.B.; Bourns, A.N. *Can. J. Chem.* ***1962***, *40*, 2007. See also, Ando, T.; Yamataka, H.; Tamura, S.; Hanafusa, T. *J. Am. Chem. Soc.* ***1982***, *104*, 5493.

[68] For a review of carbon isotope effects, see Willi, A.V. *Isot. Org. Chem.* ***1977***, *3*, 237.

[69] For reviews, see Westaway, K.C. *Isot. Org. Chem.* ***1987***, *7*, 275; Sunko, D.E.; Hehre, W.J. *Prog. Phys. Org. Chem.* ***1983***, *14*, 205; Shiner, Jr., V.J., in Collins, C.J.; Bowman, N.S. *Isotope Effects in Chemical Reactions*, Van Nostrand-Reinhold, Princeton, NJ, ***1970***, pp. 90–159; Laszlo, P.; Welvart, Z. *Bull. Soc. Chim. Fr.* ***1966***, 2412; Halevi, E.A. *Prog. Phys. Org. Chem.* ***1963***, *1*, 109. For a review of model calculations of secondary isotope effects, see McLennan, D.J. *Isot. Org. Chem.* ***1987***, *7*, 393. See also, Sims, L.B.; Lewis, D.E. *Isot. Org. Chem.* ***1984***, *6*, 161.

[70] Leffek, K.T.; Llewellyn, J.A.; Robertson, R.E. *Can. J. Chem.* ***1960***, *38*, 2171.

[71] Bender, M.L.; Feng, M.S. *J. Am. Chem. Soc.* ***1960***, *82*, 6318; Jones, J.M.; Bender, M.L. *J. Am. Chem. Soc.* ***1960***, *82*, 6322.

[72] Shiner, Jr., V.J.; Jewett, J.G. *J. Am. Chem. Soc.* ***1964***, *86*, 945; DeFrees, D.J.; Hehre, W.J.; Sunko, D.E. *J. Am. Chem. Soc.* ***1979***, *101*, 2323. See also, Siehl, H.; Walter, H. *J. Chem. Soc. Chem. Commun.* ***1985***, 76.

[73] Shiner, Jr., V.J.; Kriz, Jr., G.S. *J. Am. Chem. Soc.* ***1964***, *86*, 2643.

origin[74] (e.g., a CD_3 group has a smaller steric requirement than a CH_3 group) and a field-effect explanation has also been suggested (CD_3 is apparently a better electron donor than CH_3[75]), but hyperconjugation is the most probable cause in most instances.[76] Part of the difficulty in attempting to explain these effects is their small size, ranging only as high as ~1.5.[77] Another complicating factor is that they can change with temperature. In one case,[78] k_H/k_D was 1.00 ± 0.01 at 0°C, 0.90 ± 0.01 at 25°C, and 1.15 ± 0.09 at 65°C. Whatever the cause, there seems to be a good correlation between β secondary isotope effects and carbocation character in the transition state, and they are thus a useful tool for probing mechanisms.

The other type of secondary isotope effect results from a replacement of hydrogen by deuterium at the carbon containing the leaving group. These (called *secondary isotope effects*) are varied, with values so far reported[79] ranging from 0.87 to 1.26.[80] These effects are also correlated with carbocation character. Nucleophilic substitutions that do not proceed through carbocation intermediates (S_N2 reactions) have a isotope effects near unity.[81] Those that do involve carbocations (S_N1 reactions) have higher a isotope effects, which depend on the nature of the leaving group.[82] The accepted explanation for a isotope effects is that one of the bending C—H vibrations is affected by the substitution of D for H more or less strongly in the transition state than in the ground state.[83] Depending on the nature of the transition state, this may increase or decrease the rate of the reaction. The α isotope effects on S_N2 reactions can vary with concentration,[84] an

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[74] Bartell, L.S. *J. Am. Chem. Soc.* ***1961***, *83*, 3567; Brown, H.C.; Azzaro, M.E.; Koelling, J.G.; McDonald, G.J. *J. Am. Chem. Soc.* ***1966***, *88*, 2520; Kaplan, E.D.; Thornton, E.R. *J. Am. Chem. Soc.* ***1967***, *89*, 6644; Carter, R.E.; Dahlgren, L. *Acta Chem. Scand.* ***1970***, *24*, 633; Leffek, K.T.; Matheson, A.F. *Can. J. Chem.* ***1971***, *49*, 439; Sherrod, S.A.; Boekelheide, V. *J. Am. Chem. Soc.* ***1972***, *94*, 5513.

[75] Halevi, E.A.; Nussim, M.; Ron, M. *J. Chem. Soc.* ***1963***, 866; Halevi, E.A.; Nussim, M. *J. Chem. Soc.* ***1963***, 876.

[76] Karabatsos, G.J.; Sonnichsen, G.; Papaioannou, C.G.; Scheppele, S.E.; Shone, R.L. *J. Am. Chem. Soc.* ***1967***, *89*, 463; Kresge, A.J.; Preto, R.J. *J. Am. Chem. Soc.* ***1967***, *89*, 5510; Jewett, J.G.; Dunlap, R.P. *J. Am. Chem. Soc.* ***1968***, *90*, 809; Sunko, D.E.; Szele, I.; Hehre, W.J. *J. Am. Chem. Soc.* ***1977***, *99*, 5000; Kluger, R.; Brandl, M. *J. Org. Chem.* ***1986***, *51*, 3964.

[77] Halevi, E.A.; Margolin, Z. *Proc. Chem. Soc.* ***1964***, 174. A value for k_{CH_3}/k_{CD_3} of 2.13 was reported for one case: Liu, K.; Wu, Y.W. *Tetrahedron Lett.* ***1986***, *27*, 3623.

[78] Halevi, E.A.; Margolin, Z. *Proc. Chem. Soc.* ***1964***, 174.

[79] A value of 2.0 has been reported in one case, for a cis–trans isomerization, rather than a nucleophilic substitution: Caldwell, R.A.; Misawa, H.; Healy, E.F.; Dewar, M.J.S. *J. Am. Chem. Soc.* ***1987***, *109*, 6869.

[80] Shiner, Jr., V.J.; Buddenbaum, W.E.; Murr, B.L.; Lamaty, G. *J. Am. Chem. Soc.* ***1968***, *90*, 418; Harris, J.M.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 2551.

[81] For reported exceptions, see Tanaka, N.; Kaji, A.; Hayami, J. *Chem. Lett.* ***1972***, 1223; Westaway, K.C. *Tetrahedron Lett.* ***1975***, 4229.

[82] Willi, A.V.; Ho, C.; Ghanbarpour, A. *J. Org. Chem.* ***1972***, *37*, 1185; Shiner Jr., V.J.; Neumann, A.; Fisher, R.D. *J. Am. Chem. Soc.* ***1982***, *104*, 354; and references cited therein.

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effect attributed to a change from a free nucleophile to one that is part of an ion pair[85] (see p. 492). This illustrates the use of secondary isotope effects as a means of studying transition state structure. The γ secondary isotope effects have also been reported.[86]

Another kind of isotope effect is the *solvent isotope effect*.[87] Reaction rates often change when the solvent is changed from H_2O to D_2O or from ROH to ROD. These changes may be due to any of three factors or a combination of all of them.

1. The solvent may be a reactant. If an O—H bond of the solvent is broken in the rate-determining step, there will be a primary isotope effect. If the molecules involved are D_2O or D_3O^+ there may also be a secondary effect caused by the O—D bonds that are not breaking.
2. The substrate molecules may become labeled with deuterium by rapid hydrogen exchange, and then the newly labeled molecule may become cleaved in the rate-determining step.
3. The extent or nature of solvent–solute interactions may be different in the deuterated and nondeuterated solvents; this may change the energies of the transition state, and hence the activation energy of the reaction. These are secondary isotope effects. Two physical models for this third factor have been constructed.[88]

It is obvious that in many cases the first and third factors at least, and often the second, are working simultaneously. Attempts have been made to separate them.[89]

The methods described in this chapter are not the only means of determining mechanisms. In an attempt to elucidate a mechanism, the investigator is limited only by their ingenuity.

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